Gestational Diabetes Mellitus in Early Pregnancy: Evidence for Poor Pregnancy Outcomes Despite Treatment

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OBJECTIVE

Recent guidelines recommend testing at <24 weeks of gestation for maternal dysglycemia in "high-risk" women. Evidence to support the early identification and treatment of gestational diabetes mellitus (GDM) is, however, limited. We examined the prevalence, clinical characteristics, and pregnancy outcomes of high-risk women with GDM diagnosed at <24 weeks of gestation (early GDM) and those with pre-existing diabetes compared with GDM diagnosed at ≥24 weeks of gestation, in a large treated multiethnic cohort.

RESEARCH DESIGN AND METHODS

Outcomes from 4,873 women attending a university hospital antenatal diabetes clinic between 1991 and 2011 were examined. All were treated to standardized glycemic targets. Women were stratified as pre-existing diabetes (*n* = 65) or GDM diagnosed at <12 weeks of gestation (*n* = 68), at 12–23 weeks of gestation (*n* = 1,247), or at ≥24 weeks of gestation (*n* = 3,493).

RESULTS

Hypertensive disorders in pregnancy including pre-eclampsia, preterm delivery, cesarean section, and neonatal jaundice (all *P* < 0.001) were more prevalent in women with pre-existing diabetes and early GDM. Macrosomia (21.8% vs. 20.3%, *P* = 0.8), large for gestational age (39.6% vs. 32.8%, *P* = 0.4), and neonatal intensive care admission (38.5% vs. 39.7%, *P* = 0.9) in women in whom GDM was diagnosed at <12 weeks of gestation were comparable to rates seen in women with pre-existing diabetes.

CONCLUSIONS

Despite early testing and current best practice treatment, early GDM in high-risk women remains associated with poorer pregnancy outcomes. Outcomes for those in whom GDM was diagnosed at <12 weeks of gestation approximated those seen in pre-existing diabetes. These findings indicate the need for further studies to establish the efficacy of alternative management approaches to improve outcomes in these high-risk pregnancies.

Gestational diabetes mellitus (GDM) is associated with significant transgenerational maternal and neonatal morbidity (1–3). The prevalence of GDM is rising, in part reflecting the changing demographics of women of childbearing age, with an increasing incidence of both obesity and advanced maternal age (4–6). These observations have important implications for the current GDM testing paradigm.

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The seminal Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (1) unequivocally demonstrated a continuous positive relationship between maternal blood glucose levels (BGLs) and several adverse maternal and neonatal outcomes, while intervention studies (7,8) have shown that treatment of GDM after 24 weeks of gestation significantly ameliorates this risk. This evidence formed the basis for the recently revised International Association of Diabetes and Pregnancy Study Groups and World Health Organization (WHO) recommendations for the diagnosis and classification of GDM (9,10).

Screening for maternal dysglycemia prior to 24 weeks of gestation is now recommended for "high-risk" women, with the purpose being primarily to identify "overt diabetes during pregnancy" (International Association of Diabetes and Pregnancy Study Groups terminology) (9) or "diabetes mellitus in pregnancy" (WHO terminology) (10); that is, to identify women with likely undiagnosed pre-existing diabetes early in pregnancy. It is important to note that women in whom GDM is diagnosed rather than diabetes mellitus in pregnancy at this early time point may also represent a cohort of women with a similar high risk, as evidenced by early dysglycemia. Furthermore, at present, there is a paucity of evidence with regard to the efficacy of a strategy of early identification and treatment of GDM prior to 24 weeks of gestation to further support these guideline recommendations.

A compelling rationale for the identification of dysglycemia early in pregnancy arises from the effect of early maternal hyperglycemia on excessive fetal growth in women with type 1 diabetes (11,12). The existing literature on early GDM has reported similarly poor pregnancy outcomes, but interpretation is confounded by the presence of pre-existing diabetes within this cohort. Importantly, a recent Israeli observational study (13) explicitly excluded pre-existing diabetes, and still found an association between GDM and even milder first trimester fasting BGLs and adverse outcomes.

To date, no studies have addressed whether this early maternal dysglycemia, at thresholds less than that of diabetes mellitus in pregnancy, is associated with adverse pregnancy outcomes in a multiethnic cohort and critically whether it is attenuated by early intensive intervention. Indeed, recent GDM screening and intervention guidelines (14,15) have explicitly acknowledged this as a priority area for research.

