Published in final edited form as:
Am J Obstet Gynecol. 2014 May ; 210(5): 431.e1–431.e14. doi:10.1016/j.ajog.2013.12.026.

Changes in Diabetes Status Between Pregnancies and Impact on Subsequent Newborn Outcomes

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Abstract

Objective—Pregnancies complicated by gestational (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 (2002-2010). 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 (<37wks; PTB), respiratory distress syndrome (RDS), and other neonatal morbidities were examined adjusting for study site, maternal age, race, parity, interpregnancy interval, prepregnancy body mass index (BMI), 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 PTB (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.

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Reprints will not be available.

The authors report no conflict of interest.

Paper presentation information: The findings of this study have been presented in abstract forms at the 2013 Pediatrics Academic Societies annual meeting, Washington, DC, May 4-6, 2013 (oral presentation), at the Society for Pediatric and Perinatal Epidemiologic Research (SPER), Boston, MA, June 17-18, 2013 (poster), and at the Society for Epidemiologic Research (SER), Boston, MA, June 18-20, 2013 (poster).

Financial disclosure: Supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (Contracts numbers: HHSN275200800002I, HHSN27500004)

Conclusions—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.

Keywords

diabetes; large for gestational age; macrosomia; shoulder dystocia; respiratory distress

Introduction

Gestational diabetes mellitus (GDM) complicates approximately 7% of pregnancies in the U.S.[1] In normal pregnancy, insulin resistance arises during mid-pregnancy 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 over a 13-fold increased recurrence risk in subsequent pregnancies[6] and over a 7-fold increased future type II 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 U.S.[8]

Pregnancies complicated by gestational or preexisting diabetes are associated with several adverse newborn outcomes including perinatal mortality, congenital anomalies, preterm birth, 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 National Institute of Child Health and Human Development (NICHD) Consecutive Pregnancy Study which captured data from women with at least two pregnancies to assess the risks of adverse newborn outcomes associated with changes in GDM status between pregnancies; i.e. GDM history, recurrence, and transition to overt diabetes mellitus.

Materials and Methods

Study Population

The NICHD Consecutive Pregnancy Study collected data retrospectively from electronic medical records of 20 hospitals in Utah (Appendix 1). Women with at least 2 pregnancies delivered between 2002-2010 were included resulting in 114,679 pregnancies (livebirths or stillbirths at ≥20 weeks' gestation) from 51,086 women. Extensive data on maternal demographic, 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 (NICU) were collected from birth to hospital discharge or death. International Classification of Diseases, 9th 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 more than 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 transition to DM between their previous and current pregnancy; and 7) women with pregestational DM (type I or II) prior to the first observed pregnancy in the dataset. Women with more than 2 pregnancies could have been included in more than one 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, will be 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 Diabetes Mellitus

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 (Supplemental Table S1 lists the ICD-9 codes used to identify diabetes and other maternal complications). Women whose records indicated pregestational diabetes in one pregnancy were categorized as such for all subsequent pregnancies.

Neonatal Outcomes

Preterm (PTB) was defined as birth <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 (PPROM). Indicated PTB was defined among women without PPROM 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 birth weight >90th percentile and <10th percentile for gestational age (by week), respectively.[15] Macrosomia was defined as

birthweight >4000 grams. 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 supplementary table 1.

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. (Supplementary table 2 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 adjusted analyses. In unadjusted models, we first assessed whether GDM in the previous pregnancy influenced neonatal outcomes in the current pregnancy by testing the significance of two interaction terms. The first interaction term (i.e., GDM in previous pregnancy × GDM in current pregnancy) tested whether recurrent GDM conveyed greater risks of neonatal outcomes than expected based on the independent (additive) risks of having a previous GDM and a current GDM pregnancy. Similarly, the second interaction term (i.e., GDM in previous pregnancy × DM in current pregnancy) tested whether transitioning from GDM to DM between pregnancies led to greater risks of neonatal outcomes than expected based on the independent risks of having a previous GDM and a current DM pregnancy. We decided *apriori* to keep both interaction terms in the model if at least one had a p-value<0.05 based on the score test, and for these models we reported the risk estimates from the model with both interaction terms included. To be parsimonious, for models with non-significant interaction terms, we calculated risk estimates obtained from the additive effects model. Of all examined neonatal morbidities, only macrosomia had a significant interaction term (GDM in previous pregnancy × DM in current pregnancy p-value=0.013) and as such, the reported risk estimates for macrosomia were based on the model with interaction terms. In subsequent models, we adjusted for study site, maternal age, race, parity, interpregnancy interval, current prepregnancy BMI, and maternal smoking (noted in table footnotes). For some of the outcomes, certain study sites were excluded due to sample size limitations (noted in the table footnotes). No further risk estimates were reported for neonatal outcomes displayed in the descriptive table when there were no significant differences in the percentages between the

GDM/DM groups based on the global score test. Sensitivity analyses among women nulliparous at study entry were conducted in similar fashion. Indicated PTB was not examined in sensitivity analysis due to limited sample size. For all comparisons, the same referent group of women with no GDM/DM in the previous and current pregnancy was used. Statistical analyses were conducted using SAS (version 9.3; SAS Institute, Cary, NC).

