Preconceptional Folate Supplementation and the Risk of Spontaneous Preterm Birth

A Cohort Study

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ABSTRACT

A number of studies have reported an association between low concentrations of serum folate and preterm birth. Folate supplementation during pregnancy increased the length of pregnancy in some but not all clinical trials. This cohort study investigated whether preconceptional folate supplementation (as ascertained by patient questionnaire in the first trimester of pregnancy) lowers the risk of spontaneous preterm birth. The investigators analyzed data collected from a cohort of 34,480 low-risk singleton pregnancies in women enrolled in a previous prospective cohort study on Down syndrome screening conducted at 15 US centers between 1999 and 2002. Duration of pregnancy was estimated by ultrasound measurement in the first trimester. Spontaneous preterm birth was defined as preterm birth between 20 and 37 weeks with no medical or obstetrical complications that constituted indications for delivery. The effects of the duration of preconceptional folate supplementation of \( \geq 1 \) year (long-term), \(< 1 \) year and the effect of no supplementation on risk of spontaneous preterm birth were compared using time-to-event analysis. Data were subjected to analysis with multivariable logistic regression.

Compared to women who did not take a folate supplement, the risk of spontaneous preterm delivery between 20 and 28 weeks was 70% lower in women who took folate supplements for a year or longer before pregnancy (0.27% vs 0.04%); the hazard ratio was 0.22, with a 95% confidence interval of 0.08 to 0.61, \( P = 0.004 \). Long-term folate supplementation reduced the risk between 28 and 32 weeks by over 50% (0.38% vs 0.18%) (hazard ratio, 0.45; 95% confidence interval, 0.24–0.83, \( P = 0.010 \)). Supplementation had no significant effect on the risk of spontaneous preterm birth beyond 32 weeks. Adjustment for maternal variables (age, body mass index, race and ethnicity, educational level, marital status, smoking, parity and history of prior preterm birth) did not affect the association between long-term folate and risk of spontaneous preterm birth but did eliminate the association found in unadjusted analysis between duration of preconceptional folate supplementation less than one year and risk.

These findings suggest that preconceptional folate supplementation for a year or longer may substantially reduce the risk of early spontaneous preterm birth. The risk is lower with longer duration of folate supplementation before pregnancy. The beneficial effect of folic acid does not appear to be associated with other complications of
EDITORIAL COMMENT

(From an analytic standpoint, the abstracted report by Bukowski et al is sophisticated and well done. The limitations of this study relate to its design—it is a retrospective cohort study rather than a prospective randomized trial. This design gives direct rise to 2 of its main limitations. The first relates to ascertainment of folate exposure. Women were categorized into folate-duration groups based on reported as opposed to measured folate consumption—specifically, “consistent” consumption. And while participants may have been instructed on what constituted “consistent,” we are not told whether they were, and if so, what was meant by it. Moreover, women were asked only about duration, but not amount of supplementation. In a well-done randomized trial, we would know with much more validity, whether, when, and how much folate was actually taken.

The second major study limitation that arises directly from its nonrandomized design is the lack of group comparability. To wit, compared to women who reported no preconceptional folate use, those who reported consistent use for more than a year were older (33 vs 28 years old), thinner (BMI 23 vs 25 kg/m²), more likely to be Caucasian (87 vs 50%), less likely to be African-American (3% vs 8%), more likely to be married (93% vs 63%), more likely to have gone to school beyond high school (91% vs 56%, and although we are not told this, probably much more likely to have finished high school) and, if parous, less likely to have experienced a preterm birth (7% vs 8%). The respective characteristics of women who reported consistent preconceptional folate supplementation for less than a year were intermediate between the no supplementation and at least a year of supplementation groups.

The constellation of demographic factors in the group that reported consistent folate supplementation for at least a year before conception is itself associated with an inherently lower risk of spontaneous preterm birth than either of the other two groups. In a well-done randomized trial, these factors would have been comparable between groups. However in this retrospective study, we are left to rely on statistical adjustment to remove the influence of these group imbalances, and there is always a risk that this adjustment was not quite up to the task. We, in short, are less able to be confident that the differences in early preterm birth rates between the groups are in fact due to their folate consumption habits as opposed to inherent differences in their predisposition to early preterm birth.

A final limitation worth noting is that the results are predicated on a small number of cases (in the final adjusted analysis only 115 out of a cohort of ~35,000) and that they apply exclusively births before 32 weeks classified as “spontaneous,” not all births before 32 weeks. This is important because in this cohort, only about one-third of the deliveries before 32 weeks were classified as “spontaneous.” Preconceptional folate supplementation had no differential effect on the remaining two-thirds.

Limitations aside, the findings of Bukowski et al are provocative and important. They certainly justify a randomized trial. In the meantime, all reproductive age women at risk for pregnancy should comply with current recommendations for the daily ingestion of 400 μg of folic acid preconceptionally and throughout the first trimester of pregnancy. Since many pregnancies are not planned or intended, daily supplementation without regard to conception is the best course, and if the findings of Bukowski are born out, may have just gotten better.—DJR)
The Safety of Metoclopramide Use in the First Trimester of Pregnancy

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ABSTRACT

Metoclopramide has been the drug of choice in many countries to manage nausea and vomiting in pregnant women despite lack of substantial evidence of its safety in this population when used as recommended. The few studies that have investigated the safety to the fetus of maternal exposure to metoclopramide during the first trimester are small studies with a total enrollment of only 800 pregnant women. This retrospective cohort study investigated the safety for the fetus of exposure to metoclopramide during the first trimester of pregnancy. Between 1998 and 2007, computerized data on medications dispensed for pregnant Israeli women were linked to databases containing maternal and infant hospital records. The metoclopramide group (n = 3458) was comprised of infants of singleton girls and women who had taken the drug during the first trimester. The no exposure group (n = 78,245) was comprised of infants of mothers not treated with the drug. The data was adjusted for potential confounders including maternal age, parity, self-reported smoking status during pregnancy, presence or absence of maternal diabetes mellitus, and presence or absence of peripartum fever.

There were no significant differences in the risk of adverse outcomes between the 2 groups. The risks of major congenital malformations during the first trimester was 5.3% (182/3458) in the metoclopramide group and 4.9% (3834/78,245) in the unexposed group; the adjusted odds ratio (aOR) was 1.04, with a 95% confidence interval (CI) of 0.89 to 1.21. In the metoclopramide and unexposed groups, the risk of low birth weight was 8.5% and 8.3% (aOR, 1.01; 95% CI, 0.89–1.14), the risk of preterm delivery was 6.3% and 5.9% (aOR, 1.15; 95% CI, 0.99–1.34), and risk of perinatal death was 1.5% and 2.2% (aOR, 0.87; 95% CI, 0.55–1.38). No significant difference in the outcome data for major congenital malformations was found when therapeutic abortions were included in the analysis (6.1%, metoclopramide group vs 5.9%, unexposed group).

These findings are consistent with previous studies showing no significant association between exposure to metoclopramide during the first trimester and adverse perinatal outcomes.