The aim of the current study was to determine the prevalence, clinical characteristics, and pregnancy outcomes among high-risk women in whom GDM was diagnosed before 24 weeks of gestation and among women with pre-existing diabetes compared with women in whom GDM was diagnosed after 24 weeks of gestation, in a large treated multiethnic cohort.

RESEARCH DESIGN AND METHODS

Women (*N* = 4,873) attending the Royal Prince Alfred Hospital Antenatal Diabetes Clinic between 1991 and 2011 were studied. GDM was defined by the Australasian Diabetes in Pregnancy Society (ADIPS) diagnostic criteria, with universal testing between 24 and 28 weeks of gestation implemented since 1991 (16,17). At our institution, women deemed to be at high risk have been advised to undergo early testing for GDM since the 1970s, generally soon after the first antenatal appointment. High-risk criteria consisted of the following: previous GDM, macrosomia, or unexplained stillbirth; family history of type 2 diabetes; and the later addition of maternal age (≥35 years) and obesity (BMI >30 kg/m^2) in 1991. High-risk ethnicity (i.e., non-Caucasian) has also been a consideration for early testing since the 1980s (18). Thus, the prevailing clinical practice at Royal Prince Alfred Hospital of early testing determined by risk factors is aligned with the recent ADIPS recommendations for early testing (15).

To identify women with pre-existing diabetes or diabetes mellitus in pregnancy, as distinct from "true GDM," two approaches were taken. For the primary analysis, pre-existing diabetes was defined as known type 2 diabetes diagnosed prior to the index pregnancy. For the secondary analysis, WHO diagnostic criteria for diabetes mellitus in pregnancy were retrospectively applied and were defined as follows: fasting BGL ≥7.0 mmol/L (126 mg/dL); 2-h BGL ≥11.1 mmol/L (200 mg/dL) after a 75-g oral glucose load or random BGL of ≥11.1 mmol/L (200 mg/dL) in the presence of diabetes symptoms (10). In total, six women in whom GDM was diagnosed prior to 24 weeks of gestation met the WHO criteria for diabetes mellitus in pregnancy and were excluded in the secondary analysis, as follows: five women in the <12 weeks of gestation cohort and one woman in the 12–23 weeks of gestation cohort. Women with known type 1 diabetes were excluded. Baseline maternal clinical and biochemical data taken at the time of GDM diagnosis were collected prospectively in a standardized manner (18). Ethics committee approval and informed consent were obtained.

Treatment involved the following multidisciplinary approach: lifestyle (diet and exercise) intervention and the addition of insulin therapy if BGL targets were not achieved with lifestyle modification alone. Women undertook home blood glucose monitoring four times daily aiming to achieve a capillary fasting BGL target of <5.2 mmol/L (93.6 mg/dL) and a 1-h postprandial BGL target of <7.5 mmol/L (136 mg/dL) (prior to 1998, a capillary fasting BGL target of <5.5 mmol/L [100 mg/dL] and a 2-h postprandial BGL target of <6.7 mmol/L [120 mg/dL] were used). Although there is no consensus as to treatment targets in GDM, all subjects were treated to standardized BGL targets with similar insulin intervention thresholds across all groups. Importantly, the efficacy of this management approach was recently validated in an independent audit (19) at our institution, which found a neonatal body fat percentage in the offspring of women with well-controlled GDM that was similar to that in normoglycemic women.

Data were analyzed using NCSS 2007. Continuous data were checked for normality and presented as the mean or median. Data not normally distributed were transformed for analysis. ANOVA or Kruskal-Wallis tests were used to compare means or medians. The post hoc *q* test with Bonferroni or Kruskal-Wallis *z* tests were used to adjust for multiple comparisons. Categorical data were presented as a percentage. The χ^2 test was used to compare groups. Data were grouped according to *1*) type of diabetes and *2*) the timing of GDM diagnosis at <12, 12–23 (collectively referred to as "early GDM"), or ≥24 weeks

("later GDM") of gestation. The maternal adverse outcomes assessed included rates of preterm delivery (defined as <37 weeks of gestation), cesarean section, hypertensive disorders of pregnancy (defined as pre-eclampsia or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg in a previously normotensive pregnant woman who is at ≥20 weeks of gestation and has no proteinuria or new signs of end-organ dysfunction), and persisting postpartum dysglycemia (impaired glucose tolerance and diabetes). Neonatal adverse outcomes included rates of macrosomia (defined as a birth weight of ≥4,000 g), large for gestational age (LGA) and small for gestational age (SGA) (sex- and gestational age–specific birth weight >90th centile and <10th centile for the New South Wales, Australia population [20]), stillbirth, hyperbilirubinemia (jaundice), intensive care admission, respiratory distress syndrome, and hypoglycemia.