Results

Of the 111,857 singleton deliveries to 49,844 women in the study, 1,847 (1.7%) deliveries were complicated by pregestational diabetes while 3,504 (3.1%) were complicated by GDM. Table 1 presents the characteristics and frequency of outcomes according to the different diabetic status categories in the previous and current pregnancy. Women with any diabetic status in the previous and current pregnancy tended to be significantly older, were less likely to be white, and had higher parity than women with no diabetes in the previous and current pregnancy. While prepregnancy BMI was at least 2 kg/m^2 higher among women with any diabetic status in the previous and current pregnancy in comparison to women with no diabetes in either pregnancy, gestational weight gain was lower. Women with GDM in the current pregnancy alone and women with DM in the current pregnancy alone, were more likely to experience major postpartum weight retention (PPWR) (difference in pre-pregnancy weight between the previous and the current pregnancy ≥4.55 kg).[17] No significant differences in major PPWR were observed comparing women with GDM in the previous pregnancy only against women with recurrent GDM (p-value>0.10) and against women who transitioned from GDM to DM (p-value>0.10).

Below we summarize findings on neonatal outcomes according to different diabetes status categories. Table 2 risk estimates are based on the whole dataset while table 3 risk estimates are restricted to women nulliparous at study entry.

GDM in previous pregnancy

GDM in a previous pregnancy, but not in the current was associated with an increased risk of LGA (RR=1.20; 95% CI: 1.05-1.38), PTB, and spontaneous PTB. The observed RR for shoulder dystocia was not reliable due to the small sample size (n=3) (Table 2). After restricting to nulliparous women, the risk estimate of LGA was similar in magnitude albeit non-significant and the risk of PTB and spontaneous PTB was no longer increased (Table 3).

GDM in current pregnancy only

Women with GDM in the current pregnancy alone had increased risk for all examined neonatal morbidities except for spontaneous PTB and shoulder dystocia. The majority of the risk estimates were increased by at least 30%. Risk estimates were similar when we examined the nulliparous cohort except for an increase in risk of spontaneous PTB (RR=1.47; 95% CI: 1.07-2.01).

Recurrent GDM

Infants of women with recurrent GDM had increased risk for almost all of the examined neonatal morbidities except for RDS and congenital anomalies. Specifically, LGA risk

increased by over 70% (RR=1.76; 95% CI: 1.56-1.98) while the risk of shoulder dystocia almost doubled (RR=1.98; 95% CI: 1.46-2.70). Similar risks were observed in analyses restricted to nulliparous women.

Transitioning from no diabetes to DM

Having DM in the current pregnancy increased the risk of all the examined morbidities except for macrosomia, jaundice, and spontaneous PTB. The risks of RDS and shoulder dystocia were increased by more than 70%. Risk estimates although less likely to be significant, were similarly increased when the dataset was restricted to nulliparous women.

Transitioning from GDM to DM

Infants of women who transitioned from GDM to DM had over 2-fold increased LGA risk (RR=2.21; 95% CI: 1.86-2.63), almost 3-fold increased shoulder dystocia risk (RR=2.92; 95% CI: 1.85-4.59), and 60% increased RDS risk (RR=1.61; 95% CI: 1.07-2.42). All the other neonatal morbidities except for congenital anomalies were also increased. Risk estimates were similarly increased for nulliparous women although they were attenuated for macrosomia and RDS while no increased risk was observed for jaundice.

Pregestational diabetes prior to previous pregnancy

Women with pregestational diabetes in both pregnancies had a 1.5-3.5 fold increased risk for all outcomes. The risk estimates were very similar for the nulliparous women.

Comment

In this large longitudinal dataset of women with at least two consecutive pregnancies, we evaluated the independent and joint effect of diabetes in the previous and current pregnancy on neonatal outcomes. We present the novel finding that prior diabetes history does not influence the majority of neonatal outcomes in the current pregnancy except for LGA risk. Compared to women with no GDM/DM in the previous and current pregnancy, women with GDM in the previous pregnancy alone still had an increased risk of LGA in a subsequent pregnancy with no diabetes diagnosis. While the risk of PTB and particularly spontaneous PTB appeared to be elevated, this association disappeared when the data were restricted to women nulliparous at study entry. GDM in the current pregnancy and recurrent GDM were both associated with increased risks for the majority of neonatal outcomes while progression from GDM to DM between pregnancies and pregestational diabetes prior to the previous pregnancy further magnified the risk of adverse neonatal outcomes.

