ORIGINAL ARTICLE

Treatment of Gestational Diabetes Mellitus Diagnosed Early in Pregnancy

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ABSTRACT

BACKGROUND

Whether treatment of gestational diabetes before 20 weeks' gestation improves maternal and infant health is unclear.

METHODS

We randomly assigned, in a 1:1 ratio, women between 4 weeks' and 19 weeks 6 days' gestation who had a risk factor for hyperglycemia and a diagnosis of gestational diabetes (World Health Organization 2013 criteria) to receive immediate treatment for gestational diabetes or deferred or no treatment, depending on the results of a repeat oral glucose-tolerance test [OGTT] at 24 to 28 weeks' gestation (control). The trial included three primary outcomes: a composite of adverse neonatal outcomes (birth at <37 weeks' gestation, birth trauma, birth weight of ≥4500 g, respiratory distress, phototherapy, stillbirth or neonatal death, or shoulder dystocia), pregnancy-related hypertension (preeclampsia, eclampsia, or gestational hypertension), and neonatal lean body mass.

RESULTS

A total of 802 women underwent randomization; 406 were assigned to the immediate-treatment group and 396 to the control group; follow-up data were available for 793 women (98.9%). An initial OGTT was performed at a mean (±SD) gestation of 15.6±2.5 weeks. An adverse neonatal outcome event occurred in 94 of 378 women (24.9%) in the immediate-treatment group and in 113 of 370 women (30.5%) in the control group (adjusted risk difference, −5.6 percentage points; 95% confidence interval [CI], −10.1 to −1.2). Pregnancy-related hypertension occurred in 40 of 378 women (10.6%) in the immediate-treatment group and in 37 of 372 women (9.9%) in the control group (adjusted risk difference, 0.7 percentage points; 95% CI, −1.6 to 2.9). The mean neonatal lean body mass was 2.86 g in the immediate-treatment group and 2.91 g in the control group (adjusted mean difference, −0.04 g; 95% CI, −0.09 to 0.02). No between-group differences were observed with respect to serious adverse events associated with screening and treatment.

CONCLUSIONS

Immediate treatment of gestational diabetes before 20 weeks' gestation led to a modestly lower incidence of a composite of adverse neonatal outcomes than no immediate treatment; no material differences were observed for pregnancy-related hypertension or neonatal lean body mass. (Funded by the National Health and Medical Research Council and others; TOBOGM Australian New Zealand Clinical Trials Registry number, ACTRN12616000924459.)

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Gestational diabetes mellitus, a common pregnancy complication, is associated with increased risks of preeclampsia, obstetrical intervention, large-for-gestational-age neonates, shoulder dystocia, birth trauma, and neonatal hypoglycemia.[1] Screening and treatment for gestational diabetes at 24 to 28 weeks' gestation are now recommended.[2,3] In cohort studies, women with pregnancies complicated by early (<20 weeks' gestation) hyperglycemia showed accelerated fetal growth by 24 to 28 weeks' gestation[4] and had greater perinatal mortality than women who received a diagnosis of gestational diabetes later in pregnancy.[5] Furthermore, a linear relationship has been shown between fasting glucose levels in early pregnancy and adverse pregnancy outcomes.[6,7]

Testing early in pregnancy to exclude undiagnosed diabetes is recommended for women who are at high risk for diabetes.[2] If glucose levels are increased but below values that are diagnostic of diabetes in nonpregnant adults, early gestational diabetes is diagnosed and treated. However, data from randomized, controlled trials that show a benefit from such treatment are lacking. We performed a randomized, controlled trial to assess pregnancy outcomes after treatment for gestational diabetes had been initiated before 20 weeks' gestation, as compared with deferred or no treatment that depended on the results of repeat oral glucose-tolerance testing (OGTT) at 24 to 28 weeks' gestation.

Methods

Trial Design and Oversight

The Treatment of Booking Gestational Diabetes Mellitus (TOBOGM) trial was a multicenter, randomized, controlled trial performed at 17 hospitals in Australia, Austria, Sweden, and India (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). An independent data-monitoring committee reviewed trial safety data. The planned protocol, informed by a pilot study and approved by local ethics committees (Table S2),[8] has been published previously[9] and is available at NEJM.org. The first author vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The trial design is summarized in Figure S1. Neither the funding sources nor the author-affiliated institutions took part in the trial design; the collection, analysis, and interpretation of the data; or the writing of the manuscript or the decision to submit it for publication.

Participants

Women 18 years of age or older with a singleton pregnancy between 4 weeks' and 19 weeks 6 days' gestation and at least one risk factor for hyperglycemia[10] (previous gestational diabetes, body-mass index [the weight in kilograms divided by the square of the height in meters] higher than 30, age ≥40 years, first-degree relative with diabetes, previous macrosomia, polycystic ovary syndrome, or non-European ancestry [Table S3]) were recruited after written informed consent had been obtained. All the women were offered early ultrasonography to estimate gestational age.

