the pathophysiologic mechanisms early, before they are well established. Dr Roberto Romero, who has done much work in this area, refers to these conditions as the “Great Obstetrical Syndromes,” which share a common underlying placental basis and perhaps represent a continuum of placental maldevelopment and malfunction. It is disappointing that aspirin given before conception had no impact on obstetrical outcomes because it has been hypothesized that part of the reason that it has been difficult to demonstrate benefit is that aspirin needs to be started very early in pregnancy. Again, however, it is important to remember that the number of patients in this study was relatively small, and the number of adverse events in both the aspirin and placebo groups was also small (the number of patients with perinatal complications in the aspirin and placebo groups was 22 and 31, corresponding to 4% and 6%, respectively).

Despite the promising results of studies of low-dose aspirin for treatment of perinatal complications such as preeclampsia, widespread recommendations for this preventive measure have not been embraced. This is likely because of several reasons, one being the lack of (or minimal) demonstrated benefit in some large US studies, including one conducted by the Maternal Fetal Medicine Units Network (N Engl J Med. 1993;329:1213–1218). That large trial also found a higher risk for abruption; other studies have not confirmed this risk. This current abstracted article found no increase in adverse events, although the women taking low-dose aspirin had a 20% higher rate of vaginal bleeding. In general, randomized clinical trials have shown no adverse fetal sequelae if low-dose aspirin is given in doses of less than 150 mg/d (Br J Obstet Gynaecol. 1995;102[11]:861–868; BMJ. 2001;322[7282]:329–333), nor is low-dose aspirin thought to increase the risk for birth defects (Am J Obstet Gynecol. 2002;187[6]:1623–1630).

Because aspirin is very inexpensive, and quite safe, it continues to be studied (and used) for a variety of indications in reproductive medicine and obstetrics. Given its mechanism of action, as well as the pathophysiology of pregnancy loss and a variety of obstetrical adverse outcomes such as preeclampsia and preterm birth, it continues to be appealing as a safe and inexpensive preventive measure for these disorders. However, the data are still not convincing, and we should be cognizant of the lack of evidence of benefit and potential for harm, and, at this point, it seems logical to follow the authors’ recommendation that these data do not support the general use of low-dose aspirin to decrease pregnancy loss or increase live birth rates.—MEN

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Corticosteroid Use and Risk for Orofacial Clefts

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**ABSTRACT**

Orofacial clefts are one of the most common birth defects, with a worldwide prevalence of 1.7 per 1000 live births. Epidemiologic studies have reported inconsistent results regarding an association between corticosteroid use in early pregnancy and delivering an infant with an orofacial cleft. Although corticosteroids are used in women of reproductive
age for many common conditions, the safety of these medications during pregnancy is uncertain. The authors previously reported that maternal corticosteroid use was associated with an increased risk for cleft lip with or without palate (CLP) but not cleft palate only (CPO) in deliveries in 1997 to 2002. Since that report, the pertinent population has more than doubled, allowing the largest study of corticosteroids and clefts to date. The aim of the present study was to assess the association using larger and more recent data from the National Birth Defects Prevention Study (NBDPS).

Information on deliveries in 1997 to 2009 was collected from 10 centers. Infants or fetuses with CLP or CPO were considered cases and analyzed separately. Cases were considered isolated if there were no accompanying major unrelated birth defects or if nonisolated if more than 1 additional major unrelated defect was present. Live-born control infants without birth defects were randomly selected from birth records. Mothers were interviewed by telephone 6 weeks to 24 months after delivery. The mothers were asked whether they had specific medical conditions before or during pregnancy and what medications were used to treat them. The focus was on periconceptional corticosteroid use by any administration route and component that occurred between 4 weeks before and 12 weeks after conception. All data were reanalyzed adjusting for maternal demographics, race/ethnicity, education, intake of folic acid, smoking, and study center. Results were presented for deliveries from January 2003 through December 2009 and for pooled data for deliveries from October 1997 through December 2009.

