impressive that these 2 large steroids trials have been conducted, there may be some benefit to examining the difference between the no more than 2 courses versus the weekly steroids approaches in a future trial. As antenatal corticosteroids are among the best therapy we have for preterm birth, they certainly deserve additional research studies to examine populations that might benefit, timing of dosage, and how best to optimize multiple doses.—ABC)

Prenatal Biochemical Screening and Long Term Risk of Maternal Cardiovascular Disease: Population Based Cohort Study

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ABSTRACT

Placental vascular disease is thought to arise within the temporary interface of the trophoblast and endometrial decidua, resulting in adverse outcomes for mother and fetus, including preeclampsia, placental abruption, poor fetal growth, and preterm birth. Some risk factors for placental vascular disease, including for preeclampsia, are the same as those for cardiovascular disease. A maternal placental syndrome in pregnancy seems to forecast a woman's cardiovascular health in the years that follow, including premature onset before age 65 years of coronary artery disease, heart failure, and dysrhythmias, as well as death after coronary revascularization. Although maternal serum screening has been used primarily to detect anomalies in the fetus, a particular pattern of prenatal biochemical screening results—a high serum α-fetoprotein, human chorionic gonadotropin, or dimeric inhibin A and low unconjugated estriol or pregnancy-associated plasma protein A—has been found to identify women at risk of preeclampsia in the index pregnancy. Given that certain prenatal biochemical screening hormones are associated with preeclampsia and that preeclampsia is associated with a higher future risk of cardiovascular disease in women, it is uncertain whether abnormal concentrations of prenatal hormones are associated with a higher risk of cardiovascular disease after pregnancy.

This is a population-based cohort study conducted in Ontario, Canada, where universal health care includes prenatal screening and obstetric care. All prenatal biochemical screening records were eligible and aggregated within the Ontario Maternal Multiple Marker Screening Database for 1993 to 2011. The researchers linked screened pregnancies in the Ontario Maternal Multiple Marker Screening Database to administrative health databases at the Institute for Clinical Evaluation Sciences, using each woman's unique encoded identifiers. Female patients aged 12 to 55 years who underwent prenatal biochemical screening at 11 to 20 weeks' gestation during 1993 to 2011 were included in the study, regardless of the outcome of pregnancy (ie, miscarriage or ectopic pregnancy at 11 to <20 weeks, induced abortion at 11 to <20 weeks, stillbirth ≥20 weeks, or live birth ≥20 weeks of gestation). Exclusions included women diagnosed as having any cardiac, cerebrovascular, or peripheral arterial disease 5 years or less before the prenatal biochemical screening in the index pregnancy, non-Ontario residents, and those without a valid OHIP health card number. Of all remaining deliveries, the researchers randomly selected 1 pregnancy per woman as the index pregnancy to simplify the data analyses. These pregnancies formed the screened cohort. Recognized pregnancies without prenatal biochemical screening were assembled in a nonscreened cohort and analyzed in a supplementary manner.

The exposure of interest was each prenatal biochemical screening analyte—α-fetoprotein, human chorionic gonadotropin, unconjugated estriol, dimeric inhibin-A, and pregnancy-associated plasma protein A. The unit of analysis for each analyte was its multiple of the median, a convention commonly used in clinical reporting that standardizes test results between different laboratories, describing how far an individual test result deviates from the median concentration at a given gestational age. The primary outcome was a cardiovascular disease composite of any hospital admission or revascularization for coronary artery disease, cerebrovascular disease, or peripheral arterial disease or any hospital admission for heart failure or dysrhythmia,
arising at least 365 days after the start of the index pregnancy (“time zero”). The secondary outcome was major adverse cardiovascular events, comprising all-cause mortality or any hospital admission for myocardial infarction or stroke, arising at least 365 days after the start of the index pregnancy, without censoring on death.

Among 855,536 pregnancies, and after a median of 11.4 years (interquartile range, 6.8–17.5 years) of follow-up, 6209 women developed the main cardiovascular disease outcome. Abnormal results for each of the 5 prenatal biochemical screening analytes, especially dimeric inhibin-A, were associated with a higher risk of cardiovascular disease. Women with an abnormally high dimeric inhibin-A (≥95th centile) had the highest rate of cardiovascular disease (30 events or 8.3 per 10,000 person-years versus 251 events or 3.8 per 10,000 person-years for those at less than 95th centile; multivariable adjusted hazard ratio, 2.0; 95% confidence interval, 1.4–3.0). Compared with women without any abnormal biochemical measure, the hazard ratio for the cardiovascular disease composite outcome was 1.2 to 1.3 times higher with 1 abnormal analyte and 1.5 to 2.0 times higher with 2 or more abnormal analytes.