Logistic regression was used to determine whether there was an additional independent effect of gestation at GDM diagnosis on the clinically important outcomes of LGA and macrosomia, in the context of a known high burden of risk factors in the early GDM cohort. Gestation at GDM diagnosis and variables known to impact on LGA/macrosomia were also included in the model, as follows: maternal age, ethnicity, family history of diabetes, prepregnancy BMI, gestational weight gain (GWG) (in kilograms), fasting oral glucose tolerance test (OGTT) value, HbA_{1c} level at diagnosis, area under the curve (AUC) for glucose (in millimoles per liter per minute), preterm delivery, insulin therapy, cesarean section, and maternal hypertensive disorders of pregnancy. A forward stepwise method was used. Statistical significance was accepted at the $P < 0.05$ level.

RESULTS

Baseline Characteristics and Treatment

Baseline maternal characteristics of 4,873 women stratified by type of diabetes and timing of GDM diagnosis (<12, 12–23, and ≥24 weeks of gestation) are presented in Table 1. Overall, this was a well-distributed multiethnic cohort, and women in whom GDM was diagnosed were predominantly of Anglo-Celtic and Southeast Asian background.

Nearly one-third of GDM diagnosis occurred prior to 24 weeks of gestation (27.4%) (early GDM). Compared with women in whom GDM was diagnosed at or after 24 weeks of gestation (later GDM), women with early GDM were older, had a higher prepregnancy BMI, and were more likely to have an immediate family history of diabetes and to be multiparous, essentially reflecting the selection criteria used for early testing at our institution.

Gestation at GDM diagnosis was also associated with differential treatment requirements; specifically, a greater need for early intensive insulin therapy, reflecting the more severe baseline dysglycemia seen in early GDM (Table 2). The earlier the diagnosis of GDM, the more likely that insulin therapy was required (75.0%, 59.1%, and 42.7% [$P < 0.0001$], respectively, for GDM at <12, 12–23, and ≥24 weeks of gestation) and at a higher median total daily dose at confinement (median 48 units [range 20–89 units], 33 units [range 16–62 units], and 20 units [range 10–38 units] [$P < 0.0001$], respectively, for GDM diagnosed at <12, 12–23, and ≥24 weeks of gestation), albeit much lower than that for women with type 2 diabetes (106 units [range 69–165 units]), following our treat-to-target approach. Despite a higher prepregnancy BMI, there was less GWG among the early GDM cohorts (median weight gain 6.4 kg [range 3.5–13.0 kg], 10.5 kg [range 7.4–14.0 kg] vs. 12.5 kg [range 9.0–16.0 kg] [$P < 0.0001$], respectively, for GDM diagnosed at <12, 12–23, and ≥24 weeks of gestation).

Association Between Early GDM and Adverse Maternal and Neonatal Outcomes

Despite this intensive treatment regimen, our results demonstrate a continuum of risk for adverse maternal outcomes according to the type and timing of diabetes diagnosis (Table 3). Women with type 2 diabetes had the highest rates of preterm delivery, cesarean section, and hypertensive disorders of pregnancy. The next highest incidence of adverse outcomes was seen in women with early GDM, followed by women diagnosed with later GDM.