EDITORIAL COMMENT

(Almost all pregnant women suffer some degree of nausea and vomiting in the first trimester. In up to 2% of women the severity and persistence of the nausea and vomiting qualifies it as “hyperemesis gravidarum,” characterized by evidence of acute starvation such as large ketonuria, and weight loss of at least 5%. Hyperemesis gravidarum is the leading cause of hospitalization in the first half of pregnancy (ACOG Practice Bulletin #54, April 2004). Pharmacologic treatment of hyperemesis gravidarum is stepwise. The following approach is outlined in ACOG Practice Bulletin #54. Vitamin B₆, 10 to 25 mg, TID or QID is first line therapy. If that is insufficiently effective, or ineffective altogether, the addition of the antihistamine (H₁ blocker) doxylamine, 12.5 mg TID or QID, is recommended. If that does not work, then promethazine (a phenothiazine) in oral or rectal doses of 12.5 to 25 mg doses every 4 hours is added. In the ACOG algorithm (adapted from Levichek Z., et al. Can Fam Physician 2002;48:267) the dopamine antagonist metoclopramide (Reglan) is not recommended until the preceding medications have failed. However, in some European countries and Israel, metoclopramide is the first-line choice. But despite its fairly widespread use during the first trimester of pregnancy, until the abstracted report of Matok et al, there has been a
paucity of robust safety data for metoclopramide. In this report, 3458 of the 81,703 women (4.2%) were prescribed and presumably ingested metoclopramide during the first trimester of pregnancy. Reassuringly, such ingestion was not associated with significantly increased risks of major or minor congenital malformations, preterm birth, low or very low birth weight, low Apgar scores, or perinatal death.

Strengths of this study include the uniform evaluation of all infants under the supervision of neonatologists, and precise information on the doses of metoclopramide dispensed. The study has several potentially important limitations. Most women were exposed to less than a week of metoclopramide. Thus, the power of the study to detect an increase in malformations of individual organs or organ systems is limited, as the number exposed during any critical period of particular organ development is necessarily much lower than the total number exposed at any time in the first trimester. Another limitation is that adherence was not assessed—only whether metoclopramide was dispensed. Spontaneous abortions were not recorded in the dataset so this study can not speak to any potential effect of metoclopramide on spontaneous abortions. Lastly, since women who experience nausea and vomiting are more likely to have favorable pregnancy outcomes (Brown R., et al. Am J Epidemiol 1999;149:717) it is conceivable that any deleterious effects of metoclopramide were masked by this inherent predisposition to salutary outcomes.

The limitations that I have enumerated are not specific to this study but rather are characteristic of almost all studies that assess the potential adverse effects of drugs taken during pregnancy. At the end of the day, we can never say with certainty that a drug is without fetal risk. But studies such as the one by Matok et al help us decide when the potential risk is acceptable.—DJR

A Randomized Controlled Trial of Cervical Scanning vs History to Determine Cerclage in Women at High Risk of Preterm Birth (CIRCLE Trial)

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ABSTRACT

Cervical cerclage may be useful either as a preventative or therapeutic measure in women at risk for preterm delivery (PTD). The 2 common types of management currently used in pregnant women at high risk of PTD are transvaginal measurement of cervical length, or assessment of risk and need for intervention based on obstetric history. Because the RR of a preterm birth increases with shortening cervical length, ultrasound measurement of cervical length in a woman with a previous preterm birth could help target those needing cerclage. Currently, history-indicated cerclage is inserted only in women with prior multiple pregnancy losses. Suggestions have been made that identification of the ultrasonographically short cervix with cerclage may reduce the need for a cerclage based on a history of only 1 previous PTD.
This randomized controlled trial compared use of ultrasound-indicated cervical cerclage in pregnant women with a short cervix (<20 mm in length), with elective management without ultrasound in which the decision to insert a prophylactic history-indicated suture was based solely on obstetric history. Eligible pregnant women were enrolled in the study between 2003 and 2006 from hospitals in the United Kingdom. The study subjects were asymptomatic women at high risk, who had at least 1 previous delivery between 16 and 34 weeks. Of the eligible 248 women, 123 were randomized to the ultrasound scanning group and 125 to history-indicated management group. The primary outcome measure was PTD before 34 weeks.

There was no difference between the 2 groups in the incidence of preterm birth between 24 and 34 weeks of gestation (19/125 [15%] in the history-indicated management group vs 18/122 [15%] in the ultrasound scanning group); the relative risk [RR] was 0.97, with a 95% confidence interval (CI) of 0.54 to 1.76. Women in the ultrasound scanning group were significantly more likely than those in the history-indicated management group to receive a cerclage (32% vs 19%; RR, 1.66; 95% CI, 1.07–2.47) or progesterone (39% vs 25%; RR, 1.55; 95% CI, 1.06–2.25).

These data suggest that the decision on placement of cervical cerclage in a women with a previous preterm birth should be made on the basis of clinical history, not on the basis of ultrasound scanning. However, the data do not support routine placement of history-indicated sutures routinely in this population. Scanning may still be beneficial in women at higher risk.

**EDITORIAL COMMENT**

(In the December 2008 Survey, we published a review article by Blikman et al entitled “Ultrasound-Predicated Versus History-Predicated Cerclage in Women at Risk of Cervical Insufficiency.” It was a systematic review of 6 studies, 4 of which were retrospective and 2 of which were prospective randomized trials. The conclusion of that review was that “using ultrasound to identify women at risk of cervical insufficiency because of a history of preterm birth reduces cerclage rates and results in similar pregnancy outcomes as cerclage placement on the basis of history alone.”

The authors of that review noted that “the two randomized trials included only women who in a previous pregnancy met the classic clinical criteria for cervical insufficiency (ie preterm delivery or second trimester loss with painless and progressive dilation of the cervix), whereas the other four studies included a broader spectrum of women at risk of cervical insufficiency (ie previous preterm delivery, second trimester loss, or cervical surgery).” They concluded that “a properly designed, conducted, and analyzed randomized trial is required to confirm our findings. Important elements of such a trial would include a carefully specified ultrasound surveillance protocol, meticulous collection of cerclage complications, and, ideally, a sample size adequate enough for robust sub-group comparisons.”

With the exception of the robust sub-group comparison element, Simcox et al seem to have conducted just such a trial (abstracted above). Women were eligible for this trial if they had a history of at least 1 spontaneous PTD between 16 and 34 weeks’ gestation. They were randomized to cerclage placement either on the basis of a trans-vaginally measured cervical length of 20 mm or less before 24 weeks’ gestation, or to cerclage placement of the basis of their history as assessed by their managing clinician. Importantly, the determination as to whether the patient was a candidate for cerclage on the basis of history was made before randomization. Once randomized, in the clinician-indicated group the cerclage was placed on the basis of the prerandomization determination, whereas in the ultrasound-indicated group, history was not taken into account—cervical length was the determining factor.

The results of the Simcox trial may appear turn the conclusions of the Blikman review on their head. In this group of women, when short cervical length as assessed by transvaginal ultrasound was used to decide whether a cerclage was indicated, more not fewer cerclages were placed. Even so, the rate of early preterm birth was identical between the groups. This trial seems to vindicate clinical judgment in deciding who will benefit from cerclage, and repudiate the blanket application of transvaginal cervical length assessment to arrive at this determination.

