OBSTETRICS

Gestational diabetes and fetal growth in twin compared with singleton pregnancies

Eran Ashwal, MD; Howard Berger, MD; Liran Hiersch, MD; Eugene W. Yoon, MSc; Arthur Zaltz, MD; Baiju Shah, MD, PhD; Ilana Halperin, MD; Jon Barrett, MD; Nir Melamed, MD, MSc

BACKGROUND: Gestational diabetes mellitus is associated with accelerated fetal growth in singleton pregnancies but may affect twin pregnancies differently because of the slower growth of twin fetuses during the third trimester of pregnancy and their greater predisposition to fetal growth restriction.

OBJECTIVE: This study aimed to evaluate the association of gestational diabetes mellitus with longitudinal fetal growth in twin pregnancies and to compare this association with that observed in singleton pregnancies.

STUDY DESIGN: This was a retrospective cohort study of all women with a singleton or twin pregnancy who were followed up at a single tertiary referral center between January 2011 and April 2020. Data on estimated fetal weight and individual fetal biometric indices were extracted from ultrasound examinations of eligible women. Generalized linear models were used to model and compare the change in fetal weight and individual biometric indices as a function of gestational age between women with and without gestational diabetes mellitus in twin pregnancies and between women with and without gestational diabetes mellitus in singleton pregnancies. The primary outcome was estimated fetal weight as a function of gestational age. The secondary outcomes were longitudinal growth of individual fetal biometric indices and the rate of small for gestational age and large for gestational age at birth.

RESULTS: A total of 26,651 women (94,437 ultrasound examinations) were included in the analysis: 1881 with a twin pregnancy and 24,770 with a singleton pregnancy. The rate of gestational diabetes mellitus in the twin and singleton groups was 9.6% (n=180) and 7.6% (n=1893), respectively. The estimated fetal weight in singleton pregnancies with gestational diabetes mellitus was significantly higher than that in pregnancies without gestational diabetes mellitus ($P<.001$) starting at approximately 30 weeks of gestation. The differences remained similar after adjusting for maternal age, chronic hypertension, nulliparity, and neonatal sex ($P<.001$). In twin pregnancies, fetal growth was similar between pregnancies with and without gestational diabetes mellitus ($P=.105$ and $P=.483$ for unadjusted and adjusted models, respectively). The findings were similar to the association of gestational diabetes mellitus with the risk of large for gestational fetuses and the growth of each biometric index. When stratified by type of gestational diabetes mellitus treatment, twin pregnancies with gestational diabetes mellitus was associated with accelerated fetal growth only in the subgroup of women with medically treated gestational diabetes mellitus ($P<.001$), which represented 12% (n=21) of the twin pregnancy group with gestational diabetes mellitus.

CONCLUSION: In contrast to singleton pregnancies, twin pregnancies with gestational diabetes mellitus is less likely to be associated with accelerated fetal growth. This finding has raised the question of whether the diagnostic criteria for gestational diabetes mellitus and the blood glucose targets in women diagnosed with gestational diabetes mellitus should be individualized for twin pregnancies.

Key words: gestational diabetes mellitus, growth, macrosomia, large for gestational age, multifetal pregnancy, twin pregnancy

Introduction

The incidence of gestational diabetes mellitus (GDM), recently redefined by the American Diabetes Association as diabetes mellitus diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes mellitus before gestation,[1] is increasing worldwide because of the increasing prevalence of obesity and advanced maternal age.[2] GDM is associated with maternal and neonatal complications in singleton pregnancies,[3–5] with accelerated fetal growth and macrosomia being the main adverse effects of GDM.[6–8]

There is a reduction in fetal growth velocity during the third trimester of pregnancy and an increased risk of fetal growth restriction (FGR) in twin pregnancies compared with singleton pregnancies.[9–13] Thus, we hypothesized that the effect of GDM on fetal growth would be less pronounced in twin pregnancies compared with singleton pregnancies. In addition, it is possible that the mild increase in serum glucose that is seen in women with mild GDM may have a beneficial role in the presence of 2 fetuses and may decrease the risk of FGR in twin pregnancies.[14,15] In fact, it has been suggested that treatment of GDM in twin pregnancies does not improve neonatal outcomes and can increase the risk of FGR.[16]

Data on the effect of GDM on fetal growth in twin pregnancies are limited and conflicting.[14–27] Moreover, one of the main limitations of available studies is the use of birthweight as the measure of fetal growth, most often described dichotomously as large for gestational age (LGA; a birthweight of >90th percentile for gestational age) or macrosomia (a birthweight of >4000 g). Birthweight is a summative measure of fetal growth throughout pregnancy that may be attained along different growth trajectories. Thus, birthweight provides partial information only on the effect of GDM on fetal growth and does not provide insight into the timing of onset of accelerated fetal growth, on the effect of GDM on

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AJOG at a Glance

Why was this study conducted?

This study aimed to evaluate the association of gestational diabetes mellitus (GDM) with longitudinal fetal growth in twin pregnancies and to compare this association with that observed in singleton pregnancies.

Key findings

The estimated fetal weight in singleton pregnancies with GDM was significantly higher than that in pregnancies without GDM ($P < .001$). The differences remained similar after adjusting for maternal age, chronic hypertension, nulliparity, and neonatal sex. In twin pregnancies, fetal growth was similar between pregnancies with and without GDM ($P = .105$). The findings were similar to the association of GDM with the risk of large-for-gestational-age fetuses and the growth of each biometric index. Twin pregnancies with GDM were associated with accelerated fetal growth only in the subgroup of women with medically treated GDM.

What does this add to what is known?

This study has provided information on longitudinal fetal growth in a large cohort of women with singleton and twin pregnancies, with and without GDM. The differential association of GDM with fetal growth between singleton and twin pregnancies has raised the question of whether the diagnostic criteria for GDM and the blood glucose targets in women with GDM should be individualized for twin pregnancies.

the fetal growth rate at different time points along gestation, and on the growth rate of individual fetal biometric indices, such as abdominal circumference. In addition, using LGA or macrosomia at birth as endpoints may not be sensitive enough to detect an effect of GDM on the fetal growth trajectory as these outcomes are dependent on the a priori growth potential of the individual fetus and on gestational age at birth. Therefore, there is a need for data on the effect of GDM on longitudinal fetal growth in twin pregnancies, as reflected by sonographic fetal biometry, that may provide insight into the clinical significance of GDM in twin pregnancies. However, such data are limited,[15] which is in line with the recent statement by the Society for Maternal-Fetal Medicine that highlighted the need for further studies on the diagnosis and management of GDM in twin pregnancies.[28]

Thus, our study aimed to evaluate the association of GDM with longitudinal fetal growth in twin pregnancies and to compare this association with that observed in singleton pregnancies.