A 2-hour 75-g OGTT was performed before 20 weeks' gestation. Women fulfilling World Health Organization (WHO) diagnostic criteria for gestational diabetes[11] (a fasting glucose level of ≥92 mg per deciliter [≥5.1 mmol per liter], a 1-hour glucose level of ≥180 mg per deciliter [≥10.0 mmol per liter], or a 2-hour glucose level of ≥153 mg per deciliter [≥8.5 mmol per liter]) before 20 weeks' gestation were eligible for randomization. Women were excluded if they had known preexisting diabetes, a fasting glucose level of 110 mg per deciliter or greater (≥6.1 mmol per liter) or a 2-hour glucose level of 200 mg per deciliter or greater (≥11.1 mmol per liter), or active medical disorders that local investigators considered to be contraindications to participation. The fasting glucose threshold for exclusion was based on consensus by the investigators for safety reasons.

Randomization

Eligible women were randomly assigned in a 1:1 ratio to receive immediate treatment for gestational diabetes or deferred or no treatment, depending on whether the results of a repeat OGTT performed at 24 to 28 weeks' gestation met WHO criteria for gestational diabetes (control).[11] Randomization was stratified according to hospital site and glycemic range, which was based on the 1.75 and 2.0 odds ratios for adverse pregnancy outcomes at 24 to 28 weeks' gestation, as identified in the Hyperglycemia and Adverse Pregnancy Outcome study.[12,13] Women in the higher glycemic range had a fasting glucose level of 95

to 109 mg per deciliter (5.3 to 6.0 mmol per liter), a 1-hour glucose level of 191 mg per deciliter or greater (≥10.6 mmol per liter), or a 2-hour glucose level of 162 to 199 mg per deciliter (9.0 to 11.0 mmol per liter). Women in the lower glycemic range had a fasting glucose level of 92 to 94 mg per deciliter (5.1 to 5.2 mmol per liter), a 1-hour glucose level of 180 to 190 mg per deciliter (10.0 to 10.5 mmol per liter), or a 2-hour glucose level of 153 to 161 mg per deciliter (8.5 to 8.9 mmol per liter) and did not meet any criteria for the higher range.

Randomization was performed with the use of a central computerized system with a minimization procedure to balance the trial groups according to hospital site and glycemic range by means of an electronic randomizer (Techtonic). To conceal the trial-group assignment from the women in the control group and the treating health care team, some women without early gestational diabetes ("decoys") were randomly assigned in a 2:1 ratio to the same trial procedures (immediate treatment or control). The clinic and trial staff and participants were unaware of the OGTT results. OGTT was not repeated at 24 to 28 weeks' gestation in women with gestational diabetes that was already being managed.

MANAGEMENT OF GESTATIONAL DIABETES

Management included education, dietary advice, and instructions on how to monitor capillary blood glucose levels. Thresholds for the initiation and intensification of pharmacotherapy were consistent with those used in previous randomized, controlled trials.[14,15] Obstetrical management was performed according to local practice. As specified in the protocol, neonates underwent heel-prick blood glucose testing within 1 to 2 hours after birth, and biometric measurements were recorded within 72 hours after birth.[9]

OUTCOMES

The trial had three prespecified primary outcomes. The first primary outcome was a composite of adverse neonatal outcomes: birth before 37 weeks' gestation, birth weight of 4500 g or greater, birth trauma,[16] neonatal respiratory distress (i.e., distress warranting ≥4 hours of respiratory support with supplemental oxygen, continuous positive airway pressure, or intermittent positive-pressure ventilation [or combinations thereof] during the 24 hours after birth), phototherapy, stillbirth or neonatal death, or shoulder dystocia (vaginal birth in which additional obstetrical maneuvers were performed to deliver the fetus after delivery of the head and failed gentle traction). The second primary outcome was pregnancy-related hypertension (a composite of preeclampsia, eclampsia, or gestational hypertension), the incidence of which has been reported to be reduced in randomized, controlled trials of treatment for gestational diabetes[14,15]; women with chronic hypertension were excluded from the analysis of this outcome.[9] The third primary outcome was neonatal lean body mass, as measured with a caliper and calculated with the use of the Catalano equation[17]; the inclusion of this outcome was based on findings from a pilot study that suggested that early treatment might lead to undernutrition.[8]

Prespecified secondary outcomes evaluated in mothers were total gestational weight gain, cesarean delivery, induction of labor, perineal injury,[16] quality of life as measured by the EQ-5D[18] at 24 to 28 weeks' gestation (scores on the EQ-5D range from 0 to 1, with higher scores indicating better quality of life), and maternal hypoglycemia (i.e., hypoglycemia warranting assistance). The secondary outcomes of interest in infants were birth weight, large-for-gestational-age status (above the 90th percentile) and small-for-gestational-age status (below the 10th percentile), as determined according to ethnic group– and sex-adjusted customized percentiles for birth weight [gestation.net]), mean upper-arm circumference, sum of neonatal calipers, neonatal fat mass, severe neonatal hypoglycemia (any heel-prick blood glucose level of <29 mg per deciliter [<1.6 mmol per liter] up to 72 hours after birth), birth heel-prick glucose level of ≤40 mg per deciliter [≤2.2 mmol per liter] at 1 to 2 hours after birth (all mothers were encouraged to breast-feed within 1 hour after birth), and bed days in a neonatal intensive care unit (ICU) or in a special care unit at sites with no or an insufficient number of separate neonatal ICU beds.[9]

STATISTICAL ANALYSIS

Assuming a loss to follow-up of 10%, we estimated that 400 women in each trial group would provide the trial with 80% power to detect a between-group difference of 6 percentage points, at an alpha level of 0.05, with respect to the first

primary outcome (a composite of adverse neonatal outcomes). A gate-keeping procedure for avoiding type I errors was used.[19] If the P value for the comparison with respect to the first primary outcome was less than 0.05, then the trial groups were compared with respect to the second primary outcome (pregnancy-related hypertension). If the P value for the second comparison was less than 0.05, then the trial groups were compared with respect to the third primary outcome (neonatal lean body mass). This approach was adopted after the protocol had been published[9] and registered in the Australian New Zealand Clinical Trials Registry[20] but before the final data were collected and analyzed.