But the study has some serious limitations. We are not told on what basis the history-indicated cerclages were placed, and without a control group we can not be certain that women in either
group benefitted from cerclage. The lack of a control group is not a mere quibble—previous reviews have suggested that only women with 3 mid-trimester losses or preterm deliveries benefit from cerclage, and few women in this trial (n = 5) had such a history (Berghella V, Seibel-Seamon J. Clin Obstet Gynecol 2007;50:468). Twelve women in the history-indicated group delivered before 24 weeks, versus 4 in the ultrasound group. These women were not included in the primary outcome, which is odd, since previable delivery is generally what cerclage is intended to prevent. Had they been included, the rate of the primary outcome would have been 18% in the ultrasound-indicated group versus 25% in the history-indicated. One woman in the ultrasound group declined a protocol-indicated cerclage and delivered at 26 weeks. Eight women in the history-indicated group in fact underwent cervical length assessment, and 3 of them had a cerclage placed for a short cervix.

Before this trial, I would have said that transvaginal ultrasound was a good way to pick candidates for cerclage from among women with prior second or early third trimester deliveries. This trial has not convinced me to change that view.—DJR

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Maternal Mortality and Serious Maternal Morbidity in Jehovah’s Witnesses in The Netherlands

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ABSTRACT

Refusal of blood by women with major obstetric hemorrhage who are Jehovah’s witnesses increases their risk of maternal death. This retrospective study of case notes assessed the risk of maternal morbidity and mortality from major obstetric hemorrhage in Jehovah’s witnesses. The data was obtained from all tertiary care centers and general hospitals in The Netherlands. The investigators examined case notes of Jehovah’s witnesses who had serious maternal morbidity between 2004 and 2006. Mortality data for the years between 1983 and 2006 was also examined. The incidence of maternal morbidity and mortality in Jehovah’s witnesses was compared with the total incidence of maternal morbidity reported in a previous study and the total incidence of maternal mortality reported to the Maternal Mortality Committee. The primary study outcome was the maternal mortality ratio (MMR) and risk of serious maternal mortality.

A total of 8850 deliveries by Jehovah’s witnesses was reported during the study years. Death occurred in 6 of these mothers as a direct result of major obstetric hemorrhage. This represents a MMR of 68 per 100,000 live births, which is 6 times higher than in the general Dutch population and 130 times higher than the reported MMR from major obstetric hemorrhage. The risk of serious maternal morbidity because of obstetric hemorrhage among Jehovah’s witnesses was 14 per 1000 births, whereas the risk in the total population of pregnant Dutch women was 4.5 per 1000. This represents a 3.1 times higher risk of serious maternal morbidity in Jehovah’s witnesses compared with the general Dutch population.
These findings demonstrate the consequences of the refusal of Dutch Jehovah’s witnesses with major obstetric hemorrhage to accept transfusion of blood or major blood components. Because some Witnesses may accept treatment with blood products such as coagulation factors and erythropoietin, the investigators suggest that available alternatives to red blood cell transfusion should be discussed with these women early in pregnancy.

EDITORIAL COMMENT

(Over 7 million Jehovah’s witnesses around the world actively preach, and as many as 12–18 million attend religious services. One aspect of their faith has major implications for obstetric care: “Jehovah’s witnesses have absolutely refused the transfusion of blood and primary blood components (red cells, white cells, plasma and platelets) even as these techniques became universally available. This is a deeply held core value, and they regard a non-consensual transfusion as a gross physical violation” (Royal College of Surgeons; 2002:5).

In a prior Survey I discussed the relative paucity of published information on the maternal outcomes of Jehovah’s Witnesses (2008;63:71). The largest series included 332 women and their 391 infants (Singla AK, et al. Am J Obstet Gynecol 2001;185:893). The next largest series included 90 women and outcomes of their 116 deliveries (Massiah N, et al. Arch Gynecol 2007;276:339). Both were single-center studies from referral hospitals. In these two reports, rates of maternal mortality among Jehovah’s witnesses were increased 44 and 35-fold, respectively, above the general obstetric population. However, these rates were calculated on the basis of only 3 deaths, all of which were due to complications from hemorrhage.

The abstracted study of Wolfswinkel is important because it is, as far as I know, the first population-based evaluation of maternal mortality in Jehovah’s witnesses. And as would be expected, the maternal mortality rate in this report is lower than in the two reports from referral centers, 68 per 100,000 births, or a 6-fold increase over the general Dutch population. This rate was calculated based on 6 deaths, again all due to hemorrhage, among the 8850 deliveries to Jehovah’s witnesses. A limitation of this study is that the number of deliveries was only estimated, based on the known number of Dutch Jehovah’s witnesses and the assumption that their fertility rate is same as all women in the Netherlands. In fact, because the fertility rate of Jehovah’s witnesses may be higher, their mortality rate may have been overestimated. Ten Jehovah’ witnesses experienced serious maternal morbidity. This rate is elevated 3-fold above the general Dutch population. This excess of serious morbidity was due exclusively to complications of hemorrhage.

So, on a population level, the maternal outcomes of Jehovah’s witnesses seem to look better than heretofore reported. But they are still not nearly as good as the general population, and this report certainly is not grounds for complacency. In 3 of the maternal deaths, substandard care was implicated, in 2 because a hysterectomy was not performed and, in one, because cesarean delivery was performed on an unstable patient.

To achieve optimal maternal outcomes in Jehovah’s witnesses, anemia should be avoided in the antenatal period (ie, iron status should be normalized and erythropoietin used if necessary and acceptable, although the trace amounts of albumin in the latter render it unacceptable to some Jehovah’s witnesses). Likewise, hemorrhage should be avoided if possible, and managed appropriately if it occurs. Extra oxytocics should be administered in the third stage of labor and skilled obstetric surgeons and anesthesiologists should be at the ready. Blood salvage and autotransfusion are acceptable to some Jehovah’s witnesses, as are albumin, and clotting factors, including recombinant factor VIIa. Whether these in fact are acceptable to the patient should be known in advance. Finally, if hemorrhage is unrelenting, hysterectomy should be performed sooner rather than later.—DJR)
Resuscitation at Birth and Cognition at 8 Years of Age: A Cohort Study

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ABSTRACT

Severe hypoxic injury causing encephalopathy during the neonatal period is associated with impaired cognitive function in later life. It is unclear whether mild degrees of hypoxia that do not cause encephalopathy during the neonatal period can result in reduced intelligence quotient (IQ) scores in childhood. The aim of this cohort study was to determine whether infants who received resuscitation after birth, but had no symptoms of encephalopathy have reduced IQ scores in childhood. IQ scores in 3 groups of children at mean age of 8.6 years (SD 0.33) were measured. The groups included neonates asymptomatic for encephalopathy who needed resuscitation but had no further care (n = 815), neonates symptomatic for encephalopathy who were resuscitated and required neonatal care (n = 58), and healthy infants asymptomatic for encephalopathy who were not resuscitated, and had no further neonatal care (n = 10,609). An IQ score below 80 was defined as a low IQ. A shortened version of the Weschler intelligence scale for children (WISC-III) provided full-scale IQ data for 5887 children but only 4857 of these had complete data on resuscitation status, IQ data, and covariables. There was no data for 5529 children in the cohort. To reduce selection bias, the chained equations missing data method was used to impute missing confounder values in the 5529 nonresponders. Data were adjusted for clinical and socioeconomic potential confounders.