Methods

Study design and participants

This was a retrospective cohort study of all women with a singleton or twin pregnancy who were followed up at a single tertiary referral center (Sunnybrook Health Sciences Center, Toronto, Ontario, Canada) between January 1, 2011, and April 31, 2020. Women with any of the following conditions were excluded from the study: (1) lack of first-trimester ultrasound examination to confirm dating; (2) preexisting type 1 or type 2 diabetes mellitus; (3) missing information on GDM screening results or ultrasound examination data; (4) birth at <24 0/7 weeks of gestation (based on the assumption that in most cases information on GDM screening results is unlikely to be available before 24 weeks of gestation); (5) complications related to monochorionic placentation, including twin-to-twin transfusion syndrome, twin anemia polycythemia sequence, or selective FGR; (6) monochorionic-monoamniotic twins; (7) stillbirth or reduction of 1 of both fetuses; or (8) genetic or structural fetal anomalies. The study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board.

Data source

All ultrasound examinations that included assessment fetal biometry in singleton and twin pregnancies were identified through the electronic database of the obstetrical ultrasound unit. Each examination contains information on the number of fetuses, gestational age at the time of examination, fetal presentation, amniotic fluid level, and fetal biometry, including biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and. femur length (FL). The estimated fetal weight was calculated using the Hadlock 1985 formula that incorporates all 4 indices (BPD, HC, AC, and FL).[29] The HC-to-AC ratio was calculated as a measure of disproportionate growth and was interpreted according to the reference of Campbell et al.[30]

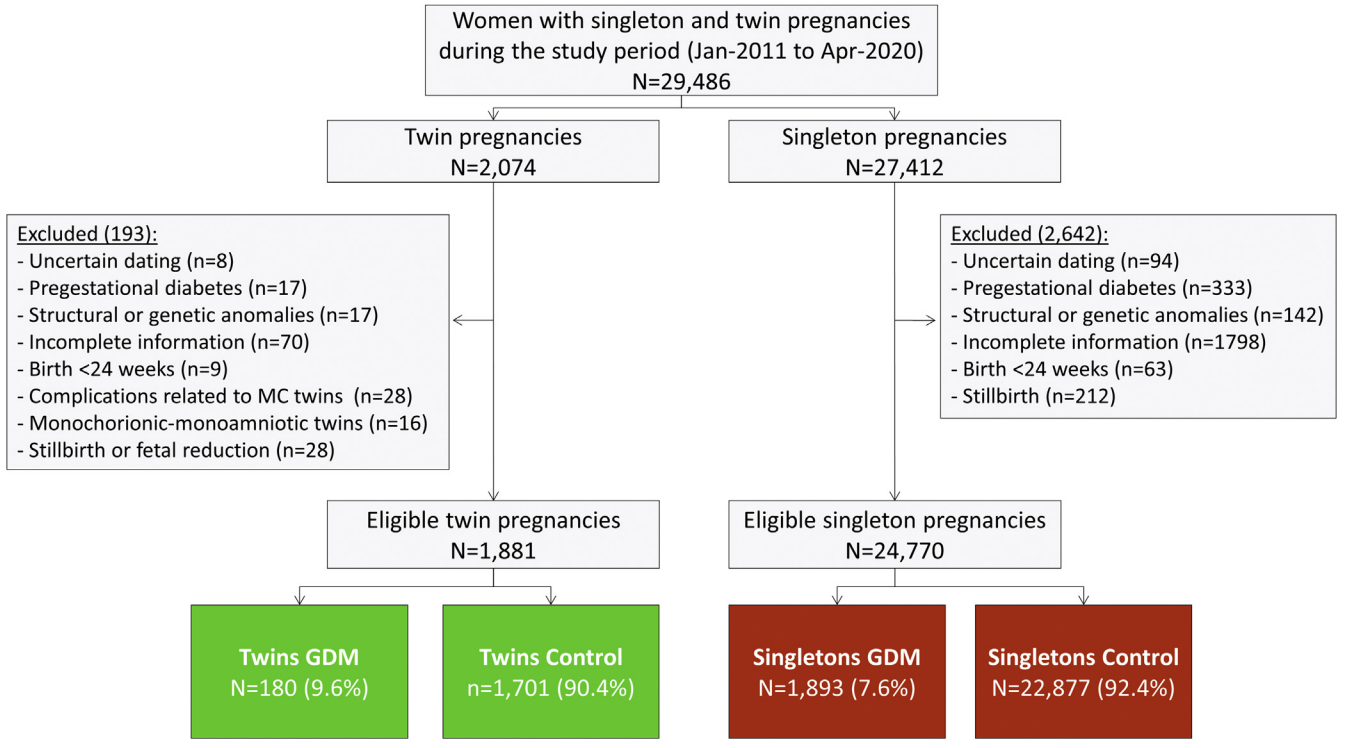
Data were linked using a unique patient identifier to the institutional comprehensive perinatal database, which contains information on demographic; medical and obstetrical history; information on the current pregnancy, including complications during pregnancy; mode of delivery; gestational age at birth; birthweight; neonatal sex; and short-term neonatal outcomes.

Exposures and outcomes

The primary exposures were GDM and the number of fetuses (twin vs singleton pregnancy). Thus, women were classified into 4 mutually exclusive groups: (1) singleton pregnancies without GDM (control); (2) singleton pregnancies with GDM; (3) twin pregnancies without GDM (control); and (4) twin pregnancies with GDM.

The primary outcome was estimated fetal weight as a function of gestational age. The secondary outcomes were (1) longitudinal growth of individual fetal biometric indices (HC, AC, FL) and the HC-to-AC ratio as a measure of asymmetric fetal growth and (2) rate of small for gestational age and LGA at birth, defined as an estimated fetal weight or birthweight of <10th or >90th percentile for gestational age, respectively. In addition, we used the Hadlock 1991 standard to calculate the estimated fetal weight percentiles[31] and a national sex-

FIGURE 1
Selection of the study groups



GDM, gestational diabetes mellitus; *MC*, monochorionic.