The risk associated with early GDM was even more pronounced for neonatal outcomes (Table 4), such that outcomes for GDM diagnosed at <12 weeks of gestation were as poor as those for women with type 2 diabetes. Notably, there was no difference in the incidence of macrosomia (21.8% vs. 20.3%, $P = 0.8$), LGA (39.6% vs. 32.8%, $P = 0.4$), and neonatal intensive care admission (38.5% vs. 39.7%, $P = 0.9$), respectively, in women with type 2 diabetes and GDM diagnosed at <12 weeks of gestation. Alarmingly, the highest rate of stillbirth was seen in women in whom GDM was diagnosed at <12 weeks of gestation rather than (as would be expected) in women with type 2 diabetes (1,21). Conversely, later GDM was associated with the lowest risk of adverse neonatal outcomes. Reassuringly, the incidence of SGA (5.2% and 8.5% vs. 7.3% [$P = 0.2$], respectively, for GDM diagnosed at <12, 12–23, and ≥24 weeks of gestation) was not increased in women with early GDM despite their greater insulin treatment regimen, suggesting that our early intensive treatment approach is not associated with excessive growth restriction. We note also that the incidence of neonatal hypoglycemia was not different between the cohorts of GDM diagnosed at <12 weeks of gestation and later GDM.

Importantly, the adverse outcomes associated with early GDM diagnosis are not due to an over-representation of diabetes mellitus in pregnancy in this cohort. Specifically, although the diagnostic OGTT values and HbA_{1c} and AUC glucose levels were higher in women with early GDM compared with later GDM (Table 2), these glucose thresholds were still much lower than those for diabetes mellitus in pregnancy or that seen in the type 2 diabetes cohort (9). Moreover, of the early GDM cohort with available follow-up data, diabetes did not persist postpartum in the majority, further supporting the absence of pre-existing diabetes in this cohort. Secondary analysis, which specifically excluded women who fulfilled WHO diagnostic criteria for diabetes mellitus in pregnancy ($n = 6$), yielded similar results (i.e., P values as for primary analysis) for adverse pregnancy (Supplementary Table 1) and neonatal outcomes (Supplementary Table 2), except for neonatal jaundice and respiratory distress syndrome, which were no longer statistically different between the GDM diagnosed at <12 weeks of gestation and the later GDM cohorts.

Table 1—Baseline maternal characteristics stratified by type of diabetes and timing of GDM diagnosis

Maternal demographics (*N* = 4,873)	Type 2 diabetes (*n* = 65)	GDM <12 weeks (*n* = 68)	GDM 12–23 weeks (*n* = 1,247)	GDM ≥24 weeks (*n* = 3,493)	*P* value
Ethnicity (%)					0.0001
Anglo-Celtic	14	35	16	24	
Chinese/Southeast Asian	29	32	47	38	
Indian	14	13	11	10	
Mediterranean	5	4	10	11	
Middle Eastern	5	4	5	5	
Aboriginal and Torres Strait Islander	21	6	4	4	
Other	12	4	8	8	
Age (years)	34.5 ± 5.6	34.7 ± 4.5*	35.1 ± 4.9*	32.9 ± 5.0	<0.0001
Prepregnancy BMI (kg/m^2)	30.2 ± 6.2*	28.0 ± 6.9*	25.3 ± 6.2*	24.2 ± 5.3	<0.0001
Final BMI (kg/m^2)	35.6 ± 6.3* (*n* = 32)	32.4 ± 7.5* (*n* = 40)	29.6 ± 6.0 (*n* = 1,069)	29.2 ± 5.3 (*n*= 2,955)	<0.0001
GWG (kg)	12.8¶ (9.1–19.2)	6.4* (3.5–13.0)	10.5*¶ (7.4–14.0)	12.5¶ (9.0–16.0)	<0.0001
Family history DM (%)	84.4	61.8	58.0	47.5	<0.0001
Parity (%)					<0.0001
Primiparous	45	25	34	42	
Multiparous	55*	75*	66*	58	

Data are presented as mean ± SD or median (interquartile range), unless otherwise indicated. *Different from GDM diagnosed after 24 weeks of gestation (comparator group). ¶Different from GDM diagnosed before 12 weeks of gestation.

Exploring the Independent Role of Early Versus Late GDM Diagnosis on Adverse Outcomes

To examine the independent contribution of the timing of GDM diagnosis on the significant fetal outcomes of LGA and macrosomia, we performed multivariate regression analysis and included known risk factors for both LGA and macrosomia in the models. This showed that the timing of GDM diagnosis was not an independent risk factor for adverse outcomes; rather, the risk associated with early GDM was encompassed by the known high-risk factors of prepregnancy BMI, GWG, fasting OGTT values, and cesarean section for macrosomia (Supplementary Table 3), while prepregnancy BMI, GWG, cesarean section, and hypertensive disorders of pregnancy were significant independent associates of LGA (Supplementary Table 4).