In the final logistic regression model, infants without symptoms of encephalopathy in the neonatal period who required resuscitation were at increased risk of a low full-scale IQ score (adjusted odds ratio, 1.65; 95% confidence interval [CI], 1.13–2.43, P < 0.010). The risk of a low IQ among resuscitated infants who developed encephalopathy was almost 4 times greater (adjusted odds ratio, 6.22; 95% CI, 1.57–24.65, P < 0.009). Because the total number of resuscitated infants asymptomatic for encephalopathy was 14 times greater than that of infants with encephalopathy, the proportion of infants with low IQ scores that might be attributable to the need for resuscitation at birth was higher for asymptomatic infants (3.4%, with a 95% CI of 0.5–6.3) compared with symptomatic infants (1.2%, with a 95% of 0.2–2.2).

These findings suggest that mild hypoxia or other perinatal events at birth may cause subtle brain damage that increases the risk for low IQ in childhood. Because of differences in population size, resuscitated infants without encephalopathy may account for a larger proportion of children and potentially adults with low IQ scores than that attributable to infants who develop encephalopathy.

EDITORIAL COMMENT

(I hope it is because of where I practice, and not how I practice, that I deliver a lot of term babies who require some degree of resuscitation. I have always taken solace in what I believed to be the fact that if such babies perk up and show no signs of encephalopathy, they therefore have sustained no long-term damage. In most cases, their umbilical artery cord pH is also comforting, at least from the standpoint of exculpating the intrapartum care, because it is normal in most infants who require resuscitation.

Now I have run across the abstracted study of Odd et al, and it is challenging to my san-guinity, for it suggests that perhaps we do need to worry about the intellectual future of term infants who require resuscitation but do not become encephalopathic. In this study, resuscitation was defined as the need for positive pressure respiratory support (by either face mask or endotracheal tube) or cardiac compressions. Encephalopathy was defined as seizures, jitteriness, high-pitched cry, hypotonia or hypertonia, or hyper-reflexia.

Not surprisingly, and consistent with other studies, was Odd et al’s finding that infants who require resuscitation and are encephalopathic...
are at markedly increased risk of subsequent low IQ score. Their surprising finding was the apparent higher risk for subsequent low IQ faced by resuscitated but nonencephalopathic infants.

How they arrived at this finding and what they actually found bears scrutiny. First, their results are based on the slightly more than half of infants in their larger cohort who were followed up, and on fewer than half (42%) who had complete data on resuscitation, IQ, and confounder variables. Infants resuscitated but not encephalopathic differed in important ways from control infants—their mothers were more frequently primiparous and febrile, and the infants themselves were more likely to be presenting by the breech.

What they found is not highly compelling. In the reference group, the mean verbal IQ was 107.6 versus 106.4 in the resuscitated but not encephalopathic group. Respective mean performance IQ scores were 100.0 and 99.7, and full-scale IQ scores were 104.6 and 103.8. None of these differences is meaningful or statistically different. Low (<80) full-scale IQ scores occurred in 7% and 10%, respectively, and this difference was statistically significant. But <80 is not a standard threshold for dichotomizing IQ and in the fully adjusted linear regression analysis, there was no significant difference in the full scale IQ of the 2 groups.

Thus, only in certain full scale IQ analyses, but not verbal or performance IQ analyses, were infants who were resuscitated but not encephalopathic at an IQ disadvantage. Moreover, this disadvantage was demonstrable only with a nonstandard IQ threshold and was the product of multiple statistical comparisons. Too often “need for resuscitation” is conflated with “birth asphyxia” and while Odd et al do not explicitly conflate the two, they do not go out of their way not to. They are clearly not the same thing, as most infants who require resuscitation are not acidemic. On the basis of this study, I am not ready to tell parents that face mask respiratory support of their neonates comes with an IQ penalty.—DJR)

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**Selective Use of Recombinant Human Erythropoietin in Pregnant Patients With Severe Anemia or Nonresponsive to Iron Sucrose Alone**

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**ABSTRACT**

Iron deficiency is a common problem for women in both third world countries and industrialized nations, but treatment during pregnancy with orally administered high-dose iron is limited by adverse effects and noncompliance. Previous studies have demonstrated that parenteral administration of iron sucrose alone or combined with recombinant human erythropoietin (rhEPO) is effective and safe in the treatment of anemia in pregnancy. Because of the high cost of this combined therapy, the investigators designed this study to distinguish patients who need this therapy from those who can be managed with intravenous iron sucrose alone.
This study utilized a stepwise protocol for administration of iron sucrose to pregnant women, either alone or in combination with rhEPO for rapid treatment of severe iron deficiency or for those who are nonresponsive to intravenous iron. The study subjects were 84 pregnant women who had gestational anemia, defined as a hemoglobin (Hb) level <10.0 g/dL and a ferritin level ≤15 mcg/L, despite routine oral iron therapy initiated in the second trimester. Patients were divided into 3 groups. At baseline, group A patients (n = 27) had a Hb level ≥9.0 g/dL and <10.0 g/dL and received intravenous doses of iron sucrose monotherapy 200 mg twice weekly. Group B patients (n = 32) were those who responded poorly to iron sucrose monotherapy and additionally received intravenous doses of rhEPO twice weekly. Group C patients (n = 25) had a baseline Hb level <9.0 g/dL and received combined iron sucrose and rhEPO twice weekly from the beginning of therapy. For all 3 groups, therapy was stopped after a Hb level of ≥11.0 g/dL was reached or after infusion of a maximum iron dose of 1600 mg.

The mean duration of therapy was 3.5 weeks. Of the 84 patients, 31 achieved a Hb level between 10.0 and 10.9 g/dL, and 53 patients reached a level of 11.0 g/dL or higher. There was no difference between the 3 groups in mean gestational age at delivery, infant birth weight, or other clinical parameters. No serious adverse events were noted in any of the groups.

The investigators conclude from these findings that combined use of iron sucrose and rhEPO may be indicated in patients with severe iron deficiency anemia or poor response to parenteral iron monotherapy.

EDITORIAL COMMENT

(As Krafft et al point out, according to the World Health Organization, 4 to 5 billion people or 66% to 80% of the world’s population may be iron deficient, and 2 billion or 30% are anemic; anemia contributes to 20% of all maternal deaths worldwide (The World Health Organization Health Report 2002: Reducing Risks, Promoting Healthy Life. Geneva, WHO; 2002). Although we might think of severe iron deficiency as a third world problem, 10% to 15% of the population of industrialized nations (as well as 75% of the population of underdeveloped countries) are anemic. Women are especially vulnerable due to menstrual blood loss, the blood loss of delivery, and short inter-pregnancy intervals. Foods with high iron content—such as meat, eggs, dried beans, fortified grains, and dark green leafy vegetables—are regularly available to only a fraction of the world’s population, and even then may not provide sufficient iron for pregnancy. A normal singleton gestation requires a total of 1000 mg of iron or absorption of 4 to 5 mg of elemental iron per day to support normal fetal and placental growth and expansion of the maternal blood volume. Since adequate iron absorption requires an acidic environment in the duodenum, antacid use during pregnancy as well as chronic use of H2 blockers and proton pump inhibitors significantly reduce iron absorption efficiency (Samuels P, et al. Obstetrics: Normal and Problem Pregnancies. Philadelphia: Churchill Livingstone Elsevier; 2002:1052).