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specific birthweight reference to calculate birthweight percentiles.[32] The term "longitudinal growth" was used to reflect the fact that multiple measurements were obtained from each fetus at different points during pregnancy.

Diagnosis of gestational diabetes mellitus

This study spanned 2 periods concerning the criteria for diagnosis of GDM in our institution. Up until April 2013, the criteria for diagnosis were according to the 2008 Canadian Diabetes Associations (CDA) guidelines.[33] These guidelines recommended screening for GDM using a 50-g glucose challenge test (GCT), and when positive (>7.8 mmol/L or 140 mg/dL), a 75-g oral glucose tolerance test (OGTT) followed (cutoff values: fasting or before meals, ≥5.3 mmol/L or 96 mg/dL; 1 hour after meal, ≥10.6 mmol or 191 mg/dL; 2 hours after meal, ≥8.9 mmol/L or 160 mg/dL). GDM was defined as ≥2 abnormal OGTT values or a GCT result of ≥10.3 mmol/L or 185 mg/dL. The presence of a single abnormal OGTT value was defined as impaired glucose tolerance (IGT). In April 2013, new CDA criteria were published.[34] The new guidelines allowed 2 options for screening or testing for GDM. The "preferred" option (which was used in our institution) was essentially identical to the 2008 CDA guidelines aside from increasing the diagnostic 50-g GCT value from 10.3 mmol (185 mg/dL) to ≥11.1 mmol (200 mg/dL) and the 2-hour 75-g OGTT threshold from 8.9 mmol/L (160 mg/dL) to 9.0 mmol/L (162 mg/dL). The distinction between IGT and GDM was eliminated in these new guidelines. Despite the change in the diagnostic criteria, no change in management was anticipated as women with both IGT and GDM were referred to specialty clinics for dietary modification and glycemic monitoring. In addition, the criteria were applied equally to singleton and twin pregnancies.

Definitions and protocols

All women diagnosed with GDM at our center were followed up by a team that consists of a specialist in maternal-fetal medicine, endocrinologist, diabetes specialist nurse, and nutritional consultant experienced in the management of diabetes mellitus in pregnancy. The patients' blood glucose levels were monitored 4 times a day (fasting and 2-hour after meal), and when the target glucose levels (fasting blood sugar level of <5.3 mmol/L or <95 mg/dL and blood sugar level 2 hours after meal of <6.7 mmol/L or <121 mg/dL) were not achieved with diet and lifestyle changes, treatment with metformin or insulin was started and the dose was titrated until adequate glycemic control was achieved.

Women with singleton pregnancies and GDM underwent sonographic evaluation of fetal growth and well-being every 1 to 4 weeks from the time of diagnosis to birth, with the frequency of ultrasound examinations being determined on the basis of obstetrical factors and glycemic control. Before the diagnosis of GDM, all women with singleton pregnancies underwent routine

TABLE
Characteristics and outcomes of the study population

Variable	Twin pregnancies			Singleton pregnancies		
	GDM (n=180)	Control (n=1701)	*P* value	GDM (n=1893)	Control (n=22,877)	*P* value
Maternal age (y)	35.1±5.3	33.1±5.1	<.001[a]	34.6±4.8	32.7±4.8	<.001[a]
>35	76 (42)	531 (31)	.003[a]	795 (42)	6176 (27)	<.001[a]
Nulliparity	97 (55)	770 (53)	.598	804 (43)	9557 (45)	.047[a]
Chronic hypertension	7 (4)	11 (1)	.001[a]	30 (2)	172 (1)	.003[a]
GHTN or preeclampsia	33 (19)	114 (10)	<.001[a]	159 (9)	1027 (6)	<.001[a]
Medically treated GDM	21 (12)	N/A	N/A	423 (22)	N/A	N/A
Induction of labor	28 (16)	278 (23)	.036[a]	664 (36)	5051 (27)	<.001[a]
Cesarean delivery	123 (71)	822 (69)	.559	895 (49)	6788 (37)	<.001[a]
Operative vaginal delivery	4.0	4.2	.929	135 (7)	1632 (9)	.038[a]
Gestational age at birth (wk)	34.3±3.2	34.9±3.1	.011[a]	37.7±2.6	38.4±2.9	<.001[a]
<37	122 (71)	709 (60)	.005[a]	277 (15)	2035 (11)	<.001[a]
<34	49 (29)	262 (22)	.062	129 (7)	1048 (6)	.016[a]
<32	34 (20)	164 (14)	.039[a]	99 (5)	868 (5)	.168
Number of ultrasound examinations	7 (3.5–8.0)	5 (2.0–8.0)	.006[a]	4 (2.0–5.0)	2 (1.0–4.0)	<.001[a]
Female fetal sex[b]	176 (51)	1200 (50)	.724	902 (50)	9024 (49)	.624
Birthweight<10th percentile[b,c]	76 (23)	676 (29)	.013[a]	222 (12)	2438 (13)	.200
Birthweight>90th percentile[b,c]	4 (1)	24 (1)	.774	160 (9)	1085 (6)	<.001[a]
Birthweight>4000 g[b]	0 (0)	2 (0)	1.000	99 (5)	1293 (7)	.011[a]

Data are presented as mean±standard deviation, number (percentage), median (interquartile range), unless otherwise indicated.

GA, gestational age; *GDM*, gestational diabetes mellitus; *GHTN*, gestational hypertension; *N/A*, nonapplicable.

Adapted from Kramer et al.[32]

[a] Significant *P* values; [b] Unit for analysis for this variable is fetuses (rather than pregnancies), with the denominator for the GDM and control groups being 360 and 3402, respectively; [c] Using a Canadian singleton-based sex-specific birthweight reference.

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ultrasound examination at 18 to 20 weeks of gestation. Women with dichorionic twin pregnancies in our center underwent ultrasound examination every 2 to 4 weeks from 18 to 32 weeks of gestation and weekly thereafter, irrespective of the diagnosis of GDM. Women with monochorionic twins were followed up every 2 weeks from 16 to 30 weeks of gestation and weekly thereafter, irrespective of the diagnosis of GDM. All sonographic examinations were performed by certified sonographers trained in obstetrical ultrasound and were reviewed by maternal-fetal medicine specialists or radiologists with training in obstetrical ultrasound.