CONCLUSIONS

In this large multiethnic cohort study, we found that despite early testing and intensive intervention, early GDM diagnosis in high-risk women was still associated with adverse pregnancy outcomes, including preterm delivery, cesarean section and hypertensive disorders of pregnancy, macrosomia, LGA, neonatal intensive care admission, and stillbirth, which are more comparable to those of women with type 2 diabetes than those with GDM diagnosed after 24 weeks of gestation. Importantly, we also showed that this risk was not accounted for by women with diabetes mellitus in pregnancy captured within the early GDM cohort, which has confounded the interpretation of the evidence to date. Specifically for the important outcomes of LGA and macrosomia, this excess risk appears

Table 2—Treatment stratified by type of diabetes and timing of GDM diagnosis

Maternal demographics (*N* = 4,873)	Type 2 diabetes (*n* = 65)	GDM <12 weeks (*n* = 68)	GDM 12–23 weeks (*n* = 1,247)	GDM ≥24 weeks (*n* = 3,493)	*P* value
Insulin treatment (%)	100.0	75.0*	59.1	42.7	<0.0001
Maximum daily insulin dose (units)	106* (69–165)	48* (20–89)	33* (16–62)	20 (10–38)	<0.0001
Gestation insulin commenced (weeks)	8.7 ± 4.3*	15.2 ± 8.9*	25.3 ± 5.4*	33.0 ± 3.2	<0.0001
Gestation GDM diagnosis (weeks)		8.1 ± 2.6	18.0 ± 2.8	29.5 ± 2.7	
Antenatal OGTT					
0 min		5.3 ± 1.5*	4.9 ± 1.0	4.8 ± 1.7	0.04
60 min		10.8 ± 3.0*	10.0 ± 1.8	9.9 ± 1.8	0.001
120 min		9.1 ± 3.1	8.8 ± 2.3*	8.5 ± 1.9	0.001
AUC glucose (units)		1,078 ± 300*	1,004 ± 159*	988 ± 153	<0.0001
HbA_{1c} (%)	6.0 ± 0.9	5.7 ± 1.3*	5.2 ± 0.6*	5.3 ± 0.5	0.0001

Data are presented as mean ± SD or median (interquartile range), unless otherwise indicated. HbA_{1c} level was calculated at the time of GDM diagnosis and the initial antenatal visit for women with type 2 diabetes; maximum insulin dose was calculated at the time of confinement. *Different from GDM diagnosed after 24 weeks of gestation (comparator group).

Table 3—Maternal outcomes for type 2 diabetes and GDM stratified by timing of diagnosis

Maternal outcomes	T2DM (*n* = 65)	GDM <12 weeks (*n* = 68)	GDM 12–23 weeks (*n* = 1,247)	GDM ≥24 weeks (*n* = 3,493)	*P* value
Gestation at delivery (weeks)	37.4 ± 1.9*	37.5 ± 3.2*	38.3 ± 2.4*	38.8 ± 1.7	<0.0001
Preterm delivery (%)	25.9*	16.7*	11.2*	6.4	<0.0001
Cesarean section (%)	57.9*	30.7	36.2*	28.1	<0.0001
Hypertensive disorders in pregnancy (%)	34.6*	26.3*	13.8*	11.2	<0.0002
Postpartum OGTT (%)#		(*N* = 28)	(*N* = 702)	(*N* = 1,877)	<0.0001
Normal		79*	71*	85	
IGT		11	24	14	
T2DM		11	5	1	

Data are presented as mean ± SD, unless otherwise indicated. Hypertensive disorders in pregnancy, either pre-eclampsia or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg in a previously normotensive pregnant woman whose pregnancy is at ≥20 weeks of gestation and has no proteinuria or new signs of end-organ dysfunction; preterm delivery, <37 weeks of gestation. IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus. *Different from GDM diagnosed after 24 weeks of gestation (comparator group). #Performed 3 months postpartum, IGT was defined as either a fasting BGL of 6.1–6.9 mmol/L and/or a 2-h BGL of 7.8–11.0 mmol/L, and T2DM was defined as a fasting BGL of ≥7.0 mmol/L and/or a 2-h BGL of ≥11.1 mmol/L.

predominantly due to the higher rates of maternal adiposity and early dysglycemia, which characterize the early GDM cohort. This finding reflects that of the observational HAPO study (22), which identified the independent effect of both maternal adiposity and higher OGTT values in later pregnancy on LGA and macrosomia.