For these reasons, many women begin pregnancy iron deficient, and are thus at increased risk of a variety of adverse outcomes including prematurity and fetal growth restriction. Iron supplementation—usually in the form of ferrous sulfate, ferrous gluconate, or ferrous fumarate—is often prescribed during pregnancy, but noncompliance related to the side effects of oral iron, including gastrointestinal distress and constipation, is common. Red blood cell (RBC) transfusion is not an ideal alternative because it may slow or stop the bone marrow’s production of new RBCs and entails a risk of transfusion reaction or infection. Parenteral iron dextran given intravenously causes anaphylaxis in 0.6% to 0.7%, hypersensitivity in 0.2% to 0.3%, and other adverse events in nearly 50% of all patients, and when given intramuscularly is associated with anaphylaxis or some form of systemic reaction in 4%, pain at the injection site in 37%, and fever and arthralgia in 7% to 8% (Silverstein SB, Rodgers GM. Am J Hematol 2004;76:74; Sharma JB, et al. Am J Clin Nutr 2004;79:116).

Iron sucrose is a relatively new formulation which when given IV is actually safer than oral ferrous gluconate, with a rate of anaphylaxis that is 20 times lower, and results in a better hematologic response than oral iron sulfate therapy (Silverstein SB, Rodgers GM. Am J Hematol 2004;76:74). Recombinant erythropoietin is another good but expensive option, and is usually associated only with mild flu-like symptoms that disappear with repeated dosing, and
rarely with other reported complications such as hypertensive encephalopathy seizures, hyperkalemia, or hypophosphatemia (Vora M, Guslin A. Obstet Gynecol Survey 1998;53:500). Krafft et al had previously shown that the combination of iron sucrose and recombinant human erythropoietin (rhEPO) promotes a rapid recovery from anemia (Breymann C, et al. Am J Obstet Gynecol 2001;184:662), but acknowledged that this treatment is expensive. They designed the current study to determine the efficacy of each treatment given in a stepwise manner to women with severe refractory anemia in pregnancy. Women with severe anemia (<9.0 g/dL) were started immediately on twice weekly iron sucrose and rhEPO, and rapidly achieved a mean hemoglobin (Hb) of 11.2 g/dL (range, 10.1–12.6). Women with moderately severe anemia (Hb ≥9.0 mg, <10.0 mg) received iron sucrose twice weekly, and half responded well; the half who did not have an adequate response (<0.7 g/dL increase in 14 days) received rhEPO as well as iron sucrose, and achieved a mean Hb level of 11.1 g/dL within 2.5 weeks (5 infusions). The average serum ferritin level increased from 6.4 μg/L before treatment to 184.9 μg/L, and transferrin saturation increased as well. There were no adverse events, and the only side effect reported was a metallic taste during iron sucrose infusion.

Those of us practicing in the United States may become complacent about anemia, since cases of severe refractory anemia are seen infrequently. However, knowing about this protocol may come in handy, especially for patients who are approaching delivery anemic but have a religious aversion to transfusion, have refractory anemia due to renal disease, or have an obstetric complication likely to lead to hemorrhage—such as placenta previa or percreta—and who wish to do autologous blood donation before delivery. Starting with iron sucrose therapy alone seems reasonable if there is time to monitor the rise in Hb levels and initiate rhEPO if necessary, while initiating both iron sucrose and rhEPO simultaneously could be life-saving when an immediate response to therapy is required.—KDW)
Progesterone for the Prevention of Preterm Birth in Twin Pregnancy (STOPPIT): A Randomized, Double-Blind, Placebo-Controlled Study and Meta-Analysis

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ABSTRACT

Women with twin pregnancy are at high risk of spontaneous preterm delivery. Three large randomized trials have shown that progesterone reduces the rate of preterm delivery in high-risk singleton pregnancies, although evidence of significant reduction in perinatal mortality or clear neonatal benefit in singleton women is lacking. The STOPPIT study was a randomized, double-blind, placebo-controlled trial designed to evaluate the potential benefit of progesterone for prevention of preterm birth in women with twin pregnancy. Between 2004 and 2008, 500 women with twin pregnancy were enrolled from 9 antenatal clinics at hospitals in the United Kingdom. At 24 weeks of gestation, the study subjects were randomized to either 90 mg of vaginal progesterone gel (n = 250) or placebo gel (n = 250) daily for 10 weeks. The primary study outcome was delivery or intrauterine death before 34 weeks of gestation. Analysis was performed according to intention to treat. The investigators also performed a meta-analysis of all published and unpublished studies in which women with twin pregnancy were randomly allocated to treatment with a progesterone (including progesterone). No significant difference was found between the 2 groups in the combined proportion of twin pregnancies that resulted in intrauterine death or delivery before 34 weeks (24.7% or 61/247 in the progesterone group vs. 19.4% or 48/247 in the placebo group; odds ratio, 1.36; 95% confidence interval, 0.89–2.09; P = 0.16). The meta-analysis, which included pooled data from 2 studies fulfilling inclusion criteria and data from the present study, confirmed that progesterone does not reduce the risk of early preterm birth or intrauterine death in twin pregnancies (pooled odds ratio, 1.16; 95% confidence interval, 0.89–1.51). No difference between the 2 groups was found in the rate of adverse events. These findings are consistent with previous studies showing that progestogens do not prevent preterm delivery in women with twin pregnancy.

EDITORIAL COMMENT

(There have been at least 9 randomized trials, including more than 5800 women, evaluating progesterone for the prevention of recurrent preterm birth in high-risk singleton pregnancies. One of the most ambitious and well-done studies was conducted by the NIH Maternal Fetal
Medicine Units Network, and included only women who had one or more previous spontaneous preterm birth, at a mean gestational age at delivery of 31 weeks. This trial showed that weekly injections of 17 alpha-hydroxyprogesterone caproate (17P) resulted in a 24% to 42% reduction in the incidence of preterm birth; 36.3% in the progesterone group versus 54.9% in the placebo group delivered before 37 weeks (relative risk [RR], 0.66; 95% confidence intervals [CIs], 0.54–0.8), 20.6% versus 30.7% (RR, 0.67; 95% CI, 0.48–0.93) delivered before 35 weeks, and 11.4% versus 19.6%, (RR, 0.58; 95% CI, 0.37–0.91) delivered before 32 weeks (Meis PJ, et al. NEJM 2003;348:2379). A subsequent meta-analysis of 11 trials including 2425 women with a history of previous preterm birth found that, after progesterone therapy, the RR of preterm birth before 34 weeks was 0.15 (95% CI, 0.04–0.64; Dodd JL, et al. Obstet Gynecol 2008;112:127). Another analysis of 9 similar randomized controlled trials showed that progesterone therapy was associated with a 30% (95% CI, 0.12–0.76; P < 0.01) reduction in the risk of delivery before 37 weeks (Centre for Reviews and Dissemination. Database of Abstracts of Reviews and Effects. 2009;2). Although trials investigating progesterone therapy for women who are at increased risk of preterm birth for reasons other than a previous preterm birth are planned or in progress, at present there are good data for only a few other indications. The meta-analysis by Dodd et al cited above showed that progesterone significantly reduces the risk of preterm birth before 34 weeks in women with short cervices identified by ultrasound (RR, 0.58; 95% CI, 0.38–0.87). However, thus far the data indicate that progesterone does not prevent preterm birth in women with threatened preterm labor.