Women with a singleton pregnancy and GDM underwent induction of labor at 38 to 40 weeks of gestation, depending on glycemic control and evidence of accelerated fetal growth. Women with dichorionic and monochorionic-diamniotic twin pregnancies underwent induction of labor at 37 to 38 and 36 to 37 weeks of gestation, respectively, irrespective of the diagnosis of GDM.

Data analysis

The characteristics of the GDM and control groups were compared for twin and singleton pregnancies, separately. For the univariate comparisons, the chi-square test and Fisher exact test were used for categorical variables, and the *t* test and Whitney-Mann U test were used for continuous variables.

The means (with 95% confidence interval [CI]) of estimated fetal weight and individual biometric indices at each gestational week were calculated for each of the groups. For the twin group, the unit of analysis was the fetus (ie, each fetus was analyzed separately). Curves were fitted using locally weighted regression to illustrate the growth pattern of each group. Because the data for the singleton control (non-GDM) group may be biased (as women in this group may be more likely to undergo ultrasound when there are concerns about fetal growth), we compared the mean estimated fetal weight of this group with the 50th percentile of the ultrasound-based standard of Hadlock et al.[31]

Generalized linear models were used to model and compare the change in fetal weight and individual biometric indices

as a function of gestational age in the GDM and control groups. This was done in twin and singleton pregnancies, separately. Generalized estimating equations were implemented in all models to account for repeated measures from the same fetus and the correlation within twin pairs, by using a 2-level nested structure (the first level being pregnancy and the second level being the twin pair).[35] Furthermore, we developed both unadjusted models and models that were adjusted for the following factors that were determined a priori: maternal age, chronic hypertension, nulliparity, and neonatal sex. The *P* value of the GDM term in the model was used to determine whether the differences in fetal growth between pregnancies with GDM and control are statistically significant.

Analysis was further stratified by type of treatment of GDM (diet vs medically treated GDM, which we used as a proxy for the severity of GDM) and fetal sex.[36,37] In addition, in the twin group, analysis was stratified by chorionicity and twin order.[38]

The hypotheses were tested using 2-tailed tests with a significance level of 0.05. All statistical analyses were performed using the Statistical Analysis System software (version 9.4; SAS Institute Inc, Cary, NC).

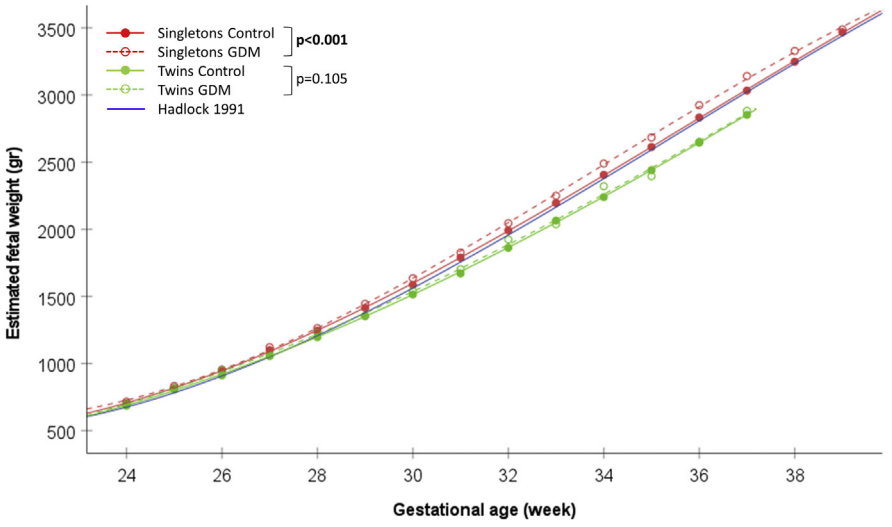
Results

Characteristics of the study population

Of the 29,486 women with singleton or twin pregnancies during the study period, 26,651 women (94,437 ultrasound examinations) met the study criteria (Figure 1). Of the 26,651 women, 1881 had twin pregnancies and 24,770 had singleton pregnancies. The proportion of women with GDM in the twin and singleton groups were 9.6% (n=180) and 7.6% (n=1893), respectively (*P*=.003) (Figure 1).

Women with GDM were older and were more likely to have chronic hypertension, hypertensive disorders of pregnancy, and preterm birth than women without GDM in both twin and singleton pregnancies (Table). GDM was associated with a higher rate of cesarean delivery and birthweight of >90th percentile and >4000 g in singleton pregnancies (Table). In women with twin pregnancies, those with GDM were less likely to have an infant with a birthweight of <10th percentile than controls. The median number of ultrasound examinations was higher in women with twin pregnancies than in women with singleton pregnancies and in women with GDM than in women without GDM (Table).

FIGURE 2
Mean fetal weight as a functional of gestational age



Mean fetal weight as a function of gestational age is presented for women with singleton pregnancies without GDM (*solid red line*) and with GDM (*dashed red line*) and for women with twin pregnancies without GDM (*solid green line*) and with GDM (*dashed green line*). The 50th percentile of Hadlock 1991 fetal weight standard (*blue solid line*) is included, along with a second control group of women with singleton pregnancies without GDM. The differences between the GDM and control groups were assessed using a generalized linear model. Adapted from Hadlock et al.[31]

GDM, gestational diabetes mellitus.

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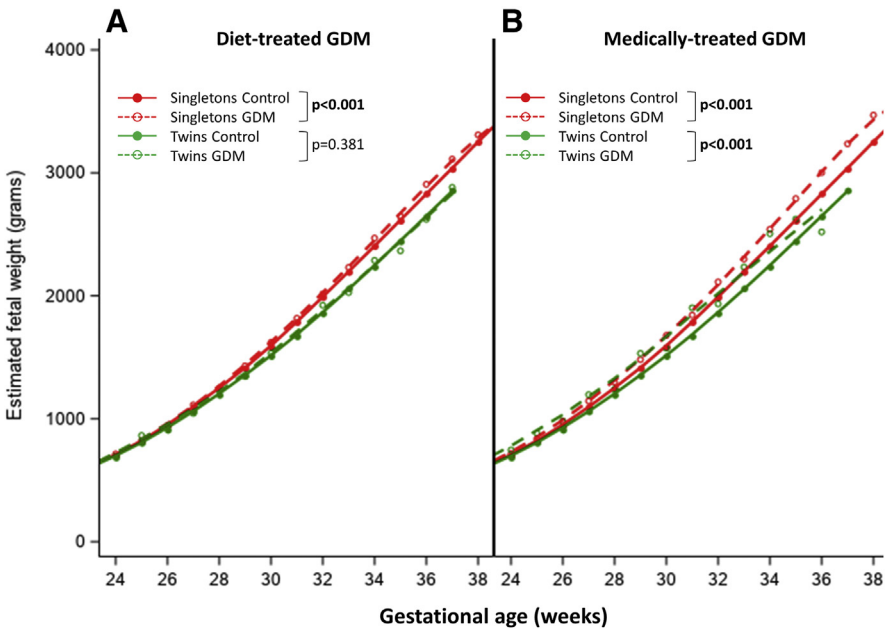
Gestational diabetes mellitus and fetal weight in twin and singleton pregnancies