The researchers concluded that women with abnormal prenatal biochemical screening results, especially for dimeric inhibin-A, may be at higher risk of cardiovascular disease. If these findings are replicated elsewhere, a massive amount of data exists that could aid in identifying women at higher risk of premature cardiovascular disease and that could be conveyed to them or their health care providers.

EDITORIAL COMMENT

(Increasingly, it is recognized that pregnancy provides an important window to future maternal health, particularly cardiovascular health. Women with preeclampsia or gestational diabetes have been found to be at higher risk of hypertension and diabetes later in life. It is not really surprising that the added metabolic stress of pregnancy would unmask these conditions, which would then subside until another pregnancy occurs or the woman ages a bit. The association of fetal growth restriction and preterm birth with cardiovascular diseases later in life is a bit more surprising and unanticipated, although it is now recognized that spontaneous preterm birth, fetal growth restriction, and preeclampsia exist on a spectrum of “great obstetrical syndromes” that are mediated by the placenta (Am J Obstet Gynecol 2011;204(3):193–201). So again, it is not all that surprising that these conditions too would be associated with cardiovascular disease later in life.

In pregnancy, prenatal screening for aneuploidy and other fetal congenital anomalies has been part of routine prenatal care for many years. Traditionally, this screening has involved measurement of various analytes in maternal serum; these analytes are largely produced by the placenta. One association that has been recognized through many years of performing such screening is that abnormal analyte levels, when substantially higher or lower than average, can reflect poor placental function and be associated with preeclampsia, fetal growth restriction, and spontaneous preterm birth (Obstet Gynecol 2010;115(5):1052–1061). In this abstracted study, the authors sought to determine whether abnormal serum analytes are also, by themselves, associated with a higher risk of later maternal adverse cardiovascular outcomes, including coronary artery disease, cerebrovascular disease, peripheral artery disease, or heart failure or arrhythmias. They found that in fact there was such an association, not really surprising given the shared association with preeclampsia and other “placental syndromes.” This risk was correlated with the analyte levels—those that were highest were associated with the largest increase in risk. A bit more surprising was that this association was persistent when controlling for variables such as maternal hypertension and placental syndromes such as preterm birth or preeclampsia. Furthermore, dimeric inhibin, the analyte that is typically least associated with preeclampsia and other perinatal disorders, had the strongest association. And finally, and most surprisingly, analyte abnormalities seen in association fetal aneuploidy or other congenital disorders were also associated with these same risks of later adverse cardiovascular outcomes.

The relationship between adverse perinatal outcomes and maternal health is clearly complex. In the last year or two, an article in JAMA (2015;314(15):1588–1598) reported that women carrying a fetus with congenital heart disease were at higher risk of preeclampsia. And in this current study, the authors found that other congenital anomalies are associated with cardiovascular disease later in life. Clearly, the physiologic relationship between the mother and the fetus has lifelong
implications that are not well understood. Abnormal serum analytes have been thought to reflect placental health, which might be poor due to underlying maternal metabolic abnormalities that have not yet been clinically recognized. However, it is possible that in fact the placental analytes themselves have impact on the mother’s health. Or, possibly some shared risk factors can affect the fetal development, causing birth defects, the mother’s ability to properly form gametes in meiosis, and the mother’s long-term metabolic health. In any case, it is a fascinating field that requires much further study to better understand.

While the increases in risk, as demonstrated by the adjusted hazard ratios, were not tremendously elevated, being approximately 2 with multiple abnormal analytes, this is nevertheless clinically important. For women who have had pregnancies, clearly eliciting that pregnancy history is important to the providers caring for her later in life. If the findings of this current study are confirmed, that would suggest that, in addition to counseling women with abnormal serum analytes about risks of aneuploidy, risks of preeclampsia, and risks of preterm birth, we must also add to the list of potential adverse outcomes—risk of early cardiovascular diseases. It appears at this time that regardless of the cause or perinatal associations of those abnormal analytes the mother’s long-term health is at higher risk and likely bears closer follow-up. Exactly what that should entail remains to be elucidated.—MEN)

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Vaginal Progesterone Is as Effective as Cervical Cerclage to Prevent Preterm Birth in Women With a Singleton Gestation, Previous Spontaneous Preterm Birth, and a Short Cervix: Updated Indirect Comparison Meta-analysis

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ABSTRACT

It is widely accepted that preterm birth is a syndrome caused by several pathological processes such as infection, vascular and decidual disorders, uterine overdistension, breakdown of maternal fetal tolerance, a decline in progesterone action, and