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Timing of treatment initiation for mild gestational diabetes and perinatal outcomes

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Abstract

Objective—To examine the association between gestational age (GA) at the time of treatment initiation for gestational diabetes (GDM) and maternal and perinatal outcomes.

Study Design—A secondary analysis of a multicenter randomized treatment trial of mild GDM in which women with mild GDM were randomized to treatment versus usual care. The primary outcome of the original trial, as well as this analysis, was a composite perinatal adverse outcome that included neonatal hypoglycemia, hyperbilirubinemia, hyperinsulinemia, and perinatal mortality. Other outcomes examined included the frequency of large for gestational age (LGA), birth weight, neonatal intensive care unit admission (NICU), gestational hypertension / preeclampsia and cesarean delivery. The interaction between GA at treatment initiation (stratified as 24-26 weeks, 27 weeks, 28 weeks, 29 weeks, ≥30 weeks) and treatment group (treated vs.

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Timing of treatment initiation for mild GDM: Earlier initiation of treatment of mild GDM was not associated with a stronger effect of treatment on maternal or perinatal outcomes.

routine care), with the outcomes of interest, was used to determine whether GA at treatment initiation was associated with outcome differences.

Results—Of 958 women analyzed, those who initiated treatment at an earlier GA did not gain an additional treatment benefit compared to those who initiated treatment at a later GA (p-value for interaction with the primary outcome is 0.44). Similarly, there was no evidence that other outcomes were significantly improved by earlier initiation of GDM treatment (LGA p=0.76; NICU admission p=0.8; cesarean delivery p=0.82). The only outcome that had a significant interaction between GA and treatment was gestational hypertension/preeclampsia (p=0.04), although there was not a clear cut GA trend where this outcome improved with treatment.

Conclusion—Earlier initiation of treatment of mild GDM was not associated with stronger effect of treatment on perinatal outcomes.

Keywords

Gestational age; Gestational diabetes; Obstetric outcomes

High-quality evidence now exists regarding the association of maternal hyperglycemia with adverse perinatal outcomes, and that these outcomes may be improved with the treatment of mild GDM.[1-3] However, international consensus is still lacking on optimal screening and diagnostic guidelines.

In the United States, pregnant women undergo universal screening and a two-step approach for GDM diagnosis.[4-5] This approach involves performing a 50-gram glucose challenge test (GCT), followed by an oral 100-gram glucose tolerance test (OGTT) when the GCT results are beyond a certain threshold. The optimal time to perform these tests remains uncertain and may differ depending on the population screened.[6-12] Currently, ACOG recommends screening women without risk factors for GDM between 24 and 28 weeks of gestation.[13] However, when the screening, and subsequent diagnostic testing, is done at the end of this range, the interval from subsequent therapeutic intervention to delivery is obviously shorter than with earlier testing and diagnosis. We hypothesized that earlier diagnosis, and a corresponding longer period of treatment, would result in improved outcomes compared to later diagnosis and treatment, after controlling for clinical covariates. Therefore, the objective of this analysis was to examine whether earlier initiation of screening and subsequently treatment of mild GDM can lead to improved maternal and perinatal outcomes.

Materials and Methods

This was a secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network randomized GDM treatment trial.[3] The trial was designed to determine whether treatment of mild GDM reduces perinatal and obstetrical complications. Pregnant women between 24 weeks 0 days and 30 weeks 6 days gestation were screened for GDM with a 50-g GCT and those with a 1-hour blood glucose value between 135-200 mg/dL underwent a 3-hour OGTT. Ultrasonography was performed on all subjects before the OGTT to confirm the gestational age. Samples for the OGTT were analyzed at a central laboratory. Mild GDM was defined as a fasting blood glucose level of less than 95 mg/dL and ≥ 2 post-challenge

glucose above the following thresholds: 1-hour>180 mg/dL, 2-hour >155 mg/dL, 3-hour >140 mg/dL.[14] Women who met these criteria were randomized to treatment that included nutritional counseling, diet therapy, and, if required, insulin versus usual prenatal care. The details of the study protocol have been previously reported.[3] All women with mild GDM who participated in the parent study and who had complete maternal and perinatal outcome data were eligible for this analysis. Each center's institutional review board approved the study protocol.