Our findings are also consistent with those of the single prospective cohort study in this field (23). This showed that women in whom GDM was diagnosed early (before 24 weeks of gestation) were more likely to be hypertensive, to have poorer glycemic control, and to have greater need for insulin therapy, with all cases of neonatal morbidity and mortality occurring in this cohort (23). Similar findings have been reported in retrospective cohort studies (24–27); however, all these studies were limited by the heterogeneity of their early GDM cohorts. In contrast, our data, by removing the confounder of pre-existing diabetes from the early-onset cohort, convincingly demonstrate that early GDM per se in high-risk women represents a particularly high-risk subset.

Although the true prevalence of early GDM is unknown, due to the differing diagnostic criteria used and the population screened, our rate of ~30% is consistent with those of other studies reporting early GDM prevalence in both unselected and high-risk cohorts of 29–42% (23,28–30), although, notably, rates have been as high as 62–66% in certain high-risk populations (25,31). Thus, early GDM is a frequent finding, and the application of systematic testing in early pregnancy will identify a substantial number of women and potentially affect their pregnancy outcomes.

In contrast to the improvement in outcomes seen in intervention studies after 24 weeks of gestation (7,8), we found a consistent magnitude of difference in outcomes for early GDM despite an effective within-clinic, previously validated approach (19) and a consistent standard of care. A limitation of our study was that the efficacy and compliance of glycemic intervention throughout pregnancy was not assessed, although the smaller GWG in the early GDM cohort would suggest some degree of treatment efficacy. In addition, the similarly low rates of neonatal hypoglycemia among the cohorts of women with <12 weeks of gestation and later GDM, as an index of perinatal glycemic exposure, would also suggest the efficacy of attained maternal glycemia. There is a paucity of evidence that the diagnosis and treatment of GDM before 24 weeks of gestation affects pregnancy outcomes. However, if we surmise that our glycemic management strategy was uniformly applied across the GDM cohorts, why might

Table 4—Neonatal outcomes for type 2 diabetes and GDM stratified by timing of diagnosis

Neonatal complications	T2DM (*n* = 65)	GDM <12 weeks (*n* = 68)	GDM 12–23 weeks (*n* = 1,247)	GDM ≥24 weeks (*n* = 3,493)	*P* value
Macrosomia	21.8*	20.3*	9.0	10.0	<0.0001
LGA	39.6*	32.8	21.5	22.8	0.008
Stillbirth	1.8	3.4	0.8	0.3	0.2
Jaundice	41.7*	28.1*	24.8	19.8	<0.0001
Neonatal intensive care admission	38.5	39.7	38.3*	34.0	0.04
Respiratory distress syndrome	12.3*	7.4*	3.8	4.0	0.005
Hypoglycemia	14.9	20.7	20.2*	17.2	0.1
SGA	0.0	5.2	8.5	7.3	0.2

Data are reported as %. LGA/SGA were defined as sex- and gestational age–specific neonatal birth weight >90th centile (LGA) or <10th centile (SGA) for New South Wales, Australia, population (20); macrosomia was defined as ≥4,000 g; neonatal hypoglycemia was defined as a BGL<2.5 mmol/L. *Different from GDM diagnosed after 24 weeks of gestation (comparator group).

this residual risk have been incompletely attenuated?

There are several possible explanations for the poorer outcomes seen in our early GDM cohort despite intensive intervention. First, given their higher prepregnancy BMI and antenatal glycemic parameters plus corresponding greater insulin requirements and higher rates of hypertensive disorders of pregnancy, this cohort may be characterized by a more insulin-resistant phenotype compared with later GDM. Therefore, similar to those with type 2 diabetes, their dysglycemia was potentially more difficult to manage. This possibility is supported by a recent study assessing the pathophysiological characteristics of early (median diagnosis 16 weeks of gestation) versus late ($\geq$24 weeks of gestation) GDM, which found significant differences in β-cell function and insulin sensitivity relating to the timing of GDM onset, even after accounting for maternal BMI (32). Conversely, our glycemic intervention may well have been effective throughout pregnancy (19); however, even earlier and more aggressive glycemic management may be required in this early GDM cohort, given that the mean ($\pm$SD) gestation at which insulin was commenced was 15.2 $\pm$ 8.9 weeks. Additionally, an excess of free fatty acids associated with maternal adiposity may have fueled the excess growth seen in the early GDM neonates (33), given the known impact of maternal overweight and obesity on adverse neonatal outcomes, particularly LGA (34). Despite the lower GWG seen in the early GDM cohort, it may be that even earlier intervention (i.e., at preconception) is required to ameliorate the higher prepregnancy maternal BMI in that cohort and/or that even tighter GWG targets are needed. Finally, there may be genetic aspects and socioeconomic determinants associated with the heterogeneity of the GDM phenotype that account for the disparate outcomes seen in women with early versus late GDM.