Figure 2 presents the mean estimated fetal weight as a function of gestational age in the 4 groups. In singleton pregnancies, the estimated fetal weight in pregnancies with GDM was significantly higher than in pregnancies without GDM (*P*<.001) starting at approximately 30 weeks of gestation. The differences remained similar after adjusting for maternal age, chronic hypertension, nulliparity, and neonatal sex (*P*<.001). In twin pregnancies, fetal growth was similar between pregnancies with and without GDM (*P*=.105 and *P*=.483 for unadjusted and adjusted models, respectively). The mean values of estimated fetal weight at each gestational week with 95% CI are provided in Supplemental Table. In twin pregnancies, the findings remained similar when the analysis was stratified by chorionicity or by twin order (presenting vs nonpresenting twin) (Supplemental Figure).

Here, we stratified the analysis by type of treatment, which we used as a proxy for the severity of GDM (Figure 3). The differences between the group with GDM managed with diet and control group were similar to those observed in the overall cohort: they were significant in singleton pregnancies (*P*<.001) but nonsignificant for twin pregnancies (*P*=.381) (Figure 3, A). However, the differences between the group with GDM treated medically and control group were observed in both singleton and twin pregnancies (*P*<.001) (Figure 3, B), although it should be noted that the number of women with medically treated GDM in the twin group was small (n=21).

FIGURE 3
Fetal weight as a functional of gestational age—stratified by type of treatment of GDM



Mean fetal weight as a function of gestational age stratified by diet-treated (**A**) and medically treated (**B**) GDM is presented for women with singleton pregnancies without GDM (*solid red line*) and with GDM (*dashed red line*) and for women with twin pregnancies without GDM (*solid green line*) and with GDM (*dashed green line*). The differences between the GDM and control groups were assessed using a generalized linear model.

GDM, gestational diabetes mellitus.

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The analyses described above were focused on the mean of estimated fetal weight and thus do not provide information on the effect of GDM across the whole spectrum of estimated fetal weight percentiles. Therefore, we compared the distribution of estimated fetal weight percentiles between pregnancies with and without GDM in the singleton and twin groups (Figure 4). In the singleton group, GDM was associated with a right shift of the distribution curve, so that pregnancies with GDM had a lower proportion of small fetuses (at <20th and 20−39th percentile) and a higher proportion of large fetuses (at 60−79th and ≥80th percentile), compared with pregnancies with GDM (Figure 4, A). In the twin group, the distribution curves of pregnancies with and without GDM were similar, and there was no evidence of a right shift of the distribution curve in pregnancies with GDM as was evident in singleton pregnancies (Figure 4, B). The only significant difference in the twin group between pregnancies with and with GDM was in the lowest category of fetal weight percentile ($P = .012$), where GDM in pregnancy was associated with a lower proportion of fetuses with an estimated weight of <20th percentile (Figure 4, B).

Gestational diabetes mellitus and fetal individual biometric indices in twin and singleton pregnancies

Finally, we compared the mean values of the individual biometric indices as a function of gestational age in women with vs without GDM in singleton and twin pregnancies (Figure 5). The mean HC, AC, and FL were higher in women with GDM than in women without GDM in singleton pregnancies but not in twin pregnancies (Figure 5). Similarly, the HC-to-AC ratio, a measure of asymmetric growth, was lower in women with GDM than in women without GDM in singleton pregnancies but not in twin pregnancies (Figure 5).

Comment

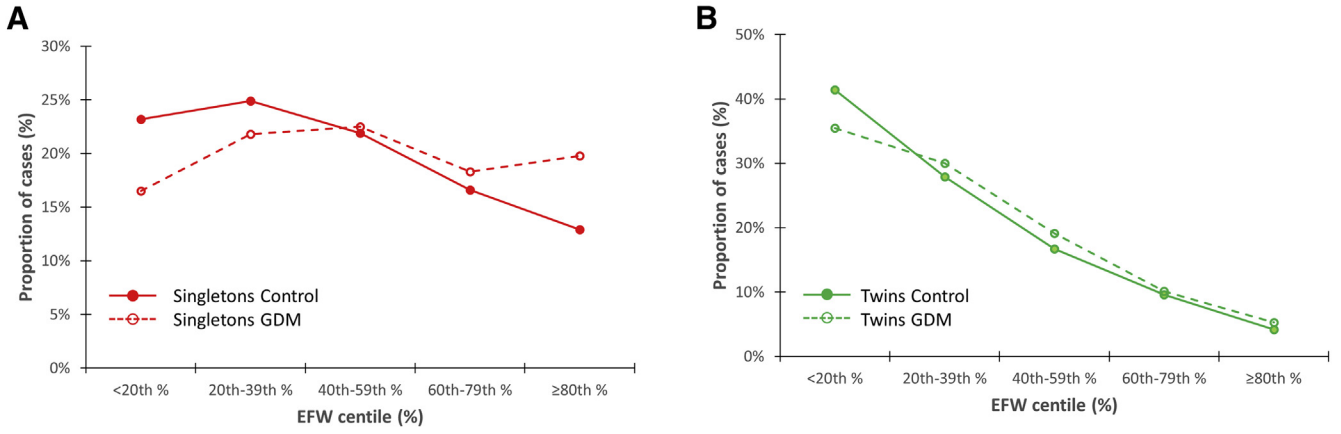
Principal findings of the study

Here, we aimed to evaluate the association of GDM with longitudinal fetal growth in twin pregnancies compared with that in singleton pregnancies. In line with our hypothesis, although GDM in singleton pregnancies was clearly associated with accelerated fetal growth (as reflected by a higher mean fetal weight, a right shift of the distribution curve of estimated fetal weight percentiles, higher mean values of individual biometric indices, and asymmetric fetal growth), such an association in twin pregnancies was only observed in the small subgroup of women with medically treated GDM. In addition, GDM in twin pregnancies was associated with a reduction in the proportion of small fetuses (<20th percentile) without the concomitant increase in the proportion of large fetuses that was observed in singleton pregnancies.