The aim of this analysis was to determine whether there is an association between gestational age at the time of treatment initiation for GDM and perinatal outcomes. The primary outcome was a composite outcome that included perinatal mortality and complications that have been associated with maternal hyperglycemia: neonatal hypoglycemia, defined as a glucose value of less than 35mg/dl; hyperbilirubinemia, defined as bilirubin value greater than the 95th percentile for any given point after birth; hyperinsulinemia, defined as a cord-blood C-peptide level greater than the 95th percentile and birth trauma, defined as brachial plexus palsy or clavicular, humeral, or skull fracture. This was the same as the primary outcome of the original trial. Secondary outcomes were pre-specified in the original trial and included: occurrence of large size for gestational age (LGA; defined as birth weight above the 90th percentile of a U.S. reference population[15]), neonatal intensive care unit (NICU) admission, gestational hypertension / preeclampsia and cesarean delivery. Shoulder dystocia was not included in the analysis as there were only 25 cases. Trained study personnel collected antepartum, intrapartum, and post delivery data for enrolled women and their newborns at the time of discharge from the hospital. All cases of hypertensive disorders underwent masked central review by two of the investigators to ensure accurate diagnosis.

Women were stratified by 5 categories of GA at the time of treatment randomization (24-26 weeks, 27 weeks, 28 weeks, 29 weeks, ≥30 weeks). The decision to select gestational age at the time of treatment initiation compared to gestational age at the time of GDM diagnosis was made to avoid bias for unaccounted time lag that may have occurred between a positive GCT and OGTT performance, as well as between positive OGTT and treatment initiation. Univariable analysis was performed to compare demographic characteristics of patients by GA group, using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. To examine whether GA at treatment initiation had an impact on the treatment effect, the interaction between GA category and treatment group (treated vs. routine care) with the outcomes of interest was examined using the Breslow-Day test for homogeneity. We examined the interaction between GA category and treatment group with birth weight Z-scores based on a gender- and ethnicity-specific U.S. reference population,[15] using analysis of variance. Additionally, regression analysis was performed to examine the interaction between GA category and treatment group for the outcomes of interest and adjust for the potential confounding effect of race/ethnicity. No adjustments were made for multiple comparisons. Statistical analysis was conducted with SAS software (SAS Institute Inc, Cary, NC).

Results

Of 19,665 women who had abnormal result on a glucose loading test, 7,298 women underwent 3-h OGTT. After exclusion of women with OGTT fasting values above 95 mg/dl, 958 women randomized, 485 were allocated to the treatment group and 473 to the control group.. Full outcomes were available for 477 women in the treatment group and 455 women in the control group (Figure 1).

Maternal characteristics of the study population stratified by gestational age group at the time of treatment are depicted in Table 1. Women in each gestational age group differed only according to race and ethnicity. Specifically, black and Hispanic women were randomized to treatment or usual care at an earlier GA. There were no significant differences in maternal BMI, GCT and OGTT results between the GA groups.

Table 2 and Figure 2 describe perinatal and maternal outcomes stratified by gestational age and treatment group. There was no significant interaction between the GA and treatment group with respect to the primary and most of the secondary outcomes. The only significant interaction between GA and treatment was for gestational hypertension / preeclampsia ($p=0.04$). However, there was not a clear GA trend where this outcome improved with treatment. In order to control for potentially confounding effects of race, we performed logistic regression analysis that included race/ethnicity in the model, as well as treatment group, gestational age at randomization and an interaction term between treatment group and gestational age. The p-values for each of the outcomes were similar to p-values reported in Table 2 (data not shown). Similarly, additional analysis stratifying women by two groups of GA, 24-26 weeks and 27-29 weeks (with the ≥ 30 week group excluded due to much smaller window for therapeutic intervention), in order to enlarge the sample size of each GA group, showed that there were no significant interactions between GA and treatment groups with the outcomes of interest (Table 3). Birth weight Z-scores based on a U.S. reference population were also examined and there was no significant interaction between GA and treatment group for this outcome (p-value of 0.86 for the interaction of gestational age and treatment group,Table 4).

