OBSTETRICS

Changes in diabetes status between pregnancies and impact on subsequent newborn outcomes

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OBJECTIVE: Pregnancies complicated by gestational diabetes mellitus (GDM) or preexisting diabetes mellitus (DM) are at high risk for adverse newborn outcomes. Whether GDM history, recurrence, or transition to DM modifies such risks is unknown.

STUDY DESIGN: Medical record data on 62,013 repeat singleton pregnancies were collected retrospectively from women who delivered at least twice in Utah (2002 through 2010). Poisson regression models with robust variance estimators were used to estimate relative risks (RR) and 95% confidence intervals (CI) associated with GDM/DM status at the previous and/or current pregnancy relative to those without GDM/DM at either. Large for gestational age (LGA), shoulder dystocia, preterm birth (<37 weeks), respiratory distress syndrome, and other neonatal morbidities were examined adjusting for study site, maternal age, race, parity, interpregnancy interval, prepregnancy body mass index, and smoking status.

RESULTS: GDM in the previous pregnancy alone increased the risk of LGA in the current pregnancy (RR, 1.20; 95% CI, 1.05—1.38). Recurrent GDM increased the risks of LGA (RR, 1.76; 95% CI, 1.56—1.98), shoulder dystocia (RR, 1.98; 95% CI, 1.46—2.70), and preterm birth (RR, 1.68; 95% CI, 1.44—1.96) beyond that observed for pregnancies with current GDM alone. Women with GDM in a previous pregnancy that transitioned to DM in the current pregnancy and women with DM prior to the previous pregnancy had increased risks of all above outcomes.

CONCLUSION: GDM in a previous pregnancy alone without recurrence may still confer an increased LGA risk. Pregnancies complicated by GDM that transition to DM and those with DM prior to the previous pregnancy have the highest risks of adverse newborn outcomes.

Key words: diabetes, large for gestational age, macrosomia, respiratory distress, shoulder dystocia

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Gestational diabetes mellitus (GDM) complicates approximately 7% of pregnancies in the United States.[1] In normal pregnancy, insulin resistance arises during midpregnancy and progresses through the third trimester with a compensatory increase in insulin secretion by pancreatic β-cells.[2,3] GDM develops among women with insufficient pancreatic β-cell function to meet this increased insulin demand during pregnancy.[4,5] With the underlying pancreatic β-cell defect, women with GDM have a >13-fold increased recurrence risk in subsequent pregnancies[6] and a >7-fold increased future type 2 diabetes risk.[7] While GDM represents the main form of diabetes complicating pregnancies, preexisting diabetes mellitus (DM) complicates around 1.3% of pregnancies in the United States.[8]

Pregnancies complicated by gestational or preexisting diabetes are associated with several adverse newborn outcomes including perinatal mortality, congenital anomalies, preterm birth (PTB), and macrosomia.[9-12] Less established however, is how the change in diabetic status between pregnancies impacts newborn outcomes. It is possible that even without recurrence, GDM in the previous pregnancy alone may increase risk of adverse neonatal outcomes due to the underlying β-cell dysfunction that results in fetal exposure to low levels of hyperglycemia.

We used data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Consecutive Pregnancy Study, which captured data from women with at least 2 pregnancies to assess the risks of adverse newborn outcomes associated

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with changes in GDM status between pregnancies; ie, GDM history, recurrence, and transition to overt DM.

Materials and Methods

Study population

The NICHD Consecutive Pregnancy Study collected data retrospectively from electronic medical records of 20 hospitals in Utah (Appendix). Women with at least 2 pregnancies delivered between 2002 through 2010 were included resulting in 114,679 pregnancies (live births or stillbirths at ≥20 weeks' gestation) from 51,086 women. Extensive data on maternal demographics, reproductive and medical history, prenatal complications, labor and delivery information, and neonatal outcomes were extracted. Data on infants admitted to the neonatal intensive care unit were collected from birth to hospital discharge or death. *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes were collected from maternal and newborn discharge summaries and linked to each delivery. All participating sites obtained approval for the study and waiver of informed consent from their individual institutional review boards.