Reasoning that multiple gestation significantly increases the risk of preterm birth, Norman et al randomized 500 women with twin gestations at 22 weeks to receive a daily intravaginal dose of either a gel containing 90 mg of progesterone or an identical appearing placebo. The women in the study and placebo groups were similar in terms of age, smoking status, gravidity, parity, incidence of medical disorders, and mono vs. dichorionicity. Unfortunately, the gestational age at delivery was also similar in the 2 groups (24.7% delivered before 34 weeks in the progesterone group versus 19.4% in the placebo group; P = 0.16). These results are consistent with those of a similar trial conducted by the NIH Maternal Fetal Medicine Units Network (Rouse DJ, et al. N Engl J Med 2007;357:454), in which 661 women with twin pregnancies at 16 to 20 weeks’ gestation were randomized to weekly injections of either 250 mg of 17P or a placebo. In this trial, 41.5% of women receiving 17P and 37.3% of those receiving placebo delivered before 35 weeks (RR, 1.1; 95% CI, 0.9–1.3). Norman et al actually did their own meta-analysis of published data from previous randomized trials of progesterone for twin gestation, and found that progesterone did not prevent intrauterine death or preterm delivery in such pregnancies (pooled odds ratio, 1.16; 95% CI, 0.89–1.51).

If we knew both what causes preterm birth and progesterone’s mechanism of action, we might be able to determine why progesterone appears to prevent preterm birth in some cases but not in others. What is known is that the onset of labor in many mammals is heralded by a decrease in plasma progesterone and an increase in plasma estrogen levels. Although this has not been demonstrated in humans, it is possible that progesterone levels decline at the tissue or cellular level, and that providing supplemental progesterone prevents or lessens that decline. Progesterone has also been shown to prevent changes in the myometrium that are necessary for labor onset; it appears to relax myometrial smooth muscle, and also blocks the action of oxytocin and/or inhibits gap junction formation (Garfield RE, Kannan MS, Daniel EE. Am J Physiol 1980;238:C81; Mitchell B, et al. J Clin Endocrinol Metab 1982;55:1237). Whether these mechanisms, and thus progesterone, can prevent all cases of preterm birth seems unlikely, since preterm birth has been associated with many different etiologic factors, including infection, inflammation, placental thrombosis or infarction, and others (Hauth JC, Andrews WW, Goldenberg RL. Prenat Neonat Med 1998;3:86). Because, regardless of what other factors may be present, twin gestations are
virtually always complicated by uterine size larger than dates if not overt uterine over-
distention, it seems likely that progesterone
has no effect on this pathophysiology.

Although it is tempting to offer progesterone
to every patient at risk of or fearful about pre-
term delivery, it has proven efficacy only in
women with a previous preterm birth or a
sonographically detected short cervix. Addi-
tional randomized trials involving women with
other specific risk factors for preterm birth are
needed before we offer progesterone therapy
to women who are at increased risk for any
other reason.—KDW)

Effect of Deviation of Nuchal Translucency Measurements on the Performance of Screening for Trisomy 21

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ABSTRACT

The single most effective marker for all major chromosomal defects including trisomy 21 (T-21) is the first trimester fetal nuchal translucency thickness (NT). Accurate measurement of the fetal NT to screen for chromosomal abnormalities requires appropriate training, adherence to a standard ultrasound technique, and regular audits of performance. The investigators theorized that an underestimate in NT measurement by individual sonographers would reduce the estimated risk of Down syndrome and thus the overall screen-positive rate; an overestimate would increase both individual risk and the screen-positive rate.

This study was designed to examine the effect of deviations in both the median NT and the spread of NT measurements on Down syndrome screening performance, using either the combination of maternal age and fetal NT, or the combination of maternal age, fetal NT, maternal serum pregnancy-associated plasma protein-A (PAPP-A), and free β-human chorionic gonadotropin (β-hCG). The effects of deviations in fetal NT medians were assessed by simulating NT measurements and PAPP-A and free β-hCG multiples of the median for 500,000 euploid and 500,000 T-21 pregnancies at 12 weeks’ gestation. Detection and false-positive rates were calculated without adjusting NT, and after overestimating and underestimating NT measurements by adding or subtracting values ranging from 0.1 to 1.0 mm to each observed measurement. The effects of variation in the scatter of NT measurements were examined by applying a multiplicative factor ranging from 0.5 to 2 to the SD of the simulated NT data.

When the false-positive rate was fixed at 3%, the Down syndrome detection rate was 72% when determined by maternal age and fetal NT, compared to 86% when determined by maternal age, fetal NT, and maternal serum biochemistry. When the false positive rate was held constant, consistent underestimates of fetal NT reduced the detection rate, while overestimates increased the false-positive rate. For example, when NT was underestimated by 0.6 mm and the false positive rate was fixed at 3%, the detection rate using maternal age and NT fell from 71% to 68% and from 86% to 83% for maternal age, NT, PAPP-A, and β-hCG. Widening the scatter of NT measurements had small impact on the detection rate, but resulted in a major increase in the false-positive rate. By illustration, if the NT scatter was increased by 50%, at a detection rate of 71% the false positive rate was 7.0% for maternal age and NT; at a detection rate of 85%, the false positive rate 4.3% for maternal age, NT, PAPP-A, and β-hCG.

These findings illustrate the screening impact of small deviations in NT measurement. The accuracy of the NT measurement techniques of individual sonographers can be assessed by determining the deviation of those measurements from the median and SD of NT measurements obtained by experts. Failure to correct such deviations can alter
the detection and false positive rates of the Down syndrome screening test. Continuous auditing and training in the correct method for measuring NT is necessary to ensure effective screening for major chromosomal abnormalities.

EDITORIAL COMMENT

(The utility of adding nuchal translucency (NT) measurement to the existing first trimester Down syndrome screening protocol, which previously was based solely on the maternal age-related risk and serum analyte levels, was demonstrated by several large multicenter randomized trials. The First and Second Trimester Evaluation of Risk (FASTER) trial, which included 38,033 study participants, showed that the combination of the first trimester serum analytes pregnancy-associated plasma protein-A (PAPP-A) and free β-hCG and NT measurement resulted in a high Down syndrome detection rate (83%) at a low (5%) screen positive rate (Malone FD, et al. N Engl J Med 2005;353:2001). The Serum, Urine, and Ultrasound Screening Study (SURUSS), which enrolled 47,053 patients receiving care in the United Kingdom, had similar results (83% detection at a 5% false positive rate; Wald NJ, et al. J Med Screen 2003;10:56). In acknowledgment of this and other accumulated data, the American College of Obstetricians and Gynecologists issued an updated practice bulletin on Down syndrome screening that included an endorsement of both NT and the need for specific training in and ongoing monitoring of NT measurement technique (ACOG Practice Bulletin Number 77; 2007).

Nuchal translucency measurement itself was not deemed difficult, but many practitioners balked at the stated need for specific training and credentialing in NT measurement, and protested any ongoing monitoring of individual sonographer’s or group practice’s NT medians. They argued that other ultrasound measurements are not monitored this way, and that demonstrated proficiency in obstetric sonography should be enough to qualify a practitioner to measure NT. Advocates of a standardized NT measurement technique countered that, because the NT itself is very small, on the order of 1 to 3 mm in most first trimester fetuses, even a tiny error in measurement could have a profound effect on the results; thus the NT measurement technique must be very precise and reproducible.