Analyses were conducted according to the updated prespecified plan[20] and were based on the intention-to-treat principle. No interim analyses were undertaken. Descriptive analyses were used to summarize demographic characteristics. All statistical analyses were performed with the use of Stata software, version 16 (StataCorp), and R statistical packages.

Adjusted effect sizes (mean between-group differences and relative risks) were determined with the use of mixed-effects models with adjustment for six prespecified factors: age, prepregnancy body-mass index, ethnic group, current smoking status, primigravidity, and university degree or higher qualification. A random-effects regression model with cluster-robust standard errors was used to account for site clusters (Table S4). Linear regression was used for continuous outcomes, and logistic regression for binary outcomes. Missing data for primary outcomes and the six prespecified adjustment factors were replaced by means of the multivariate imputation by chained equations (MICE) algorithm (10 imputations) (Table S5). Robustness of the final models was examined with the use of 1000 bootstrapped samples of the same size, drawn with replacement. The models that were used for the analysis of the primary outcome were the adjusted models after multiple imputation. The models that were used for analyses of the secondary and other outcomes were the adjusted models with complete case data. No adjustment for multiplicity was made for secondary outcomes or subgroup analyses, so the 95% confidence intervals should not be used in place of hypothesis testing.

Two prespecified exploratory analyses were undertaken. The first was a subgroup analysis according to the glycemic range at randomization (higher vs. lower), and the second was a subgroup analysis according to the timing of the initial OGTT at trial entry (<14 weeks' gestation vs. ≥14 weeks' gestation). A statistician (the penultimate author), who was independent of the investigator team and central trial management group and who was unaware of the trial-group assignments, analyzed the data.

Figure 1 (facing page). Screening, Randomization, and Follow-up.

HFG denotes high fasting glucose, ODIP overt diabetes in pregnancy, and OGTT oral glucose-tolerance testing.

RESULTS

TRIAL PARTICIPANTS

Between May 17, 2017, and March 31, 2022, a total of 43,721 women were assessed for eligibility. Of these, 802 underwent randomization — 406 (50.6%) were assigned to the immediate-treatment group and 396 (49.4%) to the control group (Fig. 1). After the exclusion of women with early pregnancy loss (Table S6), the final sample for analysis included 793 women (98.9%). The baseline characteristics of the women in the two groups were similar, except for a higher percentage of women in the control group with a history of larger infants (Table 1).

The initial OGTT was performed at mean of 15.6 weeks' gestation; OGTT was performed before 14 weeks' gestation in 23.2% of the participants. On repeat OGTT at 24 to 28 weeks' gestation, gestational diabetes was diagnosed again in 67.0% of the women in the control group. A greater percentage of women in the immediate-treatment group than in the control group received insulin (58.1% vs. 41.4%) or metformin therapy (23.6% vs. 10.4%) (Table S7). Aspirin was used by 3.5% of women in the immediate-treatment group and by 4.1% of those in the control group.

PRIMARY OUTCOMES

Among the 793 women in the final sample, data were available for 748 (94.3%) regarding the composite adverse neonatal outcome, for 750 (94.6%) regarding pregnancy-related hypertension, and for 492 (62.0%) regarding neonatal