The study was limited to women delivering singleton births in their first 2 pregnancies at study entry (parity range, 0−14). If women had >2 pregnancies during the study period, their subsequent pregnancies were only included if they were also singletons. A total of 49,868 women (78.3% with 2 pregnancies, 19.1% with 3 pregnancies, and 2.6% with 4-6 pregnancies) were included. Seven categories according to diabetes status in the previous or current pregnancy were created resulting in the following pregnancy pairs: (1) women without diabetes in the previous and the current pregnancy; (2) women with GDM in the previous pregnancy only (and not in the current pregnancy); (3) women with GDM in the current pregnancy only (and not in the previous pregnancy); (4) women with recurrent GDM (in the previous and the current pregnancy); (5) women who had no GDM in the previous pregnancy but developed DM between their previous and current pregnancy (DM in current pregnancy only); (6) women with GDM in the previous pregnancy who transitioned to DM between their previous and current pregnancy; and (7) women with pregestational DM (type 1 or 2) prior to the first observed pregnancy in the dataset. Women with >2 pregnancies could have been included in >1 of the examined groups. For example, a woman with 3 pregnancies, of which GDM was diagnosed only in her first pregnancy and not in her subsequent pregnancies, was included in the previous GDM-only group for her first and second pregnancies (category 2) and again in the no diabetes group for her second and third pregnancies (category 1). Since women could have entered the study at any parity, we performed sensitivity analyses using only the first 2 singleton births among women who were nulliparous at study entry (n = 27,064).

Gestational diabetes or DM

Maternal diabetic status was ascertained from electronic medical records supplemented with *ICD-9* codes. If the diagnosis was coded in either source, then women were considered to have the condition during that pregnancy. In the medical records, diabetic status was recorded as gestational or pregestational (the Supplementary Table lists the *ICD-9* codes used to identify diabetes and other maternal complications). Women whose records indicated pregestational diabetes in 1 pregnancy were categorized as such for all subsequent pregnancies.

Neonatal outcomes

PTB was defined as <37 weeks' gestation based on obstetrical estimate in the medical record. We further classified PTB into spontaneous, indicated, and elective using a previously published algorithm by our group.[13,14] Spontaneous PTB was the result of preterm labor or preterm premature rupture of membranes. Indicated PTB was defined among women without preterm premature rupture of membranes or spontaneous labor but with potential maternal, fetal, and/or obstetrical pregnancy complications. The elective group included women with labor inductions or cesarean deliveries recorded as elective by the study site without any obstetrical, fetal, and/or maternal indications. Large for gestational age (LGA) and small for gestational age were defined based on sex-specific birthweight >90th percentile and <10th percentile for gestational age (by week), respectively.[15] Macrosomia was defined as birthweight >4000 g. Respiratory distress syndrome (RDS) was based on medical records and discharge summaries. Hypoglycemia, congenital anomalies, and jaundice were based on the *ICD-9* codes. Shoulder dystocia, documented in both the electronic medical records and discharge summaries, was defined among women with vaginal deliveries only. Stillbirth and neonatal mortality were recorded in the electronic medical records. For a complete list of the examined newborn outcomes and the *ICD-9* codes, refer to the Supplementary Table.

Data exclusions

From the 49,868 women with at least 2 repeat singleton pregnancies, 24 women were excluded from analyses; 23 had *ICD-9* code for "infant of a diabetic mother" with no diabetes recorded for the mother and 1 had diabetes controlled by insulin with no diabetes diagnosis. This resulted in a final sample size of 49,844 women with 111,857 singleton deliveries and 62,013 repeat singleton deliveries (2 deliveries equivalent to 1 repeat, 3 deliveries equivalent to 2 repeats) for the main analyses. Sensitivity analysis restricted to women nulliparous at study entry resulted in a sample size of 27,064 repeats. (the Supplementary Figure displays the distribution of the women in regard to their parity and the change in diabetic status between pregnancies).

Statistical analysis

To examine the relative risk (RR) of adverse newborn outcomes across different groups, we used Poisson regression models with robust variance estimators.[16] This approach provides valid inference for consecutive pregnancies and allows comparison of disease risk across groups. This technique was used in both unadjusted and