Comment

In this study we found that earlier initiation of treatment for mild GDM was not associated with a stronger effect of treatment on perinatal outcomes. Specifically, women who started treatment earlier had no difference in the composite primary outcome that included perinatal mortality, hypoglycemia, hyperbilirubinemia, neonatal hyperinsulinemia and birth trauma compared to women who started treatment later in gestation. Similarly, there was no evidence that other secondary outcomes (LGA, cesarean delivery and NICU admission) significantly improved with earlier initiation of treatment.

The optimal time in gestation for GDM screening remains uncertain. The current evidence is insufficient to support screening before 24 weeks of gestation in low risk women.[16] Furthermore, because the sensitivity to insulin decreases as pregnancy progresses,[17] the GA range of 24-28 weeks is considered to be optimal for GDM screening. This interval is thought to balance the sensitivity at detecting women who will have GDM and the time

needed to affect GDM-related adverse outcomes through treatment. Nevertheless, it is possible that when women undergo screening toward the upper GA limit of that range the benefit of treatment is less.

Indeed, there is good evidence that many of the risks related to GDM may be reduced with treatment. The ACHOIS trial demonstrated a reduction in the composite outcome of perinatal death, shoulder dystocia and birth trauma, as well as in the secondary outcomes of LGA, macrosomia and preeclampsia.[2] The MFMU Network's GDM trial also demonstrated a decrease in frequency of the same secondary outcomes, as well as a reduction in neonatal fat mass with GDM treatment.[3] Notably, in both of these trials, mean GA at the time of randomization and treatment initiation was approximately 29 weeks. The hypothesis for our analysis was that earlier treatment initiation may improve perinatal outcomes of pregnancies complicated by mild GDM. However we did not find an association between earlier treatment and enhanced benefit, suggesting that treatment initiation even at the later end of the typical GA window is still early enough to make improved outcomes more likely. These data, however, shouldn't be construed as supporting delaying institution of therapy in those women who happened to be diagnosed at the early end of the GA screening range.

The strengths of this study include a large sample size, the randomized design, prospective data collection by trained study personnel, and pre-specified well-ascertained outcomes. On the other hand, this was an unplanned secondary analysis and thus has limitations that should be noted. Although significant interactions with clinically meaningful trends were not observed, a type II error remains possible. Moreover, we cannot entirely exclude selection bias for those women who were screened earlier by their provider. Finally, our findings apply only to those women who were diagnosed with mild GDM, since that was the inclusion criterion in the original trial. In the original trial, only 7 percent of women diagnosed with mild GDM required insulin. Thus, our findings may not be applicable to women with more severe forms of GDM. There may be a benefit for earlier diagnosis and treatment in these women.

In conclusion, earlier initiation of treatment of mild GDM within the recommended GA range for screening was not associated with stronger effect of treatment on perinatal outcomes. It remains to be determined whether the timing of treatment initiation among women with mild GDM could have differential effects on other outcomes, such as the long-term risk of obesity in the mother or metabolic syndrome and diabetes mellitus in the offspring.