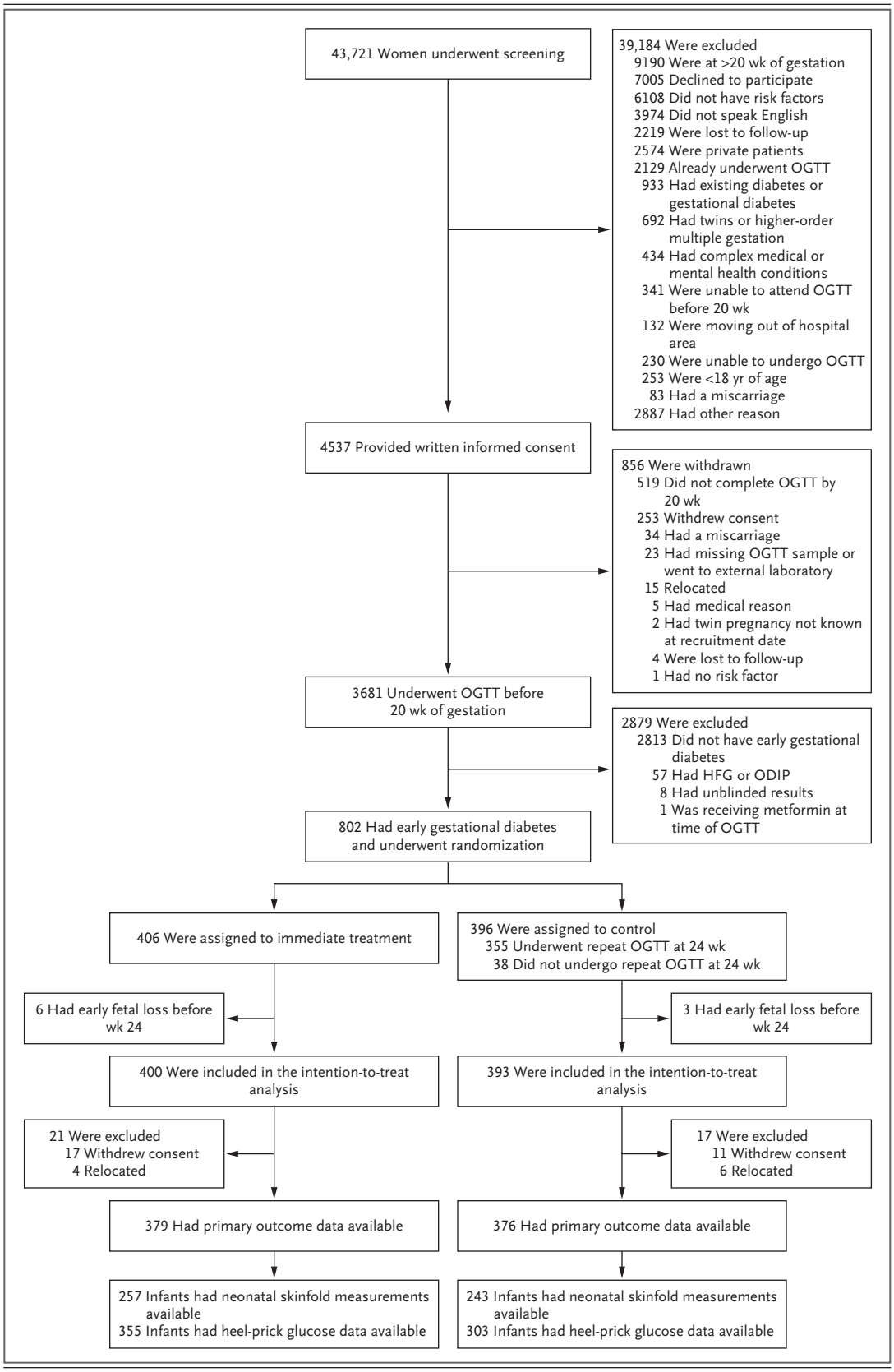

Table 1. Characteristics of the Participants at Baseline and at Oral Glucose-Tolerance Testing (OGTT) at 24 to 28 Weeks' Gestation.*

Characteristic	Immediate Treatment (N=400)	Control (N=393)
Age — yr	32.1±4.8	32.6±4.9
Ethnic group — no./total no. (%)†		
White European	150/399 (37.6)	166/391 (42.5)
South Asian	129/399 (32.3)	106/391 (27.1)
East or Southeast Asian	51/399 (12.8)	60/391 (15.3)
Middle Eastern	32/399 (8.0)	17/391 (4.3)
Maori or Pacific Island descent	24/399 (6.0)	22/391 (5.6)
Other	13/399 (3.3)	20/391 (5.1)
University degree or higher qualification — no./total no. (%)	167/380 (43.9)	174/377 (46.2)
Medical history — no./total no. (%)		
Primigravid	93/400 (23.3)	80/393 (20.4)
Current smoker	25/390 (6.4)	20/391 (5.1)
Family history of diabetes	180/379 (47.5)	183/374 (48.9)
History of PCOS	74/399 (18.5)	78/392 (19.9)
History of macrosomia	35/259 (13.5)	50/262 (19.1)
Gestational diabetes in previous pregnancy	111/307 (36.2)	115/312 (36.9)
Past IGT and IFG	48/370 (13.0)	42/372 (11.3)
Body-mass index at first visit‡	32.1±7.7	32.9±8.4
Blood pressure — mm Hg§		
Systolic	111±12	112±13
Diastolic	68±9	69±10
Chronic hypertension — no./total no. (%)¶	14/397 (3.5)	27/393 (6.9)
Timing of initial OGTT — wk of gestation	15.5±2.5	15.7±2.4
OGTT <14 wk of gestation — no./total no. (%)‖	104/400 (26.0)	80/393 (20.4)
Fasting glucose — mg/dl	92±7.2	90±9.0
1-Hr glucose — mg/dl	162±36	166±36
2-Hr glucose — mg/dl	131±29	133±29
Glycated hemoglobin — %**	5.2±0.3	5.2±0.3
OGTT at 24 to 28 wk of gestation††		
Fasting glucose — mg/dl	NA	90±11
1-Hr glucose — mg/dl	NA	175±38
2-Hr glucose — mg/dl	NA	140±32
Diagnosis of gestational diabetes at 24 to 28 wk of gestation	NA	238/355 (67.0)

* Plus–minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.05551. IFG denotes impaired fasting glucose, IGT impaired glucose tolerance, NA not applicable, and PCOS polycystic ovary syndrome.