Some potential limitations require discussion. First, the early GDM cohort was a preselected high-risk group, and we lacked a control cohort to assess outcomes among women with early GDM without early intervention. Further, we acknowledge that the selection and early testing of high-risk women in our study encompasses the prevailing clinical practice at our institution and as such represents a "real-world" setting; accordingly, there will have been variable application of these testing recommendations over time, despite the strategy at our institution since the 1970s to test early for GDM in high-risk women. The relatively small number of women with pre-existing type 2 diabetes reflected the lack of systematic recording of this cohort in the database, which was primarily developed to capture GDM. Reassuringly, however, our findings for these women are consistent with the literature (35). Finally, there was significant loss to follow-up for the postpartum OGTT values throughout the GDM cohort; however, those with undiagnosed pre-existing diabetes are less likely to contribute to the findings, given that normoglycemia occurred postpartum in the majority of women, which was substantiated by the subthreshold antenatal glycemic parameters throughout the early GDM cohort.

In summary, this is the first large, multiethnic data set comparing outcomes in women with treated GDM diagnosed in early pregnancy and pre-existing diabetes in comparison with those with GDM diagnosed after 24 weeks of gestation. This study demonstrates that, despite intensive intervention, early GDM in high-risk women is associated with suboptimal outcomes, and that this increased risk is associated with dysglycemia lower than the threshold for diabetes mellitus in pregnancy. Moreover, outcomes for those women in whom GDM was diagnosed at $<$12 weeks of gestation are the worst of the GDM cohort and approximate those of women with pre-existing diabetes. Thus, women with early GDM represent a high-risk cohort requiring systematic early identification and intensive surveillance. Given the persistence of poor outcomes in this cohort, despite early testing and current best practice treatment, prospective studies are needed to address residual risk factors and establish the efficacy of alternative glycemia and lifestyle management approaches in these high-risk pregnancies.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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References

1. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002
2. Reece EA, Leguizamón G, Wiznitzer A. Gestational diabetes: the need for a common ground. Lancet 2009;373:1789–1797
3. Barker D. *Mothers, Babies and Diseases in Later Life*. London, BMJ Publishing Group, 1994
4. Anna V, van der Ploeg HP, Cheung NW, Huxley RR, Bauman AE. Sociodemographic correlates of the increasing trend in prevalence of gestational diabetes mellitus in a large population of women between 1995 and 2005. Diabetes Care 2008;31:2288–2293
5. Chu SY, Callaghan WM, Kim SY, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care 2007;30:2070–2076
6. Torloni MR, Betrán AP, Horta BL, et al. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. Obes Rev 2009;10:194–203
7. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477–2486
8. Landon MB, Spong CY, Thom E, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339–1348
9. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676–682
10. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. Diabetes Res Clin Pract 2014;103:341–363
11. Wong SF, Chan FY, Oats JJ, McIntyre DH. Fetal growth spurt and pregestational diabetic pregnancy. Diabetes Care 2002;25:1681–1684
12. Page RC, Kirk BA, Fay T, Wilcox M, Hosking DJ, Jeffcoate WJ. Is macrosomia associated with