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Appendix

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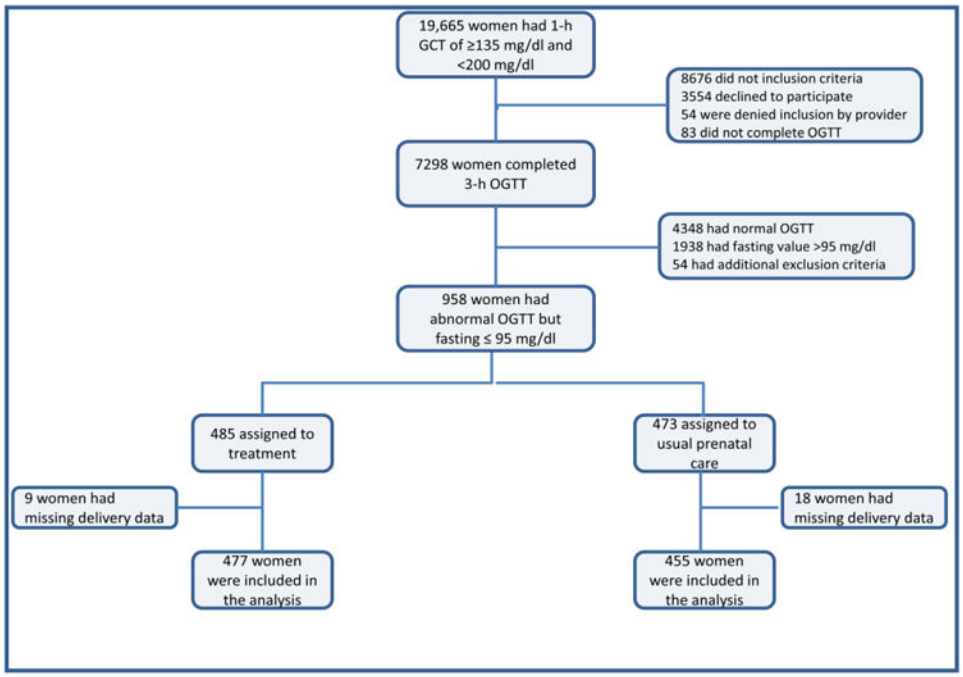