GDM represents detection of an underlying β-cell dysfunction unmasked in face of the increased insulin resistance that naturally occurs during pregnancy.[2] This dysfunction is not only limited to pregnancy but is also evident prior to conception and postpartum.[2;18] As such, recurrence risk and risk of transitioning to overt diabetes mellitus are quite high after a GDM pregnancy.[6;7] In our study, women who had GDM in a previous pregnancy alone might have made appropriate lifestyle modifications such as weight loss or weight maintenance through increased physical activity and healthier diet, preventing the occurrence of type 2 diabetes and the recurrence of GDM.[19;20] Nonetheless, when we

examined major PPWR prior to the current pregnancy, we found no significant differences when comparing women with previous GDM alone to those with recurrent GDM or to those who transitioned from GDM to DM. Given their underlying β-cell dysfunction however, they probably still had mild degrees of carbohydrate intolerance that did not meet the criteria for GDM classification in the current pregnancy. Although the levels of the 1-hr glucose challenge test for this group appear to be more elevated than the levels among women with no diabetes in the previous and the current pregnancy, we cannot make definite conclusions as the levels were not reported for the majority of the women in our study. However, our findings of increased LGA risk (RR=1.20; 95% CI: 1.05-1.38) among infants born to this group of women are relevant to previous studies that examined varying degrees of maternal glucose intolerance less severe than overt diabetes in association with the risk of adverse pregnancy outcomes.[21-23] For instance, findings from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study showed an increase in the odds of LGA (OR=1.38; 95% CI: 1.32-1.44) per 1 SD increase in fasting glucose level assessed between 24 and 32 weeks of gestation among women without GDM diagnosis.[22]

Similar to previous studies,[24-26] we found that the risk of PTB was increased among women with GDM or DM in the current pregnancy. Exploring this association further, shows an increase in the risk of both indicated and spontaneous PTB. While the increased risk of indicated PTB is expected given the higher rate of pregnancy complications associated with diabetes,[24;26;27] the increased risk of spontaneous PTB is intriguing but agrees with previous studies among women with GDM or DM.[9;24;26;27] The mechanisms are not completely understood but it has been suggested that hyperglycemia causes endothelial dysfunction and increased oxidative stress resulting in reduced nitric oxide-dependent vasodilation, a factor that has been associated with labor initiation in animals.[27]

Whether diabetes impacts the risk of RDS is debated.[28] While some studies indicate a delay in fetal pulmonary maturation of diabetic women compared to control subjects, as evidenced by the timing of phosphatidylglycerol production in the amniotic fluid; others do not report such differences.[29;30] When we stratified our results among women with preexisting diabetes at ≥37 weeks' gestation, the association between diabetes and RDS risk remained increased indicating that diabetes is still an important predictor for RDS among term pregnancies (data not shown).

Strengths of our study include the large sample size and ability to account for confounders. Additionally, our study was population-based capturing deliveries in a well-defined geographical region. Having both electronic medical records and in-patient hospital discharge codes improved our ability to correctly identify both maternal and neonatal diagnoses. Despite these strengths, our study had several limitations. Missing data on glycemic control (diet, oral or insulin) led to inability to determine if risks of neonatal outcomes were modified by therapy. Date of diagnosis was also unavailable which limited our ability to examine whether earlier GDM screening among the participants with a previous GDM pregnancy may influence neonatal outcomes. Findings may not be generalizable to non-Caucasian populations as perinatal outcomes among women with GDM differ by race/ethnicity.[31] Finally, some women might have had unrecognized pregestational DM and were misclassified as having GDM.

Our results demonstrate that GDM in the previous pregnancy without recurrence may still confer risk for only newborn LGA in a subsequent pregnancy. For the majority of the neonatal morbidities, the risk estimates for women with current GDM alone and recurrent GDM were very similar. Rates of morbidities were highest among infants of women with DM. Better management of diabetic women and good glycemic control may reduce these adverse newborn outcomes. Our findings, particularly the increased risk of LGA among women with a GDM diagnosis in the prior pregnancy, require replication and further examination as to how clinical practice can be modified to impact newborn outcomes. Ongoing trials examining how earlier screening and targeted intervention might impact perinatal outcomes are necessary for answering these important questions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix 1

Participating hospitals in the NICHD Consecutive Pregnancy Study

Alta View Hospital

American Fork Hospital

Bear River Valley Hospital

Cassia Regional Medical Center

Cottonwood Hospital

Delta Community Medical Center

Dixie Regional Medical Center

Fillmore Community Medical Center

LDS Hospital

Logan Regional Hospital

McKay-Dee Hospital Center

Orem Community Hospital

Riverton Hospital

Sanpete Valley Hospital

Sevier Valley Medical Center

Park City Medical Center

Utah Valley Regional Medical Center

Valley View Medical Center

Heber Valley Medical Center

Intermountain Medical Center

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Abbreviations

GDM	gestational diabetes mellitus
DM	diabetes mellitus
ICD9	International Classification of Diseases ninth revision
LGA	large for gestational age
NICU	neonatal intensive care unit
PPWR	postpartum weight retention
PTB	preterm birth <37 weeks
RDS	respiratory distress syndrome

Clinical Implications

- Gestational diabetes in the previous pregnancy alone increased the risk for large gestational age only.
- Gestational diabetes in the current pregnancy alone and recurrent gestational diabetes increased risk for the majority of adverse neonatal outcomes.
- Progression from gestational diabetes in the previous pregnancy to diabetes mellitus in the current pregnancy further magnified the risk for adverse neonatal outcomes.
- Ongoing trials are necessary to examine how earlier screening and targeted intervention might affect neonatal outcomes.