This study by Kagan et al proves the latter point. Using simulated data from 500,000 euploid and 500,000 Down syndrome fetuses, they were able to show that even small errors in NT measurement—on the order of 0.6 mm—can have significant negative effects on the Down syndrome detection rate. They also showed that the wider the scatter of NT measurements—that is, the range of values obtained at each gestational age—the higher the false positive rates. Thus, if an operator does not obtain accurate measurements consistently, the screening efficacy of the test is seriously reduced.

Requiring specific training in NT measurement and ongoing monitoring of measurement accuracy makes sense when you consider that in this screening test NT is used as a serum analyte; just as with PAPP-A and β-hCG, a likelihood ratio is determined from the NT measurement and is used to modify the maternal age-related Down syndrome risk. The laboratories that perform serum analyte measurements must demonstrate proficiency by correctly analyzing “unknown” samples, which is analogous to the NT certification requirement for turning in a sample of NT measurements for inspection. The laboratories must also monitor analyte medians over time and make corrections if median drift occurs, and a similar system is recommended for NT monitoring.

Over the past 30 years, obstetric ultrasound has become an integral part of prenatal care, and the components of each type of exam have been specified precisely. Many insurance companies now require that sites performing obstetric ultrasound be certified through the American Institute of Ultrasound in Medicine, a process that confirms, among other things, that the practice is meeting national standards for accuracy and completeness during each exam. It is therefore very logical to impose equally strict standards for the performance of NT measurement, and this study demonstrates clearly what could happen if such standards are not enforced.—KDW)
Maternal Age-Specific Risk of Nonchromosomal Anomalies

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ABSTRACT

With a continuing rise in the average maternal age in industrialized societies, accurate data are needed on maternal age-related obstetric risks. Although it is well known that the risk of fetal aneuploidy increases along with maternal age, it is unclear whether older mothers are at increased risk of having a fetus with nonchromosomal congenital anomalies (NCA). Much of the data on the risk data for NCA among older European mothers are either difficult to interpret or come from studies with small sample size, and little data are available on the overall risk of NCA in younger (teenage) mothers.

This population-based prevalence study compared the age-specific risk of NCA among mothers in 15 European countries. Data from 1.75 million infants born between 2000 and 2004 were obtained from the EUROCAT database, a network of population-based congenital anomaly registers in 15 European countries. The primary outcome measures were the prevalence of NCA at increasing maternal ages and the relative risk (RR) of any NCA and 84 standard NCA subgroups.

Included among the 38,958 cases of NCA were live births, fetal deaths ≥20 weeks’ gestation, and pregnancy terminations following prenatal diagnosis of malformation. The highest crude prevalence of all NCAs was among mothers <20 years old (26.5 per 1000 births). With increasing maternal age, the overall prevalence of NCA decreased: the crude prevalence per 1000 births for mothers 20 to 24, 25 to 29, 30 to 34, 35 to 39, and 40 to 44 years was 23.8, 22.5, 21.5, 21.4, and 22.6, respectively. Compared to mothers age 25 to 29, the RR of NCA adjusted for country was 1.11 (95% confidence interval [CI], 1.06–1.17) for mothers age <20 years, 0.99 (95% CI, 0.96–1.02) for mothers age 35 to 39, and 1.01 (95% CI, 0.95–1.07) for mothers age 40 to 44. There was significant variation in the pattern of maternal age-related risk between countries: the RR was higher for teenage mothers in France, Ireland, and Portugal, whereas the RR was higher for older mothers in Germany and Poland. The maternal age-specific RR was also different for specific NCAs among the 84 subgroups analyzed. Mothers <20 years old were at a significantly greater risk of nervous system abnormalities including anencephaly, tricuspid atresia, digestive system anomalies including gastroschisis, and maternal infection syndromes. Older mothers aged from 35 to 39 and 40 to 44 years were at a significantly greater risk of encephalocele, esophageal atresia, thanatophoric dwarfism, and fetal alcohol syndrome (all values P < 0.01).

These findings indicate that, while teenage mothers are at increased risk of having offspring with NCAs, older maternal age is a negligible risk factor for NCAs overall, although the risk of a few specific anomalies appears to increase with age.

EDITORIAL COMMENT

(Although information on the cause of birth defects is, in general, increasing, it is still very difficult to identify and evaluate individually all the factors that can affect fetal development. For example, investigators in both the United States and Europe have reported that gastroschisis is especially common among the offspring of teenage mothers (Opitz JM, Pysher TJ. Am J Med Genet Part C; 148C:192; Materna-Kiryukh A, et al. Pediatr Perinat Epidemiol 2009;23:29). Is this related specifically to maternal age? Or could it be the teenager’s typically poor diet; failure to take multivitamins before conception; low body mass index; abuse of cigarettes, alcohol, or recreational drugs; the medications commonly prescribed to teenagers; or some combination of these? Investigators have similarly reported that older mothers are at increased risk of having offspring with structural heart anomalies or nonchromosomal genetic syndromes (Reller MD, et al. J Pediatr 2008;153:650 Obstetrical and Gynecological Survey.
or to alcohol and cigarette abuse by older women, chronic illnesses such as hypertension or diabetes, the medication prescribed for those chronic illnesses, or some combination? And let’s not forget the fathers—are defects that seem to be more common in the offspring of older women really due to some factor or factors attributable to the older men with whom they are having children?

Although the database used for this investigation was not equipped to provide answers to all these questions, it did produce some interesting data. The good news is that, after excluding birth defects related to fetal aneuploidy, older maternal age alone did not appear to increase the risk of having a child with congenital anomalies. Although certain fetal anomalies were more common in the offspring of older women, some of these, such as defects associated with fetal alcohol syndrome, seemed to be related to environmental factors. Others, such as thanatophoric dwarfism, were likely due to older paternal age; data from a variety of sources now indicate that men over age 40 are at significantly increased risk of carrying sperm with spontaneous new genetic mutations—usually copy error mistakes such as point mutations that arise de novo and are then perpetuated through many rounds of spermatogenesis—that cause autosomal dominant genetic syndromes such as neurofibromatosis, Marfan syndrome, or achondroplasia in addition to thanatophoric dysplasia (ACOG Committee Opinion No. 189; 1997).

The data on teenage mothers were similar. In these databases, women younger than age 20 were at significantly increased risk of having a child with a birth defect; the offspring of these mothers had an anomaly rate 11% higher than the offspring of women aged 25 to 29. However, many of the specific defects whose incidence was increased—nervous system anomalies, anencephaly, tricuspid atresia or stenosis, gastrointestinal defects, gastrochisis, and syndromes related to maternal infection—are known to have environmental influences and are thus unlikely to be related solely to maternal age. Insufficient folic acid nutrure is associated with neural tube defects; microcephaly and of course congenital cytomegalovirus (CMV), and other infection syndromes are associated with antenatal infection. The increased rate of gastroschisis among teenage mothers has been reported by many other investigators in countries around the world (Rasmussen Sa, Frias JL. Am J Med Genet Part C; 48C:199). For example, in the United States, data from Tennessee, Georgia, North Carolina, California, New York, and Hawaii all indicate that the incidence of gastroschisis has increased more than 3 fold from 1989 to 2001, especially in fetuses of mothers younger than 18 (relative risk, 3.87; 95% confidence interval, 2.0–7.68; Collins, et al. J Pediatric Surg 2007;42:1221). However, gastroschisis illustrates perfectly how difficult it is to tease out the effects of maternal age alone on the development of a congenital anomaly. In addition to its association with low maternal age, gastroschisis is significantly associated with multiple factors likely to be present during a teenage pregnancy, such as the use of aspirin, ibuprofen, and acetaminophen or the decongestants pseudoephedrine and phenylpropanolamine; cigarette smoking, first trimester alcohol use; cocaine, marijuana, or methamphetamine abuse; a prepregnancy body mass index <18; low levels of the antioxidants α-carotene and total glutathione; high dietary fat intake, maternal infection, and several socioeconomic factors (Rasmussen SA, Frias JL. IBID).