Results in the context of other observations

The association of GDM with accelerated fetal growth and macrosomia in singleton pregnancies is well established.[4−6,8,39,40] In contrast, data on the effects of GDM on fetal growth in twin pregnancies are limited and conflicting. Although several studies in twin pregnancies found no significant difference in the mean birthweight and the rate of LGA neonates between women with GDM and controls,[18,21,22,25] other studies reported that GDM in pregnancy is associated with an increased risk of asymmetric fetal growth.[14,15] One possible reason for these conflicting results is that nearly all studies used birthweight as the measure of fetal growth. The main drawback of using birthweight for that purpose is that the distribution of birthweight at a given gestational week may be subject to the confounding effect of factors, such as preterm birth and provider-initiated deliveries. For example, as women with

FIGURE 4
Distribution of fetal weight percentile in pregnancies with and without GDM



N Control	4933	5279	4654	3528	2740
N GDM	508	670	693	562	608
p-value	**<0.001**	**<0.001**	0.432	**0.021**	**<0.001**

N Control	1700	1145	685	394	171
N GDM	173	146	93	49	26
p-value	**0.012**	0.338	0.183	0.747	0.228

The distribution of fetal weight percentile in singleton (**A**) and twin (**B**) pregnancies is compared between women with GDM (*dashed lines*) and without GDM (*solid lines*). Fetal weight percentiles were based on the Hadlock 1991 standard. The differences between the GDM and control groups were assessed using the chi-square test and Fisher exact test, as appropriate. Adapted from Hadlock et al.[31]

EFW, estimated fetal weight; *GDM*, gestational diabetes mellitus.

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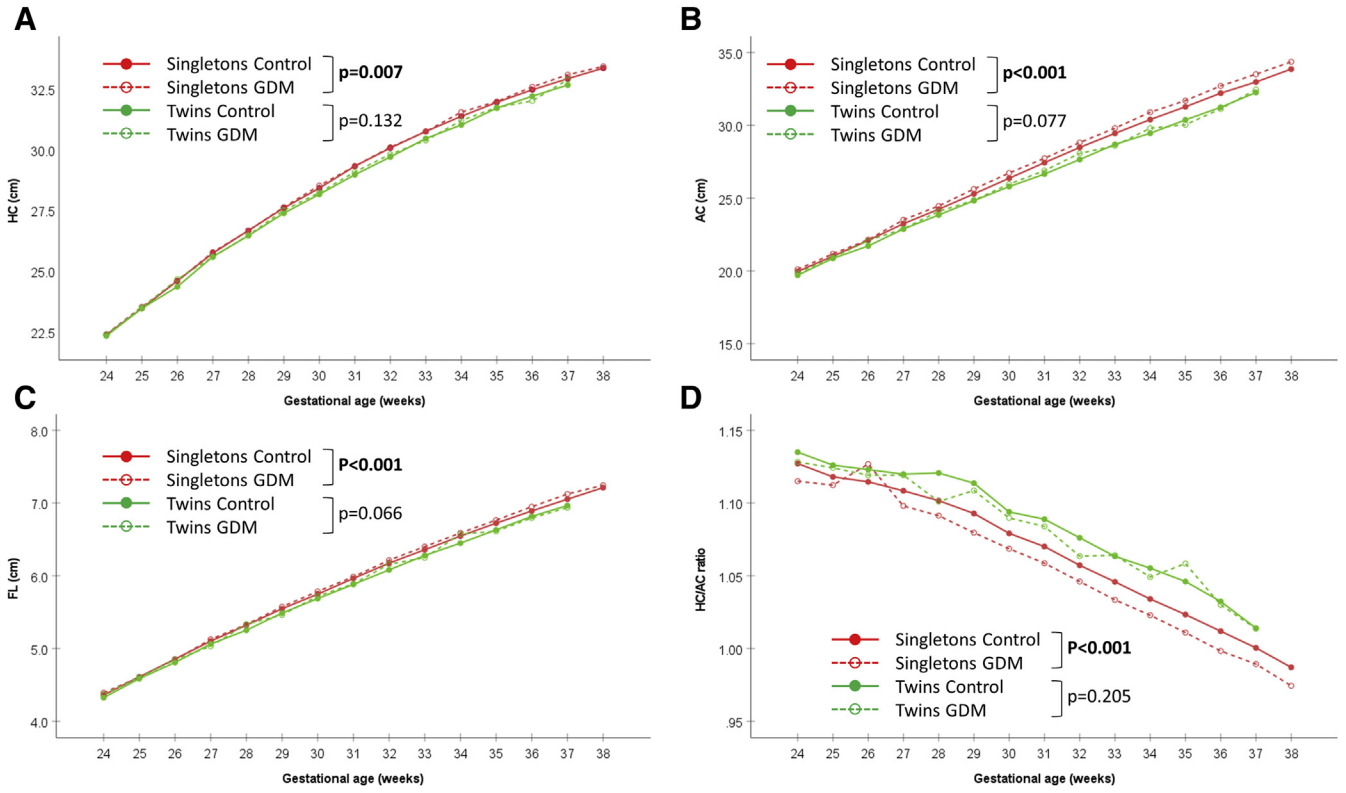
GDM are more likely to undergo labor induction at 37 to 38 weeks of gestation, especially in the presence of suspected LGA fetus,[41] the distribution of birthweight in these weeks may be biased toward a higher mean birthweight in pregnancies with GDM compared with pregnancies without. In addition, as infants born prematurely are more likely to be affected by placental dysfunction and growth restriction,[42–49] the use of birthweight of infants born before 37 weeks of gestation as a measure of fetal growth would result in underestimation of the "real" fetal growth and may thus not reflect the effect of GDM on fetal growth at this period of gestation. For these reasons, in our study, we chose to assess longitudinal sonographic fetal growth, which is more likely to reflect the true effect of GDM on fetal growth in twin and singleton pregnancies throughout gestation.