From 2003 to 2009, the NBDPS enrolled mothers of 1577 children with CLP, 795 children with CPO, and 5922 control children. A total of 1402 (89%) of the CLP cases and 631 (79%) of the CPO cases were isolated. Any use of corticosteroids 4 weeks before 12 weeks after conception was reported by mothers of 35 infants (2.3%) with CLP (OR, 1.0; 95% CI, 0.7–1.4), mothers of 13 infants (1.7%) with CPO (OR, 0.7; 95% CI, 0.4–1.2), and mothers of 137 control infants (2.4%). No association was found with route of administration or components of corticosteroids. When earlier and recent data were combined, the cohort included mothers of 2731 infants with CLP, 1429 infants with CPO, and 10,063 controls, delivered in 1997 to 2009. Mothers of 69 infants (2.6%) with CLP (OR, 1.2; 95% CI, 0.9–1.6), 19 infants (1.3%) with CPO (OR, 0.6; 95% CI, 0.4–1.0), and 214 controls (2.1%) reported using any corticosteroids during the specified period. No association was found for route of administration or component of corticosteroid in the combined data, except for prednisone (OR, 1.9; 95% CI, 1.0–3.7). For CLP, ORs ranged from 2.8 (95% CI, 1.3–5.9) for exposures only during weeks 1 to 4 and 5 to 8 after conception to 0.5 (95% CI, 0.1–1.6) for exposures during weeks 9 to 12.

Recent data from the NBDPS did not support an association between maternal corticosteroid use during early pregnancy and delivering an infant with an orofacial cleft. These data may help patients and clinicians in making their risk-benefit decisions for using corticosteroids during the first trimester.

EDITORIAL COMMENT

(Orofacial clefts, such as cleft lip and cleft palate, are some of the most common birth defects. Although these are typically isolated, and usually can be successfully repaired, they nevertheless do require significant intervention in early infancy and childhood to allow feeding and subsequent surgical repair. Numerous studies in animals and some epidemiologic studies in humans have reported that maternal corticosteroid use in early pregnancy is associated with an increased risk for cleft lip and/or cleft palate (Pediatrics. 1951; 8:527–533; Teratology. 1997;56:335–340; Am J Med Genet. 2007;197:581–587). However, not all studies consistently demonstrate this association, and reported numbers are relatively small. Given the large number of autoimmune and other disorders that are treated with corticosteroids, including asthma, rheumatoid arthritis, psoriasis, and eczema, the potential association of cleft lip and/or cleft palate with corticosteroid exposure is important.

In this abstracted article, the authors used data from the National Birth Defects Prevention Study to investigate the association of corticosteroids with cleft lip and palate. This large case-control data set includes data on deliveries taking place during a 12-year period from 1997 to 2009 in 10 states. The authors previously used this same data set, with data through 2002, to study this same topic and did find an association with a reported odds ratio of 1.7. However, they now argue that ongoing data collection has more than doubled the sample size and that, given the continued uncertainty about this association, they reassessed using the larger and more recent data. The complete data set reported here included almost 2500 cleft cases and 5900 controls, and the authors found that there was no association...
The study demonstrates the challenges of determining teratogenicity of medications in pregnancy. Those agents that do cause birth defects often have a relatively small effect, so the resultant birth defects are still uncommon. In addition, most of the common birth defects, such as cardiac, neural tube defects, and clefts, are multifactorial in origin and occur because of an interaction of genetic and environmental factors. Women requiring such medications have underlying illnesses that may also contribute; they may also be treated with additional medications. It is likely that some women and their fetuses are more susceptible to various environmental factors than others. With developments in genomic medicine, it is likely that, at some time in the future, we will be able to assess predisposition to such teratogenic effects and better determine which reproductive-aged women should avoid certain medications. Until that time, however, it is important to recognize that treatment of serious illness and comorbidities in pregnancy is often more important than inconsistently reported teratogenicity.—MEN

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**Defining an Abnormal First Stage of Labor Based on Maternal and Neonatal Outcomes**

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**ABSTRACT**

Interest in defining normal labor has grown because of rising induction and cesarean delivery (CD) rates. The times to change of each centimeter of dilation are generally reported as the median and the 95th percentile, suggesting that the 95th percentile should be used as the threshold for abnormal labor. However, interventions for labors greater than the 95th percentile may lead to unnecessary CDs without improving maternal and neonatal outcomes. This 4-year retrospective cohort study was performed to evaluate the impact of exceeding percentile thresholds of the first stage of labor on maternal and neonatal outcomes.

The cohort included all consecutive parturients with a singleton fetus in vertex presentation at 37 weeks 0 days of gestation or later who reached 10-cm dilation and had term deliveries. Receiver operating characteristic (ROC) curves were created to determine a definition of the first stage of labor, considered as the time from admission to complete dilation and the time from 4 or 6 cm of dilation to complete dilation. The areas under the ROC curves were calculated for each definition. Maternal outcomes were CD in the second stage, operative vaginal delivery, postpartum...