Since pregnancy at either end of the reproductive years seems to entail an increased risk of fetal anomalies in addition to a host of other obstetric complications, obstetrician gynecologists should focus their efforts on preventing unplanned pregnancy and providing preconception counseling to everyone who wishes to optimize their reproductive outcomes. Once a teenager or a woman past her mid 30s does become pregnant, a second trimester targeted ultrasound exam to evaluate fetal anatomy would be prudent.—KDW
Identification of Second Trimester Screen Positive Pregnancies at Increased Risk for Congenital Heart Defects

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ABSTRACT

Previous studies have shown that prenatal detection of a congenital heart defect (CHD) is associated with decreased morbidity and mortality. The investigators hypothesized that identification of second trimester biomarkers for CHD in maternal serum would identify patients who would benefit from fetal echocardiography and improve detection and outcomes of CHD—especially in pregnancies without other identified risk factors. This study investigated whether second trimester biomarkers considered in combination with ultrasound data could be used to identify screen positive pregnancies at increased risk of a CHD. The effect of using different biomarker cut points on observed CHD–biomarker relationships and on performance of predictive models was also assessed. The study population included 19,402 singleton pregnancies without chromosomal defects, which were screen positive for Down syndrome, trisomy-18 (T-18), a neural tube defect or other birth defects based on measurement of maternal serum alpha-fetoprotein, human chorionic gonadotropin (hCG), and unconjugated estriol. The associations between biomarkers and CHD were compared in cases and a control population using logistic regression models. The nuchal fold (NF) was measured by ultrasound in the second trimester.

In models that considered screen positive grouping, CHD cases were more likely than controls to have a screen positive result for T-18 (19.4% vs. 3.9%; adjusted odds ratio [aOR] 6.0, 95% confidence interval [CI], 3.5–10.3), a NF measurements ≥5 mm (6.5% vs. 0.4%; aOR, 14.8; 95% CI, 5.4–40.1), or hCG adjusted multiples of the median (MoM) ≥95th percentile (10.8% vs. 3.3%; aOR, 3.6; 95% CI, 1.8–7.2). In models that did not consider screen positive grouping, cases were more likely than controls to have NF measurements ≥5 mm, alpha-fetoprotein adjusted MoM ≤10th percentile, hCG adjusted MoM ≤25th percentile, and/or hCG adjusted MoM ≥75th percentile.

These findings and a previous study by these investigators suggest that second trimester maternal serum biomarkers, together with NF measurement, may be useful indicators of an increased risk of CHD in screen positive pregnancies without identified fetal chromosome abnormalities and indicate the need for fetal echocardiogram.

EDITORIAL COMMENT

(The most popular second trimester screening test—the Quad Screen—determines the woman’s risk of having a fetus with Down syndrome, trisomies 13 and 18, a neural tube defect, and Smith Lemli Opitz syndrome. The most popular first trimester screening protocol determines the risk of all the above except neural tube defect and Smith Lemli Opitz, but includes a sonographic marker, nuchal translucency (NT); because increased first trimester NT measurements have been shown to correlate with fetal cardiac defects, the NT by itself indicates risk of fetal cardiac anomalies. Because these 2 tests are screening tests only, and provide only the risk of a fetal abnormality, all positive screening tests must be followed with a diagnostic test of some sort to confirm or rule out a fetal defect. In current practice, the levels of all analytes are included in the test’s algorithm and the results are expressed as the numerical risk of having each of the disorders listed above. The one exception is the use of the NT measurement alone to predict the risk of a congenital cardiac defect; many report forms do not spell out the risk associated with the NT size, so the physician must interpret the meaning of each NT measurement individually and decide what to do next. Although this is not particularly difficult—according to the literature, a simple size cutoff can be cho-
3.5 mm, above which all such patients are offered a fetal echocardiogram (ACOG Pract Bull 2007;77)—it does add another element of potential error.

In this study, Jelliffe-Pawlowski et al investigated the possibility of individually interpreting 2 second trimester analyte levels—AFP and hCG—as well as a second trimester measurement of the nuchal fold (NF), to determine the risk of a congenital cardiac anomaly. They evaluated data from 6104 singleton pregnancies with euploid fetuses whose cardiac status had been confirmed, of which 93 had one or more cardiac defects. The data indicated that when screen positivity was considered in the logistic regression model, an NF ≥5 mm, a screening test positive for trisomy 18, an AFP ≤5th percentile (≤0.40 multiples of the median, or MoM), an hCG ≤5th percentile (≤0.59 MoM), or an hCG ≥95th percentile (4.11 MoM) indicated significantly increased risk of a fetal cardiac defect. When screen positivity was not considered in the model, an AFP ≤10th percentile (approximately 0.49 MoM), an hCG ≤25th percentile (1.26 MoM), or an hCG ≥75th percentile (2.5 MoM) indicated increased risk.

Although interesting, can these data be incorporated into clinical practice? In other words, is it likely that the average clinician will be able to analyze the second trimester screening test results received for each patient to determine if the AFP or hCG levels are above or below the various cutoffs associated with increased risk of cardiac anomalies, and thus identify patients who should be referred for a fetal echocardiogram? Given the ever increasing demands on physicians’ time and the many stressors involved in clinical practice, the answer seems likely to be “no.” If patients whose analyte levels are above or below the cutoffs do not undergo a fetal echocardiogram, will many life threatening cardiac anomalies be missed? Fortunately, the answer to this question also appears to be “no.”

Although the test results listed above did indicate that certain analyte levels were associated with a statistically significant increased risk of cardiac anomalies, their individual detection rates were not great. For example, of all patients whose screening test was (falsely) positive for trisomy 18, only 1 in 61 had a fetus with a cardiac defect, and for hCG ≥95th percentile, only 1 in 199 had a defect. Even NF ≥5 mm, which was a better predictor than the serum analytes, identified only 1 in 23 cases. In contrast, all patients in this study had a second trimester ultrasound exam, and ultrasound detected 89 of the 100 congenital heart defects. Because the recommended management of a pregnancy complicated by a positive Down syndrome screening test includes performing a targeted second trimester ultrasound exam, according to these data, the vast majority of heart defects would have been identified regardless of whether the individual analyte levels were used to predict risk.

Whether or not an enlarged NF or the analyte levels described indicate anything about the etiology of the cardiac defects could be the subject of another study. At present these results indicate mainly that the patient with an enlarged NT or NF should have a targeted ultrasound exam, which is very likely to detect a fetal cardiac defect if one is present.—KDW)