We found that mild (diet-treated) GDM was associated with accelerated asymmetric fetal growth in singleton pregnancies but not in twin pregnancies. Here, we have suggested 2 possible explanations for this observation. First, the effect of mildly elevated serum glucose levels (seen in cases of mild GDM) on fetal growth in twin pregnancies may be masked by factors that are responsible for the slower growth of twin fetuses during the third trimester of pregnancy.[9–13,50–52] Several mechanisms have been suggested for the slower growth of twin fetuses, including constraints imposed by uterine size,[53,54] the limited ability of the placenta to support the nutritional requirements of 2 fetuses late in gestation,[8,30] and programming in early gestation through hormonal[55,56] and epigenetic[57] processes. Therefore, the predetermined restricted growth of twin fetuses may counteract the effects of mild hyperglycemia on fetal growth, an effect that would be evident only in cases of severe and poorly controlled diabetes mellitus. This explanation is supported by previous reports where the infants' birthweight in pregnancies with GDM was related to measures of glycemic control in singleton pregnancies but not in twin pregnancies.[22,58] Furthermore, it has been suggested that the mild increase in serum glucose that is associated with mild GDM may have a beneficial role in twin pregnancies and may decrease the risk of FGR,[16,17] which is in agreement with our findings of a lower proportion of small fetuses (<20th percentile) in pregnancies with GDM compared with that in pregnancies without GDM.

The second possible explanation for our findings is that GDM in twin pregnancies may be milder and easier to control with dietary intervention than GDM in singleton pregnancies. The pathogenesis of GDM involves failure of the maternal pancreas to compensate for the physiological increase in insulin resistance during pregnancy, most likely because of the underlying maternal subclinical beta-cell dysfunction,[59,60] which explains the association of GDM with future risk of maternal type 2 diabetes mellitus.[61,62] Because of a greater increase in insulin resistance in the presence of a greater placental mass and higher levels of placental diabetic hormones,[63,28] it is likely that women with twin pregnancies with a milder degree of beta-cell dysfunction than women with

FIGURE 5
Biometric indices as a functional of gestational age



Mean values of HC (**A**), AC (**B**), FL (**C**), and HC-to-AC ratio (**D**) are presented for women with singleton pregnancies without GDM (*solid red line*) and with GDM (*dashed red line*) and for women with twin pregnancies without GDM (*solid green line*) and with GDM (*dashed green line*). The differences between the GDM and control groups were assessed using a generalized linear model.

AC, abdominal circumference; *FL*, femur length; *GDM*, gestational diabetes mellitus; *HC*, head circumference; *HC-to-AC*, head circumference—to—abdominal circumference ratio.

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singleton pregnancies may be diagnosed with GDM, women in whom dietary intervention may be more effective in controlling serum glucose levels. Therefore, although all women with GDM in the current study were treated, the differences in the pathophysiology of GDM in twin pregnancies, along with the increased utilization of serum glucose in the presence of 2 fetuses, may have made it easier to achieve optimal glycemic control of GDM in twin pregnancies compared with singleton pregnancies. In fact, previous studies found that women with GDM with twin pregnancies were less likely to require insulin than women with GDM with singleton pregnancies[22] and that the higher incidence of GDM in twin pregnancies is limited to cases of mild, diet-treated GDM.[27,64] Further studies are needed to support this explanation by comparing the degree of glycemic control of GDM between twin and singleton pregnancies.

Strengths and limitations

The main strengths of our study were the large cohort of women who were followed up in a single tertiary center and managed according to a standardized protocol and the use of longitudinal assessment of fetal growth rather than birthweight. Another strength of our study was the inclusion of a comparison group of women with singleton pregnancies with and without GDM, which allowed us to directly compare the association of GDM and fetal growth in twins with that observed in singletons.

Our study has several limitations. All women with GDM in our study were monitored and treated so that the true effect of untreated GDM on fetal growth cannot be evaluated. However, because prospective studies of women with untreated GDM are unlikely to be carried out for ethical reasons, studies involving women with treated GDM may be the only source of data on the effect of GDM on fetal growth. Because of the retrospective design, information on several potentially confounding variables, such as parental race, maternal body mass index, and gestational weight gain, was not available, and thus, residual confounding cannot be ruled out. We recognized that the singleton control group may be biased as women in this group may have been more likely to undergo ultrasound when there were concerns about fetal growth. However, the fact that the mean fetal growth in this group was nearly identical to the 50th

percentile of the ultrasound-based standard of Hadlock et al[31] suggested that such bias, if present, was of minor significance. Another limitation was related to the potential error associated with sonographic fetal weight estimation. Lastly, our findings, which represented population-based parameters, did not necessarily reflect the growth pattern for an individual fetus.

Conclusion

We found that, in contrast to singleton pregnancies, GDM in twin pregnancies was less likely to be associated with accelerated fetal growth. In addition, GDM in twin pregnancies was associated with an isolated reduction in the proportion of small fetuses and thus may have a potential beneficial effect on twin fetuses. These findings, along with previous reports that GDM in twin pregnancies is less likely to be associated with adverse outcomes than GDM in singleton pregnancies[14,15,20,21,23] and that treatment of GDM in twin pregnancies does not improve outcomes and may increase the risk of FGR,[16] have raised the question of whether the diagnostic criteria for GDM and the blood glucose targets in women with GDM should be individualized for twin pregnancies. Further prospective outcome-based studies are needed to address this question. ■

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Author and article information

From the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Tel Aviv Sourasky Medical Center, Lis Maternity Hospital, Tel Aviv University, Tel Aviv, Israel (Drs Ashwal and Hiersch); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Saint Michaels Hospital, Toronto, Ontario, Canada (Dr Berger); Maternal-Infant Care (MiCare) Research Centre, Mount Sinai Hospital, Toronto, Ontario, Canada (Mr Yoon); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (Drs Zaltz, Barrett, and Melamed); Department of Medicine and Institute for Health Policy, Evaluative Clinical Sciences, Management and Evaluation, Sunnybrook Research Institute (Dr Shah); Division of Endocrinology, Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada (Dr Shah); and Department of Endocrinology, Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada (Dr Halperin).