Figure 1. Screening, enrollement and random assignment to study group

GCT- glucose tolerance test

OGTT- oral glucose tolerance test

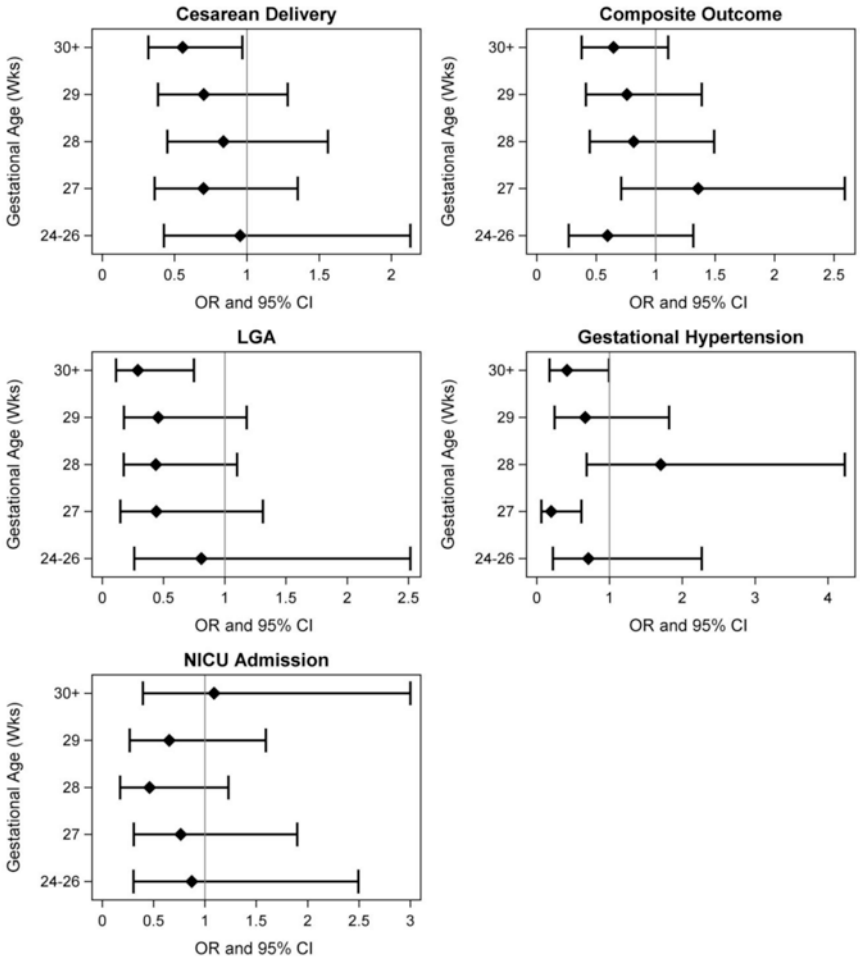

Figure 2.

Plost for Odds ratio and 95% Confidence Intervals for treatment versus control group by gestational age at rendomization for the outcomes of interest.

Table 1

Maternal demographic and baseline characteristics

Gestational age at initiation of treatment (wk)	24-26 N=116	27 N=170	28 N=193	29 N=221	30+ N=258	Total N=958	P-value
Maternal age (y)	28.7 ± 5.5	29.0 ± 5.6	29.1 ± 5.5	29.2 ± 5.9	29.2 ± 5.6	29.0 ± 5.6	0.91
Race/Ethnicity							<0.001
Black	16 (13.8)	22 (12.9)	16 (8.3)	25 (11.3)	31 (12.0)	110 (11.5)	
Hispanic	81 (69.8)	112 (65.9)	126 (65.3)	111 (50.2)	116 (45.0)	546 (57.0)	
White	16 (13.8)	26 (15.3)	40 (20.7)	74 (33.5)	86 (33.3)	242 (25.3)	
Other	3 (2.6%)	10 (5.9)	11 (5.7)	11 (5.0)	25 (9.7)	60 (6.3)	
Body-mass index at entry (kg/m^2)	30.0 ± 4.8	31.0 ± 5.5	30.4 ± 5.2	29.9 ± 4.7	29.7 ± 5.0	30.1 ± 5.1	0.23
Nulliparity	33 (28.5)	52 (30.6)	72 (37.3)	66 (29.9)	83 (32.2)	306 (31.9)	0.43
Alcohol use	1 (0.9)	4 (2.4)	6 (3.1)	13 (5.9)	10 (3.9)	34 (3.6)	0.14
Tobacco use	8 (6.9)	11 (6.5)	13 (6.7)	16 (7.2)	21 (8.1)	69 (7.2)	0.97
50g 1-hr oral glucose load (mg/dL)	158.9 ± 15.4	158.9 ± 15.3	158.4 ± 15.3	160.2 ± 15.5	159.8 ± 15.5	159.4 ± 15.4	0.74
100g 3-hr OGTT (mg/dL)							
Fasting	87.2 ± 5.9	86.3 ± 5.7	86.4 ± 5.6	85.7 ± 6.1	86.8 ± 5.4	86.4 ± 5.7	0.15
1 hr	194.1 ± 21.2	194.4 ± 18.7	190.9 ± 23.6	193.5 ± 20.0	191.3 ± 20.0	192.6 ± 20.7	0.33
2 hr	177.2 ± 22.6	173.8 ± 18.6	171.8 ± 19.5	174.0 ± 21.3	172.5 ± 21.4	173.5 ± 20.7	0.42
3 hr	136.2 ± 30.5	131.1 ± 29.3	136.5 ± 30.7	136.3 ± 30.1	137.5 ± 30.5	135.7 ± 30.3	0.16

All data presented as mean ± standard deviation or N (%)

Table 2

Maternal and neonatal outcomes stratified by gestational age at the time of treatment initiation.