Table 1

Current maternal and infant characteristics by changes in diabetic status between pregnancies in the NICHD Consecutive Pregnancy Study (N=62013).

	No diabetes in previous & current pregnancy N=58224	GDM in previous pregnancy only[#] N=254	GDM in current pregnancy only N=1279	GDM in previous & current pregnancy[††] N=996	DM in current pregnancy only N=178	GDM in previous & DM in current pregnancy[‡‡] N=280	DM in previous & current pregnancy[§§] N=802
Current Maternal Characteristics/Outcomes							
Maternal age[†] (y)	28.1 (4.5)	29.3 (4.7)***	30.3 (4.9)***	30.5 (5.0)***	30.0 (5.0)***	30.6 (4.9)***	30.0 (4.8)***
Age>35 (y)	3713 (6.4)	26 (10.2)*	206 (16.1)***	163 (16.4)***	25 (14.0)*	46 (16.4)***	106 (13.2)***
Non-Hispanic White	50800 (87.3)	204 (80.6)***	925 (72.5)***	743 (74.8)***	140 (79.1)***	210 (75.3)***	668 (83.4)***
Alcohol during pregnancy	816 (1.4)	7 (2.8)	17 (1.3)	18 (1.8)	10 (5.6)*	7 (2.5)	24 (3.0)*
Smoke during pregnancy	1743 (3.0)	7 (2.8)	41 (3.2)	39 (3.9)*	14 (7.9)*	14 (5.0)	40 (5.0)*
Interpregnancy interval[†] (d)	618.9 (354.7)	595.0 (365.3)	718.5 (419.7)***	609.4 (370.9)	908.3 (495.5)***	690.6 (388.7)**	605.2 (387.8)
Major postpartum weight retention/weight gain ≥4.55 kg[‡]	13061 (23.1)	63 (25.7)	492 (40.5)***	255 (26.7)*	73 (42.4)***	78 (29.6)*	196 (25.3)
Pre-pregnancy BMI[†] (kg/m^2)	24.9 (5.6)	27.0 (6.0)***	28.9 (7.2)***	28.8 (7.0)***	30.8 (8.2)***	30.5 (7.8)***	29.3 (7.6)***
Gestational weight gain[†] (kg)	13.4 (5.7)	12.6 (6.1)*	10.7 (6.8)***	10.8 (6.7)***	10.6 (7.4)***	11.2 (7.3)**	12.5 (7.1)
Parity[†]	2.0 (1.2)	2.2 (1.3)*	2.3 (1.5)***	2.5 (1.6)***	2.2 (1.4)*	2.2 (1.5)***	2.4 (1.6)***
Oligohydramnios	2006 (3.5)	5 (2.0)	65 (5.1)*	59 (5.9)***	8 (4.5)	24 (8.6)***	59 (7.4)***
Polyhydramnios	308 (0.53)	3 (1.2)	22 (1.7)***	19 (1.9)***	2 (1.1)	2 (0.71)	16 (2.0)***
Chorioamnionitis[§]	206 (0.35)	1 (0.39)	9 (0.70)	5 (0.50)	0 (0.0)	5 (1.8)	7 (0.87)
Induction of labor	22960 (39.4)	104 (40.9)	514 (40.2)	425 (42.7)*	87 (48.9)*	115 (41.1)	293 (36.5)
Cesarean delivery	10038 (17.2)	68 (26.8)***	366 (28.6)***	268 (26.9)***	48 (27.0)***	101 (36.1)***	295 (36.8)***
Cesarean for failing to progress	1033 (1.8)	8 (3.2)	50 (3.9)***	31 (3.1)*	5 (2.8)	12 (4.3)*	23 (2.9)
Cesarean among mothers with non-macrosomic infants ≤4000g	9281 (17.2)	62 (26.6)***	310 (27.5)***	217 (25.3)***	41 (24.9)**	77 (33.5)***	242 (34.8)***
Cesarean among mothers with macrosomic infants >4000g	750 (17.5)	6 (31.6)*	56 (37.1)***	50 (37.3)***	7 (53.9)*	23 (47.9)***	52 (50.0)***
Gestational hypertension	1274 (2.2)	15 (5.9)*	60 (4.7)***	43 (4.3)**	8 (4.5)*	11 (3.9)	35 (4.4)*