poor glycaemic control in diabetic pregnancy? Diabet Med 1996;13:170–174
13. Riskin-Mashiah S, Younes G, Damti A, Auslender R. First-trimester fasting hyperglycemia and adverse pregnancy outcomes. Diabetes Care 2009;32:1639–1643
14. Moyer VA; U.S. Preventive Services Task Force. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014; 160:414–420
15. Nankervis A, McIntyre HD, Moses R, et al. ADIPS Consensus Guidelines for the Testing and Diagnosis of Hyperglycaemia in Pregnancy in Australia and New Zealand (modified November 2014) [article online], 2014. Available from http://adips.org/downloads/2014ADIPSGDMGuidelinesV18.11.2014_000.pdf
16. Hoffman L, Nolan C, Wilson JD, Oats JJ, Simmons D; The Australasian Diabetes in Pregnancy Society. Gestational diabetes mellitus-management guidelines. Med J Aust 1998;169: 93–97
17. Martin FIR, Vogue A, Dargaville R, Ericksen C, Oats J, Tippett C. ADS Position Statement: The diagnosis of gestational diabetes. Med J Aust 1991;155:112
18. Yue DK, Molyneaux LM, Ross GP, Constantino MI, Child AG, Turtle JR. Why does ethnicity affect prevalence of gestational diabetes? The underwater volcano theory. Diabet Med 1996;13:748–752
19. Au CP, Raynes-Greenow CH, Turner RM, Carberry AE, Jeffery HE. Body composition is normal in term infants born to mothers with well-controlled gestational diabetes mellitus. Diabetes Care 2013;36:562–564
20. Beeby PJ, Bhutap T, Taylor LK. New South Wales population-based birthweight percentile charts. J Paediatr Child Health 1996;32:512–518
21. Macintosh MC, Fleming KM, Bailey JA, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ 2006;333:177
22. Catalano PM, McIntyre HD, Cruickshank JK, et al.; HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome study: associations of GDM and obesity with pregnancy outcomes. Diabetes Care 2012;35:780–786
23. Bartha JL, Martinez-Del-Fresno P, Comino-Delgado R. Gestational diabetes mellitus diagnosed during early pregnancy. Am J Obstet Gynecol 2000;182:346–350
24. Seshiah V, Cynthia A, Balaji V, et al. Detection and care of women with gestational diabetes mellitus from early weeks of pregnancy results in birth weight of newborn babies appropriate for gestational age. Diabetes Res Clin Pract 2008;80:199–202
25. Bartha JL, Martinez-Del-Fresno P, Comino-Delgado R. Early diagnosis of gestational diabetes mellitus and prevention of diabetes-related complications. Eur J Obstet Gynecol Reprod Biol 2003;109:41–44
26. Hawkins JS, Lo JY, Casey BM, McIntire DD, Leveno KJ. Diet-treated gestational diabetes mellitus: comparison of early vs routine diagnosis. Am J Obstet Gynecol 2008;198:287.e1–6
27. Most OL, Kim JH, Arslan AA, Klauser C. Maternal and neonatal outcomes in early glucose tolerance testing in an obstetric population in New York city. J Perinat Med 2009;37: 114–117
28. Berkowitz GS, Roman SH, Lapinski RH, Alvarez M. Maternal characteristics, neonatal outcome, and the time of diagnosis of gestational diabetes. Am J Obstet Gynecol 1992;167: 976–982
29. Meyer WJ, Carbone J, Gauthier DW, Gottmann DA. Early gestational glucose screening and gestational diabetes. J Reprod Med 1996;41:675–679
30. Agarwal MM, Dhatt GS, Punnose J, Zayed R. Gestational diabetes: fasting and postprandial glucose as first prenatal screening tests in a high-risk population. J Reprod Med 2007;52: 299–305
31. Super DM, Edelberg SC, Philipson EH, Hertz RH, Kalhan SC. Diagnosis of gestational diabetes in early pregnancy. Diabetes Care 1991;14:288–294
32. Bozkurt L, Gobl CS, Pfligl L, et al. Pathophysiological characteristics and impact of obesity in women with early and late manifestation of gestational diabetes diagnosed by the International Association of Diabetes and Pregnancy Study Groups criteria. J Clin Endocrinol Metab 2015; 100:1113–1120
33. Schaefer-Graf UM, Graf K, Kulbacka I, et al. Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabetes Care 2008;31:1858–1863
34. Black MH, Sacks DA, Xiang AH, Lawrence JM. The relative contribution of prepregnancy overweight and obesity, gestational weight gain, and IADPSG-defined gestational diabetes mellitus to fetal overgrowth. Diabetes Care 2013;36:56–62
35. Handisurya A, Bancher-Todesca D, Schober E, et al. Risk factor profile and pregnancy outcome in women with type 1 and type 2 diabetes mellitus. J Womens Health (Larchmt) 2011;20: 263–271