† Ethnic group was reported by the participants. The "other" category refers to women who identified as being of aboriginal, African, or South American descent or as belonging to any other ethnic groups not specifically mentioned here.

‡ Data on the body-mass index were available for 399 women in the immediate-treatment group and 390 women in the control group.

§ Data on blood pressure were available for 386 women in the immediate-treatment group and 385 women in the control group.

¶ Chronic hypertension was defined as a history of hypertension or use of antihypertensive medication before conception.

‖ Data on the initial (<14 weeks' gestation) fasting glucose level were available for 399 women in the immediate-treatment group and 393 women in the control group. Data on the initial 1-hour glucose level were available for 398 women in the immediate-treatment group and 393 women in the control group. Data on the initial 2-hour glucose level were available for 399 women in the immediate-treatment group and 392 women in the control group.

** Data on the glycated hemoglobin level were available for 388 women in the immediate-treatment group and 384 women in the control group.

†† Data on the fasting glucose level, the 1-hour glucose level, and the 2-hour glucose level at 24 to 28 weeks' gestation were available for 355, 353, and 353 women, respectively, in the control group; this analysis was not performed in the immediate-treatment group.

lean body mass. An adverse neonatal outcome event occurred in 94 of 378 women (24.9%) in the immediate-treatment group and in 113 of 370 women (30.5%) in the control group, for an adjusted mean difference of −5.6 percentage points (95% confidence interval [CI], −10.1 to −1.2; P=0.02) (Table 2); an adjusted relative risk of 0.82 (95% CI, 0.68 to 0.98); and a number needed to treat to prevent one such event of 18. Outputs of the full models for the complete-case, bootstrapped, and MICE datasets are shown in Table S8.

Pregnancy-related hypertension occurred in 40 of 378 women (10.6%) in the immediate-treatment group and in 37 of 372 women (9.9%) in the control group, for an adjusted mean difference of 0.7 percentage points (95% CI, −1.6 to 2.9). Because the results for this outcome did not differ significantly between the two groups, neonatal lean body mass (originally the third primary outcome) was considered to be secondary outcome.

SECONDARY MATERNAL AND INFANT OUTCOMES

Maternal gestational weight gain and the percentage of women who underwent cesarean delivery or induction of labor were similar in the two groups (Table 2). Severe perineal injury occurred in 3 of 375 women (0.8%) in the immediate-treatment group and in 13 of 365 women (3.6%) in the control group, for an adjusted mean difference of −2.8 percentage points (95% CI, −4.1 to −1.5). The maternal EQ-5D score at 24 to 28 weeks' gestation was 0.83 in the immediate-treatment group and 0.81 in the control group, for an adjusted mean difference of 0.02 (95% CI, 0.01 to 0.04). Results for additional maternal outcomes are provided in Table S9.

Secondary infant outcomes are summarized in Table 2 and Table S9. There were no substantive differences between the two groups. The mean birth weight was 3258 g in the immediate-treatment group and 3348 g in the control group, for an adjusted difference of −72.1 g (95% CI, −127.6 to −16.6). The median number of bed days in the neonatal ICU or special care nursery (among the neonates who had been admitted) was 2.0 in the immediate-treatment group and 2.0 in the control group, for an adjusted treatment difference (calculated among all the neonates, with a value of 0 used for those who had not been admitted) of −0.8 bed days (95% CI, −1.3 to −0.3).

OTHER OUTCOMES AND SUBGROUP ANALYSES

Results for additional maternal and neonatal outcomes are provided in Table 3 and Table S10. Among the components of the first primary outcome, respiratory distress occurred in 37 of 376 infants (9.8%) born to women in the immediate-treatment group and in 62 of 365 infants (17.0%) born to women in the control group, for an adjusted difference of −7 percentage points (95% CI, −12 to 3); neonatal respiratory distress was the main driver of the between-group difference observed for the first primary outcome (Table 3). Stillbirths or neonatal deaths were infrequent in both trial groups.

Prespecified subgroup analyses suggested the possibility of a greater effect of the intervention on the composite adverse neonatal outcome among the women with a glycemic value in the higher range than among those with a value in the lower range and among the women who underwent OGTT at less than 14 weeks' gestation than among those who underwent OGTT at 14 weeks' gestation (Fig. 2). Additional primary and secondary outcomes according to glycemic range and to gestational age at diagnosis are provided in Tables S8 and S9, and baseline data and OGTT results are provided in Tables S11 to S14. At 24 to 28 weeks' gestation, gestational diabetes was diagnosed in 78.0% of the women in the subgroup with a higher glycemic range and in 51.4% of those in the subgroup with a lower glycemic range. No between-group differences were observed with respect to serious adverse events associated with screening and treatment (Table S15).