	No diabetes in previous & current pregnancy N=58224	GDM in previous pregnancy only[#] N=254	GDM in current pregnancy only N=1279	GDM in previous & current pregnancy[††] N=996	DM in current pregnancy only N=178	GDM in previous & DM in current pregnancy[‡‡] N=280	DM in previous & current pregnancy[§§] N=802
Preeclampsia	951 (1.6)	12 (4.7)***	38 (3.0)**	31 (3.1)**	6 (3.4)	16 (5.7)***	38 (4.7)***
Chronic hypertension	415 (0.71)	1 (0.39)	35 (2.7)***	23 (2.3)**	12 (6.7)**	22 (7.9)***	56 (7.0)***
1 hr GCT[†] // mg/dl	142.2 (26.1)	157.4 (32.5)**	185.2 (26.6)***	181.2 (36.1)***	180.5 (37.4)***	179.6 (37.1)***	171.0 (38.9)***
Diabetes control //							
Insulin	NA	NA	122 (10.5)	93 (18.3)	31 (53.5)	93 (47.7)	307 (75.8)
Oral	NA	NA	227 (19.6)	117 (23.0)	19 (32.8)	44 (22.6)	46 (11.4)
Diet	NA	NA	808 (69.8)	299 (58.7)	8 (13.8)	58 (29.7)	52 (12.8)
Current Infant Characteristics/Outcomes							
Male sex	30013 (51.6)	134 (52.8)	689 (53.9)	495 (49.7)	95 (53.4)	152 (54.3)	445 (55.5)
Early term (37-38 w)	18628 (32.0)	82 (32.3)	535 (41.8)***	394 (39.6)***	68 (38.2)	128 (45.7)***	393 (49.0)***
Preterm <37 (w)	4260 (7.3)	30 (11.8)*	146 (11.4)***	117 (11.8)***	18 (10.1)	43 (15.4)***	156 (19.5)***
Spontaneous preterm <37 (w)	2984 (5.1)	21 (8.3)*	79 (6.2)	77 (7.7)**	9 (5.1)	23 (8.2)*	84 (10.5)***
Indicated preterm <37 (w)	893 (1.5)	5 (2.0)	53 (4.1)***	35 (3.5)***	8 (4.5)**	18 (6.4)***	63 (7.9)***
Elective preterm <37 (w)	383 (0.7)	4 (1.6)	14 (1.1)	5 (0.5)	1 (0.6)	2 (0.7)	9 (1.1)
SGA	3373 (5.8)	11 (4.4)	67 (5.2)	46 (4.6)	8 (4.5)	11 (4.0)	34 (4.3)
LGA	5369 (9.2)	29 (11.5)	219 (17.1)***	194 (19.6)***	30 (16.9)***	77 (27.7)***	193 (24.2)***
Macrosomia	4276 (7.4)	19 (7.5)	151 (11.8)***	134 (13.5)***	13 (7.3)	48 (17.3)***	104 (13.0)***
Jaundice	11059 (19.0)	47 (18.5)	283 (22.1)*	245 (24.6)***	42 (23.6)	73 (26.1)*	239 (29.8)***
Shoulder dystocia[¶]	1065 (2.2)	3 (1.6)	28 (3.1)	39 (5.4)***	5 (3.9)	15 (8.4)***	26 (5.1)***
Birth injury	490 (0.84)	4 (1.6)	11 (0.86)	13 (1.3)	1 (0.56)	4 (1.4)	9 (1.1)
Congenital anomaly	2641 (4.5)	8 (3.2)	77 (6.0)*	46 (4.6)	11 (6.2)	18 (6.4)	62 (7.7)***
NICU admission	4422 (7.6)	21 (8.3)	159 (12.4)***	122 (12.3)***	19 (10.7)	55 (19.6)***	165 (20.6)***
Hypoglycemia	1086 (1.9)	8 (3.2)	20 (1.6)	21 (2.1)	3 (1.7)	4 (1.4)	18 (2.2)
RDS	1864 (3.2)	9 (3.5)	63 (4.9)**	42 (4.2)	9 (5.1)	19 (6.8)**	70 (8.7)***
Stillbirth/neonatal mortality	256 (0.44)	1 (0.39)	6 (0.47)	7 (0.70)	1 (0.56)	5 (1.8)	9 (1.1)

Abbreviations: DM: diabetes mellitus (type 1 or 2); GDM: gestational diabetes mellitus; LGA: large for gestational age; NA: not applicable; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome; SGA: small for gestational age.

Data were missing for: race/ethnicity: 62; alcohol: 161; smoke: 62; major postpartum weight retention/weight gain ≥4.55 kg: 1900; pre-pregnancy BMI: 890; gestational weight gain: 1004; delivery: 1; sex: 6; SGA: 61; LGA: 61; macrosomia: 34. Among the missing SGA and LGA, 27 infants born prior to 22 weeks gestation were not coded since the Kramer et al. reference cutoff points start at 22 weeks' gestation.

All figures are N (%) unless otherwise stated.

* p≤0.05,

** p≤0.001,

*** p≤0.0001 for a test between infants born to mothers without any diabetes in the previous and current pregnancy and infants born to mothers in each of the other groups using Poisson regression models with robust variance estimators. Significant paired differences are only reported if the global test is significant.

† Mean (SD).

Distribution of non-white category in ethnicity/race: non-Hispanic Black (n=274, 0.44%); Hispanic (n=6335, 10.2%); Asian/Pacific Islander (n=1362, 2.2%); Other race (n=290, 0.47%).

