Effect of maternal chronic disease on obstetric complications in twin pregnancies in a United States cohort

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Objective: To evaluate the effect of maternal chronic disease on obstetric complications among twin pregnancies.
Design: Multicenter, retrospective, observational study.
Setting: Clinical centers (19 hospitals).
Patient(s): Twin pregnancies (n = 4,821) delivered ≥23 weeks of gestation and classified by maternal chronic disease (either none or any of the following: asthma, depression, hypertension, diabetes, and heart, thyroid, gastrointestinal or renal disease).
Intervention(s): None.
Main Outcome Measure(s): Gestational age at delivery, gestational hypertension, pre-eclampsia, gestational diabetes, placental abruption, placenta previa, hemorrhage, chorioamnionitis, maternal postpartum fever, premature rupture of membranes, labor onset (spontaneous vs. nonspontaneous), route of delivery, and maternal admission to intensive care unit.
Result(s): Women with chronic disease delivered earlier (mean gestational length, 34.1 vs. 34.6 weeks) and were less likely to have term birth (risk ratio 0.80; 95% confidence interval 0.70–0.90). Cesarean delivery after spontaneous labor (risk ratio 1.20; 95% confidence interval 1.05–1.37) was also increased with chronic disease. No statistically significant effects were observed for other complications studied. Women who used assisted reproductive technology were more likely to hemorrhage, independent of chronic disease, but other findings were generally similar to the non–assisted reproductive technology sample.
Conclusion(s): Chronic disease was associated with additional risk of earlier delivery and cesarean section after spontaneous labor in a nationwide sample of US twin pregnancies. (Fertil Steril® 2013;100:142–9. ©2013 by American Society for Reproductive Medicine.)
Key Words: Twins, obstetric complications, assisted reproductive technology (ART)

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In recent years the prevalence of obesity, diabetes, and hypertension have increased significantly among fertile-aged US women (1, 2). These changes, along with a concurrent demographic shift to later childbearing, have resulted in a larger proportion of pregnancies complicated by chronic diseases. Recent US estimates of the prevalence of chronic disease in pregnancy report 8% of pregnancies with asthma, 5% with chronic hypertension, 2% with pregestational diabetes, and 1% with heart disease (1–6). Maternal chronic diseases are known to complicate singleton gestations, including increased risks for cesarean delivery, pre-eclampsia, preterm delivery, placental abruption, and impaired fetal growth, with associated maternal and perinatal morbidity (1, 2, 7).

Another consequence of delayed childbearing has been an increase in multiple gestations, especially twins (8, 9). The US twin birth rate rose from 18.9 to 33.3 per 1,000 births between 1980 and 2009, with approximately one third of this trend directly attributed to older maternal age (9, 10). The use of fertility treatments and assisted reproductive technology (ART) has also contributed to the rise in twinning. From 1997 to 2000, the proportion of twins attributable to ART increased from 9.1% to 11.8%, whereas the proportion conceived using non-ART fertility treatments

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increased from 17.7% to 20.9% (11). Twin pregnancies are in general at increased risk for adverse pregnancy outcomes, including preterm birth, low-birth-weight infants, pre-eclampsia, and cesarean delivery (10).

According to our review of the literature, using search terms "twin pregnancy," "maternal chronic disease," and "obstetric complications," the extent to which maternal chronic disease further increases the risk of obstetric complications in twins is unknown. Given the increasing prevalence of this combination of risk factors, we investigated the effects of chronic disease during pregnancy on maternal obstetric outcomes among twin pregnancies in a large, nationwide US cohort.

MATERIALS AND METHODS

The Consortium on Safe Labor (CSL) was a multicenter retrospective observational study conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, which collected information on contemporary labor and delivery practice in the United States. The CSL included 12 clinical centers (19 hospitals) across nine American College of Obstetricians and Gynecologists US districts from 2002 to 2008, with 87% of births occurring between 2005 and 2007. A thorough description of the study is provided elsewhere (12). Detailed information was extracted from electronic medical records, including maternal demographic characteristics, medical, reproductive, and prenatal history, labor and delivery summary, and postpartum information. A validation study on several key variables indicated that the electronic medical records were an accurate representation of the medical charts (12). This project was approved by the institutional review boards of all participating institutions.