DISCUSSION

In this randomized trial involving women who had a risk factor for hyperglycemia in pregnancy and had received a diagnosis of gestational diabetes before 20 weeks' gestation on the basis of WHO criteria,[11] those who received immediate treatment had a significantly, albeit modestly, lower incidence of a composite of adverse neonatal events (the first primary outcome) than those who received deferred or no treatment. On the basis of the 95% confidence interval around the estimated difference, the results were compatible with anywhere from a 1.2 to a 10.1 percentage-point reduction in the risk of an adverse neonatal outcome event. No significant difference was shown with respect to the two other prespecified

Table 2. Primary and Secondary Pregnancy Outcomes.*

Outcome	Immediate Treatment (N=400)	Control (N=393)	Adjusted Treatment Effect†	
			Difference in Value (95% CI)	Relative Risk (95% CI)
Primary Pregnancy Outcomes				
Adverse neonatal outcomes — no./total no. (%)‡	94/378 (24.9)	113/370 (30.5)	−5.6 (−10.1 to −1.2)	0.82 (0.68 to 0.98)
Pregnancy-related hypertension — no./total no. (%)§	40/378 (10.6)	37/372 (9.9)	0.7 (−1.6 to 2.9)	1.08 (0.85 to 1.38)
Maternal Secondary Pregnancy Outcomes¶				
Median maternal gestational weight gain from first to final predelivery visit (IQR) — kg	6.0 (2.0 to 9.5)	6.9 (3.4 to 10.0)	−1.2 (−3.2 to 0.8)	NA
Cesarean delivery — no./total no. (%)	144/377 (38.2)	146/368 (39.7)	0.2 (−4.2 to 4.6)	1.00 (0.90 to 1.13)
Induction of labor — no./total no. (%)	187/377 (49.6)	177/372 (47.6)	1.0 (−8.3 to 10.3)	1.02 (0.84 to 1.23)
Perineal injury — no./total no. (%)	3/375 (0.8)	13/365 (3.6)	−2.8 (−4.1 to −1.5)	0.23 (0.10 to 0.51)
Median EQ-5D score at 24 to 28 wk of gestation (IQR)‖	0.83 (0.76 to 1.00)	0.81 (0.73 to 1.00)	0.02 (0.01 to 0.04)	1.03 (1.01 to 1.04)
Neonatal Secondary Pregnancy Outcomes**				
Neonatal lean body mass — kg	2.86±0.34	2.91±0.33	−0.04 (−0.09 to 0.02)	NA
Birth weight — g	3258±563	3343±588	−72.1 (−127.6 to −16.6)	NA
Large-for-gestational-age status — no./total no. (%)††	63/375 (16.8)	72/368 (19.6)	−4.6 (−11.8 to 2.5)	0.77 (0.51 to 1.17)
Small-for-gestational-age status — no./total no. (%)††	45/375 (12.0)	34/368 (9.2)	3.0 (−0.8 to 6.8)	1.32 (0.93 to 1.85)
Upper arm circumference — cm	10.8±1.4	10.9±1.3	−0.1 (−0.2 to 0.1)	NA
Sum of neonatal caliper measurements — mm	20.0±4.6	21.5±5.4	−1.4 (−2.2 to −0.5)	NA
Neonatal fat mass — kg	0.45±0.17	0.48±0.19	−0.03 (−0.05 to −0.01)	NA
Heel-prick blood glucose <29 mg/dl within 72 hr after birth	22/355 (6.2)	14/303 (4.6)	1.5 (−2.2 to 5.3)	1.31 (0.65 to 2.66)
Heel-prick blood glucose ≤40 mg/dl at 1 to 2 hr after birth	61/323 (18.9)	57/251 (22.7)	−4.2 (−13.4 to 5.0)	0.81 (0.55 to 1.19)
Median no. of bed days in neonatal special care nursery or neonatal ICU‡‡	2.0 (0.3 to 4.8)	2.0 (1.0 to 6.0)	−0.8 (−1.3 to −0.3)	0.60 (0.41 to 0.89)

* Plus–minus values are means ±SD. IQR denotes interquartile range.

† The 95% confidence intervals for the secondary outcomes have not been adjusted for multiplicity and should not be used in place of hypothesis testing. For the outcomes that are reported as number/total number (percent) of participants, the difference in value with respect to the adjusted treatment effect is shown in percentage points. "NA" in the "relative risk" column denotes not applicable because the variable is a continuous measure.

‡ Adverse neonatal outcome was a composite of birth before 37 weeks' gestation, birth weight of 4500 g or greater, birth trauma, neonatal respiratory distress, phototherapy, stillbirth or neonatal death, or shoulder dystocia. Birth trauma was defined according to the criteria of the International Association of Diabetes in Pregnancy Study Group (IADPSG)[16] and includes spinal cord injury, peripheral nerve injury or brachial plexus, basal skull fracture or depressed skull fracture, clavicular fracture, long bone fracture (humerus, radius, ulna, femur, tibia, or fibula), cranial hemorrhage (subdural or intracerebral of any kind [confirmed by cranial ultrasonography, computed tomography, or magnetic resonance imaging]).

§ Pregnancy-related hypertension was a composite of preeclampsia, eclampsia, or gestational hypertension.

¶ The analyses of the continuous maternal secondary pregnancy outcomes included 287 women in the immediate-treatment group and 284 women in the control group for maternal gestational weight gain from first to final predelivery visit and 317 and 334 women, respectively, for EQ-5D score at 24 to 28 weeks' gestation. One woman in the immediate-treatment group reported hypoglycemia, which was subsequently determined to be factitious.

‖ Scores on the EQ-5D index range from 0 to 1, with higher scores indicating better quality of life.