‡ Calculated as the difference in pre-pregnancy weight between the previous pregnancy and the current pregnancy.

§ Tests not run due to sample size limitations.

// Data available on 1-hr glucose challenge test (GCT) and on diabetes control, respectively for: No DM in previous & current pregnancy (n=2923; NA), GDM in previous pregnancy only (n=39; NA), GDM in current pregnancy only (n=532; n=1157), GDM in previous & current pregnancy (n=201; n=509), DM in current pregnancy only (n=23; n=58), GDM in previous & DM in current pregnancy (n=44; n=195), DM in previous & current pregnancy (n=63; n=405).

¶ Data restricted to women with vaginal deliveries only.

Diabetes control for the previous pregnancy in the ‘GDM in previous pregnancy only’ group: insulin (n=12, 4.8%); oral (n=9, 3.6%); diet (n=231, 91.7%); missing (n=2).

†† Diabetes control for the previous pregnancy in the ‘GDM in previous & current pregnancy’ group: insulin (n=89, 11.9%); oral (n=95, 12.7%); diet (n=566, 75.5%); missing (n=246).

‡‡ Diabetes control for the previous pregnancy in the ‘GDM in previous & DM in current pregnancy group’: insulin (n=80, 29.3%); oral (n=43, 15.8%); diet (n=150, 55.0%); missing (n=7).

§§ Type I diabetes:103, Type II: 118, unknown: 581. Diabetes control among those with non-missing diabetes type (data available on n=202), type I: n=103 (100%) insulin, type II: n=81 (81.8%) insulin, n=14 (14.4%) oral, n=4 (4.0%) diet.

Table 2

Relative risks (95% Confidence Intervals) of current newborn outcomes by changes in diabetic status between pregnancies in the NICHD Consecutive Pregnancy Study (N=62013).

	GDM in previous pregnancy	GDM in current pregnancy	GDM in previous & current pregnancy†	DM in current pregnancy	GDM in previous & DM in current pregnancy†	DM in previous & current pregnancy
Current Newborn Outcomes						
LGA						
Unadjusted	1.24 (1.08-1.43)	1.73 (1.54-1.95)	2.15 (1.91-2.42)	2.21 (1.83-2.66)	2.74 (2.30-3.26)	2.69 (2.36-3.06)
Adjusted	1.20 (1.05-1.38)	1.46 (1.30-1.65)	1.76 (1.56-1.98)	1.84 (1.53-2.21)	2.21 (1.86-2.63)	2.18 (1.91-2.49)
Macrosomia						
Unadjusted	0.95 (0.60-1.50)	1.55 (1.32-1.81)	1.84 (1.56-2.16)	1.07 (0.66-1.74)	2.25 (1.74-2.91)	1.78 (1.47-2.15)
Adjusted*	0.84 (0.54-1.31)	1.27 (1.09-1.49)	1.50 (1.27-1.77)	0.88 (0.54-1.43)	1.82 (1.41-2.36)	1.45 (1.20-1.76)
Jaundice						
Unadjusted	1.08 (0.96-1.21)	1.18 (1.08-1.30)	1.27 (1.15-1.41)	1.27 (1.07-1.51)	1.37 (1.16-1.61)	1.56 (1.40-1.75)
Adjusted	1.07 (0.95-1.20)	1.11 (1.01-1.22)	1.19 (1.07-1.31)	1.14 (0.96-1.35)	1.21 (1.03-1.42)	1.47 (1.31-1.64)
Shoulder dystocia¥						
Unadjusted	1.55 (1.11-2.17) ‖	1.48 (1.10-2.00)	2.30 (1.71-3.10)	2.23 (1.39-3.56)	3.46 (2.22-5.40)	2.34 (1.61-3.42)
Adjusted‡	1.53 (1.10-2.13) ‖	1.30 (0.96-1.76)	1.98 (1.46-2.70)	1.91 (1.20-3.04)	2.92 (1.85-4.59)	2.14 (1.46-3.13)
Congenital anomaly						
Unadjusted	0.79 (0.60-1.04)	1.31 (1.07-1.61)	1.04 (0.81-1.33)	1.60 (1.09-2.34)	1.26 (0.86-1.85)	1.71 (1.34-2.18)
Adjusted	0.76 (0.58-1.01)	1.24 (1.01-1.53)	0.95 (0.74-1.22)	1.47 (1.00-2.17)	1.13 (0.76-1.67)	1.52 (1.18-1.96)
Preterm birth <37 (w)						
Unadjusted	1.21 (1.01-1.46)	1.43 (1.23-1.66)	1.73 (1.49-2.02)	1.60 (1.23-2.06)	1.94 (1.52-2.47)	2.70 (2.32-3.13)
Adjusted‡	1.21 (1.01-1.46)	1.38 (1.19-1.61)	1.68 (1.44-1.96)	1.47 (1.13-1.91)	1.79 (1.40-2.28)	2.46 (2.10-2.87)
Spontaneous preterm birth <37 (w)						
Unadjusted	1.36 (1.07-1.73)	1.14 (0.93-1.40)	1.56 (1.28-1.90)	1.11 (0.77-1.60)	1.51 (1.07-2.14)	2.08 (1.68-2.57)
Adjusted‡	1.41 (1.11-1.80)	1.20 (0.98-1.48)	1.70 (1.39-2.08)	1.16 (0.79-1.69)	1.64 (1.15-2.32)	2.18 (1.76-2.72)
Indicated preterm birth <37 (w)						
Unadjusted	1.00 (0.71-1.41)	2.50 (1.91-3.27)	2.51 (1.88-3.35)	3.70 (2.44-5.62)	3.70 (2.47-5.57)	5.11 (3.95-6.62)