	Composite Outcome*		NICU admission		LGA		Cesarean Delivery		Gestational Hypertension/ Preeclampsia	
Gestational age at treatment initiation	Treated N=460**	Usual Care N=440**	Treated N=477	Usual Care N=455	Treated N=477	Usual Care N=454**	Treated N=476**	Usual Care N=455	Treated N=476**	Usual Care N=455
24-26 weeks	25 (37.3)	20 (50.0)	10 (14.5)	7 (16.3)	8 (11.6)	6 (14.0)	23 (33.8)	15 (34.9)	7 (10.3)	6 (14.0)
27 weeks	30 (40.0)	28 (32.9)	9 (11.7)	13 (14.8)	5 (6.5)	12 (13.6)	22 (28.6)	32 (36.4)	4 (5.2)	19 (21.6)
28 weeks	33 (33.7)	33 (38.4)	7 (6.9)	12 (13.8)	8 (7.8)	14 (16.3)	29 (28.4)	28 (32.2)	15 (14.7)	8 (9.2)
29 weeks	27 (25.5)	32 (31.1)	9 (8.3)	13 (12.2)	7 (6.4)	14 (13.1)	26 (23.9)	33 (30.8)	7 (6.4)	10 (9.4)
30+ weeks	34 (29.8)	50 (39.7)	8 (6.7)	8 (6.2)	6 (5.0)	20 (15.4)	28 (23.3)	46 (35.4)	8 (6.7)	19 (14.6)
P-value interaction of gestational age and treatment group	0.44		0.80		0.76		0.82		0.04	

All data presented as N (%)

* Composite outcome included perinatal mortality and complications that have been associated with maternal hyperglycemia: neonatal hypoglycemia, hyperbilirubinemia, hyperinsulinemia, and birth trauma

** Some of the denominators in each outcome are smaller than the N due to missing delivery data

NICU, neonatal intensive care unit; LGA, large for gestational age.

Table 3

Maternal and neonatal outcomes stratified by two groups of gestational age.

	24-26 weeks		27-29 weeks		
	Treated N = 69*	**Usual Care N = 43***	**Treated N = 288***	**Usual Care N = 282***	**P-value For Interaction**
Composite outcome**	25 (37.3)	20 (50.0)	90 (32.3)	93 (33.9)	0.32
NICU admission	10 (14.5)	7 (16.3)	25 (8.7)	38 (13.5)	0.55
LGA	8 (11.6)	6 (14.0)	20 (6.9)	40 (14.2)	0.36
Cesarean Delivery	23 (33.8)	15 (34.9)	77 (26.7)	93 (33.0)	0.57
Gestational hypertension/Preeclampsia	7 (10.3)	6 (14.0)	26 (9.0)	37 (13.1)	0.91

All data presented as N (%)

* Some of the denominators in each outcome are smaller than the N due to missing delivery data

** Included perinatal mortality and complications that have been associated with maternal hyperglycemia: neonatal hypoglycemia, hyperbilirubinemia, hyperinsulinemia, and birth trauma

NICU, neonatal intensive care unit; LGA, large for gestational age.

Table 4

Birth Weight Percentiles stratified by gestational age at the time of treatment initiation

Gestational age at randomization	Treated N=477	Usual Care N=454
24-26 weeks	52.4 [34.7, 69.9]	55.7 [37.7, 80.3]
27 weeks	53.7 [38.9, 71.5]	61.8 [37.7, 79.5]
28 weeks	49.7 [29.7, 69.4]	64.8 [41.9, 84.5]
29 weeks	49,9 [33.9, 70.3]	57.9 [36.1, 80.1]
30+ weeks	45.6 [30.1, 68.7]	57.8 [33.4, 78.2]
P-value interaction of gestational age and treatment group for Birth weight percentile Z-score	0.86	

Numbers are presented as median and inter-quartile ranges