Of the 228,562 total CSL deliveries, 5,050 were multiple gestation pregnancies, including 4,846 twins, 204 higher-order multiples, and 25 repeat multifetal pregnancies for the same woman. Our analysis was restricted to the first twin pregnancy of women during the study to reduce unmeasured confounding and avoid statistical dependence within participants, resulting in an analytic sample of 4,821 twin pregnancies. Information for chronic diseases and pregnancy outcomes was obtained from electronic medical records and supplemented with International Classification of Diseases, 9th revision (ICD-9) codes in the discharge summary. Women were defined as having chronic disease if they had any of the following: asthma, depression, hypertension, diabetes, thyroid disorder, heart disease, gastrointestinal disorder, and renal disease (see Supplemental Table 1 [available online] for definitions and ICD-9 codes for each chronic disease). Preliminary analyses were conducted for each individual chronic disease and then compared with the results for the aggregated group comprising any chronic disease. Because of sample size limitations and general similarity between findings for the individual diseases and the overall chronic disease group, we chose to only present findings for the overall chronic disease group. Outcomes included gestational age at delivery, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, eclampsia), gestational diabetes, placental abruption, placenta previa, hemorrhage (bleeding in the third trimester or postpartum or receiving blood transfusion postpartum), chorioamnionitis, maternal postpartum fever, premature rupture of membranes (PROM), preterm PROM (before 37 weeks), type of labor onset (prelabor cesarean section, induction, spontaneous labor), route of delivery (cesarean section, vaginal, or combination [e.g., vaginal delivery of first twin and cesarean delivery of second twin]), and maternal admission to an intensive care unit (ICU). Mothers with chronic hypertension were excluded from the analyses for gestational hypertension/pre-eclampsia, and mothers with diabetes were excluded from the analysis for gestational diabetes because the presence of the chronic condition precludes diagnosis of the gestational disorders.

We conducted bivariate analyses using the χ^2 test for categoric variables and *t* tests for continuous variables. Multivariable regression estimated crude (adjusted for site) and fully adjusted risk ratios from models that include site, maternal age (continuous), race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, and multiracial/other), prepregnancy body mass index (BMI), insurance type (private or public), and smoking during pregnancy (yes or no/unknown). Effect measures for labor admission status and route of delivery outcomes were also adjusted for prior uterine scar (yes or no). We present fully adjusted risk ratios only. Gestational age at delivery was analyzed as a binary outcome (preterm, defined as birth before 37 weeks, or term) using logistic regression, and as a continuous outcome using Kaplan-Meier survival analysis and the log–rank test.

We performed separate sensitivity analyses to determine whether the effects of maternal chronic disease varied according to gestational age at delivery, sex of the twins, and use of ART. We also restricted the sample to women with normal prepregnancy BMI to assess whether chronic disease would have a similar impact on obstetric complications in the absence of obesity. Because of the increased risk of preterm birth among twins and high prevalence of preterm birth (68%) in our study sample, we used stratified analyses to estimate distinct effect measures for preterm (n = 3,255) and term (n = 1,566) births (13, 14). Because information on twin chorionicity was not available, we used Weinberg's differential rule to estimate expected frequencies of monozygous, monochorionic, and dizygous twins (15, 16). We used discordant sex pairs (n = 1,842) as a proxy for dizygous twin pairs and conducted an additional analysis among these pregnancies only. Of the 12 CSL sites, 7 reported information on use of ART. We performed a separate analysis on these sites only (n = 2,532 pregnancies), stratified by ART use. Low prevalence for maternal admission to the intensive care unit and combined delivery (vaginal/cesarean) prevented model convergence for these outcomes in some analyses. We report frequencies, but no effect measures, for these associations. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Maternal chronic disease complicated 25% of twin pregnancies (n = 1,186). The majority of women (84%; n = 1,000)