	GDM in previous pregnancy	GDM in current pregnancy	GDM in previous & current pregnancy†	DM in current pregnancy	GDM in previous & DM in current pregnancy†	DM in previous & current pregnancy
Adjusted¶	0.99 (0.71-1.38)	1.92 (1.48-2.49)	1.90 (1.42-2.54)	2.44 (1.63-3.66)	2.43 (1.60-3.68)	3.46 (2.61-4.57)
NICU admission						
Unadjusted	1.10 (0.93-1.32)	1.55 (1.34-1.78)	1.71 (1.47-1.98)	1.99 (1.58-2.50)	2.19 (1.75-2.74)	2.71 (2.34-3.13)
Adjusted‡	1.10 (0.92-1.31)	1.44 (1.25-1.67)	1.59 (1.36-1.84)	1.72 (1.37-2.15)	1.88 (1.50-2.36)	2.30 (1.99-2.67)
RDS						
Unadjusted	0.98 (0.73-1.32)	1.44 (1.13-1.83)	1.41 (1.10-1.82)	1.94 (1.31-2.87)	1.90 (1.30-2.80)	2.72 (2.16-3.43)
Adjusted§	0.91 (0.68-1.22)	1.33 (1.05-1.68)	1.21 (0.93-1.57)	1.77 (1.19-2.63)	1.61 (1.07-2.42)	2.24 (1.76-2.86)

DM: diabetes mellitus (type 1 or 2); GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome.

RRs and CIs from a modified Poisson regression model fit to each outcome.

Analysis adjusted for study site, maternal age (<20, 20-29, 30-34, ≥35 years), ethnicity/race (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, and other), parity defined as number of previous live births (1, 2, ≥3), inter-pregnancy interval defined as time elapsed between the woman's last delivery date and the date of the last menstrual period for the current pregnancy (0-5, 6-11, 12-17, 18-23, 24-59, ≥60 months), pre-pregnancy BMI (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, ≥40 kg/m^2), and pregnancy smoking status (yes/no).

*One study site excluded due to sample size limitations.

¥Data restricted to women with vaginal deliveries.

‡Two study sites excluded due to sample size limitations.

¶Four study sites excluded due to sample size limitations.

§Three study sites excluded due to sample size limitations.

‖Risk estimates for shoulder dystocia in the GDM in previous pregnancy group were unreliable due to small sample size.

†Risk estimates for all the newborn outcomes (except for macrosomia) for exposure group GDM in previous pregnancy & GDM in current pregnancy and for exposure group GDM in previous pregnancy & DM in current pregnancy estimated through an additive term GDM in previous pregnancy + GDM in current pregnancy and GDM in previous pregnancy + DM in current pregnancy. For macrosomia, significant interaction term noted for GDM in previous pregnancy × DM in current pregnancy p=0.013, GDM in previous pregnancy × GDM in current pregnancy p=0.33 and risk estimates for these two exposure groups are reported as interaction terms rather than additive terms.

Am J Obstet Gynecol. Author manuscript; available in PMC 2015 May 01.

Table 3

Relative risks (95% Confidence Intervals) of current newborn outcomes among nulliparous women with their first 2 births in the NICHD Consecutive Pregnancy Study (N=27064).