** The analyses of the continuous neonatal secondary pregnancy outcomes included 287 infants born to women in the immediate-treatment group and 284 infants born to women in the control group for neonatal lean body mass; 377 and 369 infants, respectively, for birth weight; 257 and 247 infants, respectively, for upper arm circumference; 254 and 242 infants, respectively, for the sum of neonatal caliper measurements; 251 and 241 infants, respectively, for neonatal fat mass; and 376 and 368 infants, respectively, for the number of bed days in a neonatal special care nursery or neonatal ICU.

†† Large-small-for-gestational age status and small-for-gestational age status were determined with the use of Gestation Related Optimal Weight (GROW) software, which uses customized birth-weight percentile data that have been defined with the use of calculations from the Gestation Network of the Perinatal Institute (gestation.net).

‡‡ The median values and IQRs were determined among all the infants who had been admitted, and the treatment effects were determined among all the infants in the trial groups, with a value of 0 used for those who had not been admitted. Many facilities had combined units, and we were unable to distinguish the infants in the special care nursery from those in the neonatal ICU.

primary outcomes (pregnancy-related hypertension and neonatal lean body mass).

The major contributor to the between-group difference with respect to the first primary outcome was neonatal respiratory distress. This finding was unexpected because, although respiratory distress is known to occur more frequently in infants born to women with gestational diabetes,[21] its incidence was not shown to be lower in other trials of treatment for gestational diabetes that had been diagnosed at 24 to 28 weeks' gestation.[14,15,22] The incidence of stillbirth or neonatal death was low and similar in the two trial groups.

Previous randomized, controlled trials of treatment for gestational diabetes have largely focused on cases that were diagnosed at 24 to 28 weeks' gestation. One trial showed that 1% of the patients who had received the intervention (dietary advice, blood glucose monitoring, and insulin therapy) had serious perinatal complications (a composite of death, shoulder dystocia, bone fracture, or nerve palsy — one of several outcomes), as compared with 4% of the patients who had received routine care.[15] In another trial involving women with mild gestational diabetes, no significant reduction was observed with respect to a composite primary outcome of stillbirth or perinatal death, hyperbilirubinemia, hypoglycemia, hyperinsulinemia, or birth trauma, but lower incidences of pregnancy-related hypertension and large-for-gestational-age neonates were reported.[14] In our trial, we used a composite outcome that included conditions that are clinically important but excluded those that substantially depend on local practice (e.g., cesarean delivery and neonatal ICU admission). Because all the women in the control group who had received a diagnosis of gestational diabetes at 24 to 28 weeks' gestation received treatment, any observed reduction in the risk of adverse outcomes can be attributed to early initiation of treatment. A previous smaller trial involving 962 women showed no benefit with early screening for gestational diabetes but identified only 69 women with gestational diabetes; thus, the trial was not powered to address the effects of early treatment of hyperglycemia on pregnancy outcomes.[22]

Exploratory subgroup analyses suggested a possible benefit of early treatment with respect to the composite adverse neonatal outcome among women with OGTT results in the higher, but not the lower, glycemic range, as well as among those in whom hyperglycemia had been identified at less than 14 weeks' gestation. These analyses also suggested that with early treatment, there is a possibility of an increased risk of small-for-gestational-age infants among mothers who had OGTT results that were in the lower glycemic range (see the Supplementary Appendix). Although these analyses were exploratory and not adjusted for multiplicity (and thus should be viewed as hypothesis generating), they suggest the possibility that treatment may be more likely to benefit women with higher levels of glycemia at early screening and may be more likely to confer harm among those with lower values. The possibility of harm with treatment was previously shown by the finding of increased admissions to the neonatal ICU admission with early treatment, largely due to small-for-gestational-age status, in our pilot study.[8]

Our results showed that a third of the women who had received a diagnosis of early gestational diabetes according to the WHO criteria did not have gestational diabetes on repeat OGTT at 24 to 28 weeks' gestation, a finding that was consistent with previous observations.[23] This finding raises questions about whether criteria that had been established for OGTT at 24 to 28 weeks' gestation can be applied to testing early in pregnancy,[24] particularly if there is a potential for harm, such as an increase in the number of small-for-gestational-age births among women who had received early treatment.

Confirmatory trials and long-term follow-up studies of the offspring are warranted. Similar follow-up studies in which the diagnosis of gestational diabetes and treatment occurred later in pregnancy have not consistently shown benefits in the metabolic status of the offspring.[25,26]

A key concern in defining criteria for early gestational diabetes is the known variation in glycemia as pregnancy progresses during the first trimester.[27] The Glycemic Observation and Metabolic Outcomes in Mothers and Offspring (GO MOMs) study (ClinicalTrials.gov number, NCT04860336), a throughout-pregnancy observational study, is investigating whether the use of continuous glucose monitoring between 10 and 14 weeks' gestation would provide better understanding of glycemic changes in early pregnancy[28] and inform criteria for the diagno-