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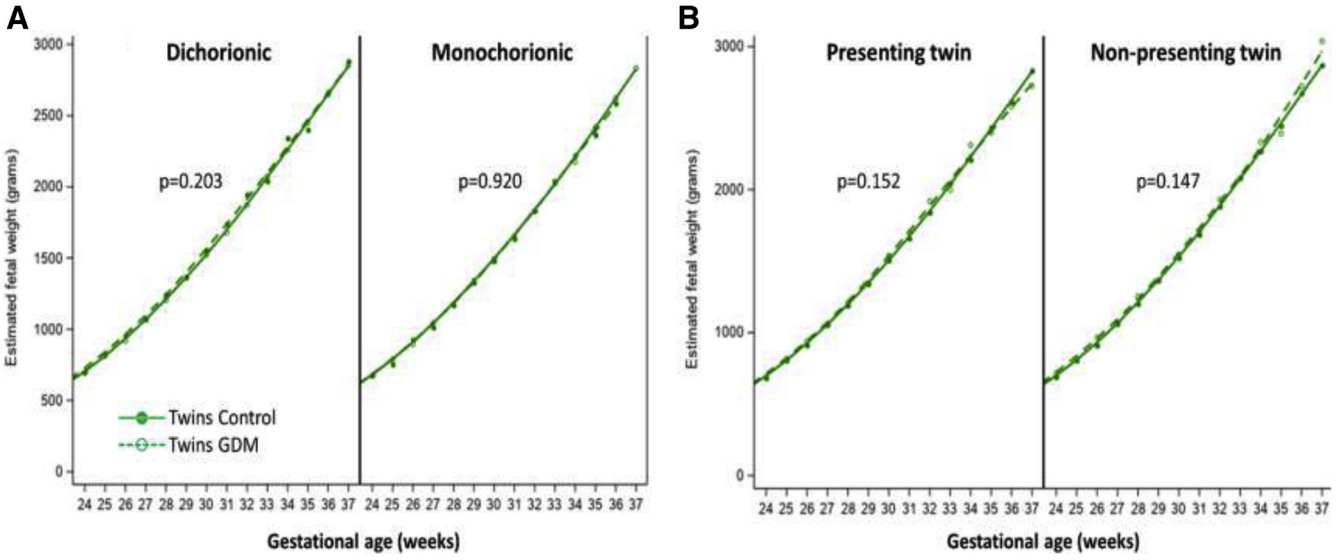
Corresponding author: Eran Ashwal, MD. eran.ashwal@gmail.com

SUPPLEMENTAL FIGURE

Mean fetal weight as a functional of gestational age in the twin groups—stratified by chorionicity and twin order



The mean fetal weight as a function of gestational age in women with twin pregnancies without GDM (*solid green line*) and with GDM (*dashed green line*) is stratified by chorionicity (**A**) and twin order (**B**). The differences between the GDM and control groups were assessed using a generalized linear model.

GDM, gestational diabetes mellitus.

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SUPPLEMENTAL TABLE

Mean fetal weight by gestational age in the 4 groups

Gestational age (wk)	Twin (GDM)				Twin (control)				Singleton (GDM)				Singleton (control)			
			95% CI (g)				95% CI (g)				95% CI (g)				95% CI (g)	
	n	Mean (gr)	Lower	Upper	n	Mean (gr)	Lower	Upper	n	Mean (gr)	Lower	Upper	n	Mean (gr)	Lower	Upper
14	18	106	101	111	149	102	100	104	14	104	97	111	186	105	103	107
15	14	132	127	137	232	147	125	173	34	128	122	134	380	130	128	131
16	58	165	159	171	436	160	158	162	56	168	158	179	552	165	157	173
17	18	186	175	198	269	197	194	199	45	219	187	256	385	202	200	205
18	33	242	232	252	453	248	245	250	124	256	250	262	1750	256	253	258
19	74	304	296	313	677	300	296	305	361	299	293	305	5463	300	299	302
20	45	372	355	390	395	354	344	363	140	366	343	391	2322	351	349	353
21	57	413	399	426	444	438	433	443	74	439	409	472	853	433	421	446
22	67	515	500	530	636	511	501	522	106	516	505	528	970	516	510	522
23	115	607	595	620	722	599	594	604	144	613	601	625	1407	606	602	611
24	90	700	684	717	973	687	681	692	167	715	703	727	1771	704	700	708
25	115	865	770	972	796	806	799	813	158	826	807	845	1509	817	812	823
26	111	947	924	970	942	912	905	919	214	949	933	966	1812	946	940	952
27	123	1056	1033	1080	864	1061	1053	1069	204	1122	1103	1142	2279	1100	1094	1105
28	128	1230	1203	1257	1004	1196	1186	1206	325	1262	1245	1280	3053	1245	1239	1250
29	121	1353	1322	1386	990	1353	1342	1364	293	1445	1425	1465	2571	1414	1407	1422
30	134	1537	1503	1572	1051	1512	1500	1524	386	1636	1617	1655	3195	1587	1581	1594
31	105	1701	1658	1745	933	1673	1659	1686	406	1824	1801	1846	3231	1787	1780	1795
32	126	1924	1884	1965	1029	1858	1843	1873	511	2043	2021	2065	4096	1991	1984	1998
33	106	2038	1995	2082	911	2062	2045	2079	459	2248	2222	2275	3768	2195	2186	2204
34	116	2321	2269	2375	858	2236	2217	2256	541	2489	2461	2517	3779	2406	2396	2416
35	68	2396	2338	2455	670	2444	2420	2467	500	2687	2656	2718	3337	2612	2601	2624
36	65	2612	2524	2703	468	2646	2620	2672	575	2931	2900	2962	3445	2833	2821	2846
37	6	2881	2706	3068	157	2858	2807	2910	434	3147	3109	3185	2514	3033	3018	3049

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(continued)

SUPPLEMENTAL TABLE
Mean fetal weight by gestational age in the 4 groups *(continued)*

Gestational age (wk)	Twin (GDM)				Twin (control)				Singleton (GDM)				Singleton (control)			
			95% CI (g)				95% CI (g)				95% CI (g)				95% CI (g)	
	n	Mean (gr)	Lower	Upper	n	Mean (gr)	Lower	Upper	n	Mean (gr)	Lower	Upper	n	Mean (gr)	Lower	Upper
38	0								296	3346	3300	3392	1854	3252	3233	3272
39	0								96	3489	3415	3565	1194	3470	3445	3496
40	0								26	3591	3474	3712	849	3649	3621	3678

GDM, gestational diabetes mellitus.

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