	Relative Risk (95% CI)					
	GDM in previous pregnancy	**GDM in current pregnancy**	**GDM in previous & current pregnancy‡**	**DM in current pregnancy**	**GDM in previous & DM in current pregnancy‡**	**DM in previous & current pregnancy**
Current Newborn Outcomes						
LGA						
Unadjusted	1.19 (0.92-1.55)	1.71 (1.39-2.11)	2.04 (1.63-2.54)	2.16 (1.54-3.03)	2.57 (1.87-3.53)	3.09 (2.50-3.82)
Adjusted	1.26 (0.97-1.62)	1.40 (1.13-1.72)	1.75 (1.41-2.18)	1.60 (1.15-2.23)	2.01 (1.46-2.75)	2.58 (2.08-3.20)
Macrosomia						
Unadjusted	1.27 (0.92-1.75)	1.39 (1.07-1.81)	1.77 (1.35-2.33)	1.49 (0.95-2.35)	1.90 (1.23-2.94)	2.09 (1.53-2.84)
Adjusted	1.34 (0.98-1.82)	1.14 (0.88-1.47)	1.52 (1.16-1.99)	1.09 (0.70-1.72)	1.46 (0.94-2.27)	1.73 (1.27-2.36)
Jaundice						
Unadjusted	0.98 (0.82-1.19)	1.29 (1.12-1.48)	1.27 (1.07-1.50)	1.24 (0.94-1.64)	1.22 (0.93-1.60)	1.75 (1.48-2.07)
Adjusted	0.97 (0.80-1.17)	1.17 (1.02-1.35)	1.14 (0.96-1.35)	1.05 (0.79-1.39)	1.01 (0.77-1.34)	1.63 (1.38-1.93)
Shoulder dystocia*						
Unadjusted	1.74 (1.02-2.96)†	1.32 (0.81-2.14)	2.30 (1.39-3.80)	1.92 (0.88-4.19)	3.34 (1.57-7.10)	4.00 (2.36-6.76)
Adjusted	1.73 (1.03-2.92)†	1.13 (0.71-1.82)	1.97 (1.18-3.27)	1.55 (0.72-3.32)	2.68 (1.25-5.76)	3.61 (2.12-6.15)
Congenital anomaly						
Unadjusted	0.88 (0.56-1.39)	1.40 (1.01-1.93)	1.23 (0.82-1.84)	1.45 (0.77-2.76)	1.28 (0.70-2.32)	2.41 (1.70-3.41)
Adjusted	0.85 (0.54-1.33)	1.35 (0.98-1.85)	1.14 (0.75-1.73)	1.37 (0.72-2.60)	1.16 (0.63-2.13)	2.12 (1.47-3.06)
Preterm birth <37 (w)						
Unadjusted	1.05 (0.77-1.44)	1.64 (1.29-2.08)	1.72 (1.32-2.25)	1.49 (0.94-2.35)	1.57 (0.99-2.47)	2.89 (2.26-3.69)
Adjusted	1.01 (0.73-1.40)	1.68 (1.31-2.15)	1.70 (1.28-2.24)	1.52 (0.95-2.43)	1.54 (0.96-2.48)	2.77 (2.14-3.60)
Spontaneous preterm birth <37 (w)						
Unadjusted	1.29 (0.89-1.87)	1.33 (0.99-1.79)	1.72 (1.24-2.38)	1.34 (0.77-2.34)	1.73 (1.03-2.92)	1.89 (1.30-2.76)
Adjusted	1.23 (0.83-1.81)	1.47 (1.07-2.01)	1.80 (1.28-2.54)	1.59 (0.88-2.87)	1.96 (1.13-3.39)	2.13 (1.47-3.09)
NICU admission						

	Relative Risk (95% CI)					
	GDM in previous pregnancy	**GDM in current pregnancy**	**GDM in previous & current pregnancy‡**	**DM in current pregnancy**	**GDM in previous & DM in current pregnancy‡**	**DM in previous & current pregnancy**
Unadjusted	1.06 (0.78-1.43)	1.43 (1.12-1.82)	1.51 (1.16-1.97)	2.02 (1.38-2.95)	2.14 (1.47-3.10)	2.92 (2.31-3.68)
Adjusted	1.06 (0.78-1.44)	1.34 (1.05-1.73)	1.42 (1.08-1.86)	1.88 (1.29-2.73)	1.98 (1.36-2.90)	2.58 (2.01-3.31)
RDS						
Unadjusted	0.82 (0.45-1.52)	1.35 (0.88-2.06)	1.11 (0.66-1.86)	1.44 (0.64-3.27)	1.19 (0.55-2.55)	3.12 (2.13-4.56)
Adjusted	0.73 (0.38-1.40)	1.32 (0.85-2.06)	0.86 (0.47-1.54)	1.49 (0.66-3.32)	1.13 (0.50-2.55)	2.70 (1.81-4.05)

DM: diabetes mellitus (type 1 or 2); GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome.

RRs and CIs from a modified Poisson regression model fit to each outcome.

Analysis adjusted for maternal age (<29, 30-34, ≥35years), ethnicity/race (non-Hispanic white, Hispanic, Asian/Pacific Islander, and non-Hispanic black/other), inter-pregnancy interval (0-5, 6-11, 12-17, 18-23, ≥24 months), pre-pregnancy BMI (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, ≥40 kg/m^2), and pregnancy smoking status (yes/no). Not adjusted for study site due to sample size limitations.

*Data restricted to women with vaginal deliveries.

†Risk estimates for shoulder dystocia in the GDM in previous pregnancy group were unreliable due to small sample size.

‡Risk estimates for all the newborn outcomes for exposure group GDM in previous pregnancy & GDM in current pregnancy and for exposure group GDM in previous pregnancy & diabetes in current pregnancy estimated through an additive term GDM in previous pregnancy + GDM in current pregnancy and GDM in previous pregnancy + DM in current pregnancy. No significant interaction (GDM in previous pregnancy × diabetes in current pregnancy, GDM in previous pregnancy × GDM in current pregnancy) was noted for any of the newborn outcomes.

Am J Obstet Gynecol. Author manuscript; available in PMC 2015 May 01.