Table 3. Other Pregnancy Outcomes.*

Outcome	Immediate Treatment (N=400)	Control (N=393)	Adjusted Treatment Effect†	
			Difference in Value (95% CI)	Relative Risk (95% CI)
Components of Primary Adverse Neonatal Outcome				
Preterm birth — no./total no. (%)‡	28/377 (7.4)	31/369 (8.4)	−1 (−4 to 2)	0.89 (0.63 to 1.26)
Birth weight ≥4500 g — no./total no. (%)	2/377 (0.5)	6/369 (1.6)	NR	NR
Birth trauma — no./total no. (%)§	3/374 (0.8)	5/367 (1.4)	−0.4 (−1 to 0.2)	0.59 (0.24 to 1.43)
Neonatal respiratory distress — no./total no. (%)	37/376 (9.8)	62/365 (17.0)	−7 (−12 to −3)	0.57 (0.41 to 0.79)
Phototherapy — no./total no. (%)	44/374 (11.8)	42/358 (11.7)	0 (−1 to 1)	0.99 (0.87 to 1.13)
Stillbirth or neonatal death — no./total no. (%)	3/378 (0.8)	2/370 (0.5)	NR	NR
Shoulder dystocia — no./total no. (%)	11/374 (2.9)	11/367 (3.0)	−1 (−2 to 1)	0.77 (0.40 to 1.48)
Other maternal outcomes¶				
Emergency cesarean delivery — no./total no. (%)	71/377 (18.8)	74/368 (20.1)	1 (−4 to 5)	1.04 (0.86 to 1.27)
Elective cesarean delivery — no./total no. (%)	73/377 (19.4)	72/368 (19.6)	−0.5 (−6 to 5)	0.98 (0.76 to 1.25)
Preeclampsia — no./total no. (%)‖	13/378 (3.4)	9/371 (2.4)	1 (−0 to 2)	1.32 (0.90 to 1.94)
Gestational hypertension — no./total no. (%)	32/378 (8.5)	30/372 (8.1)	0.2 (−1 to 1)	1.03 (0.85 to 1.24)
Maternal blood pressure at admission to birth unit — mm Hg				
Systolic	121±15	121±14	1.0 (−1.0 to 2.9)	NA
Diastolic	75±10	75±10	0.5 (−1.1 to 2.1)	NA
Other Neonatal outcomes**				
Female sex — no./total no. (%)	179/377 (47.5)	180/368 (48.9)		NA
Weeks of gestation at birth	38.2±1.8	38.3±2.0	−0.1 (−0.3 to 0.2)	NA
Median birth-weight percentile (IQR)††	52 (27 to 81)	55 (30 to 85)	−3.0 (−7.9 to 0.1)	NA
Median Apgar score (IQR)				
At 1 min	9 (9 to 9)	9 (8 to 9)	0.3 (0.1 to 0.5)	NA
At 5 min	9 (9 to 9)	9 (9 to 9)	0.1 (0.0 to 0.2)	NA
First heel-prick mean blood glucose at any time — mg/dl	56±18	56±20	−0.1 (−0.2 to 0.2)	NA
Length — cm	49.5±2.9	49.9±3.2	−0.3 (−0.6 to 0.0)	NA
Head circumference — cm	34.4±2.3	34.5±1.8	−0.1 (−0.5 to 0.3)	NA
Abdominal circumference — cm	31.6±3.1	31.8±2.7	−0.3 (−0.7 to 0.1)	NA
Admission to neonatal special care nursery or neonatal ICU — no./total no. (%)	92/376 (24.5)	101/368 (27.4)	−3 (−7 to 0)	0.9 (0.73 to 1.07)

* Plus–minus values are means ±SDs.

† Adjustment was made for age, prepregnancy body-mass index, ethnic group, current smoking, primigravidity, university degree or higher qualification, and site. The adjusted differences in value and relative risks with respect to birth weight and stillbirth or neonatal death are not reported (NR) because they were not calculated owing to small numbers. "NA" in the "relative risk" column denotes not applicable because the variable is a continuous measure. The 95% confidence intervals for the other pregnancy outcomes have not been adjusted for multiplicity and should not be used in place of hypothesis testing. For the outcomes that are reported as number/total number (percent) of participants, the difference in value with respect to the adjusted treatment effect is shown in percentage points. The differences in values and the relative risks with respect to the unadjusted treatment effects are provided in Table S11 in the Supplementary Appendix.

‡ Preterm birth was defined as less than 37 weeks' gestation.

§ Birth trauma was defined according to the criteria of IADPSG[16] together with subgaleal hematoma.

¶ The analyses of the other continuous maternal outcomes included 361 women in the immediate-treatment group and 352 women in the control group for systolic blood pressure and 361 and 351 women, respectively, for diastolic blood pressure.

Table 3. (Continued.)

‖ There were no cases of eclampsia among the participants.
** The analyses of the other continuous neonatal outcomes included 377 women in the immediate-treatment group and 369 women in the control group for weeks of gestation at birth; 375 and 368 infants, respectively, for birth-weight percentile; 374 and 368 infants, respectively, for Apgar score at 1 min; 373 and 368 infants, respectively, for Apgar score at 5 min; 354 and 298 infants, respectively, for first heel-prick mean blood glucose level; 372 and 364 infants, respectively, for length; 369 and 362 infants, respectively, for head circumference; and 251 and 244 infants, respectively, for abdominal circumference.
†† Birth-weight percentile was determined with the use of GROW software, which uses customized birth-weight percentile data that have been defined with the use of calculations from the Gestation Network of the Perinatal Institute (gestation.net).

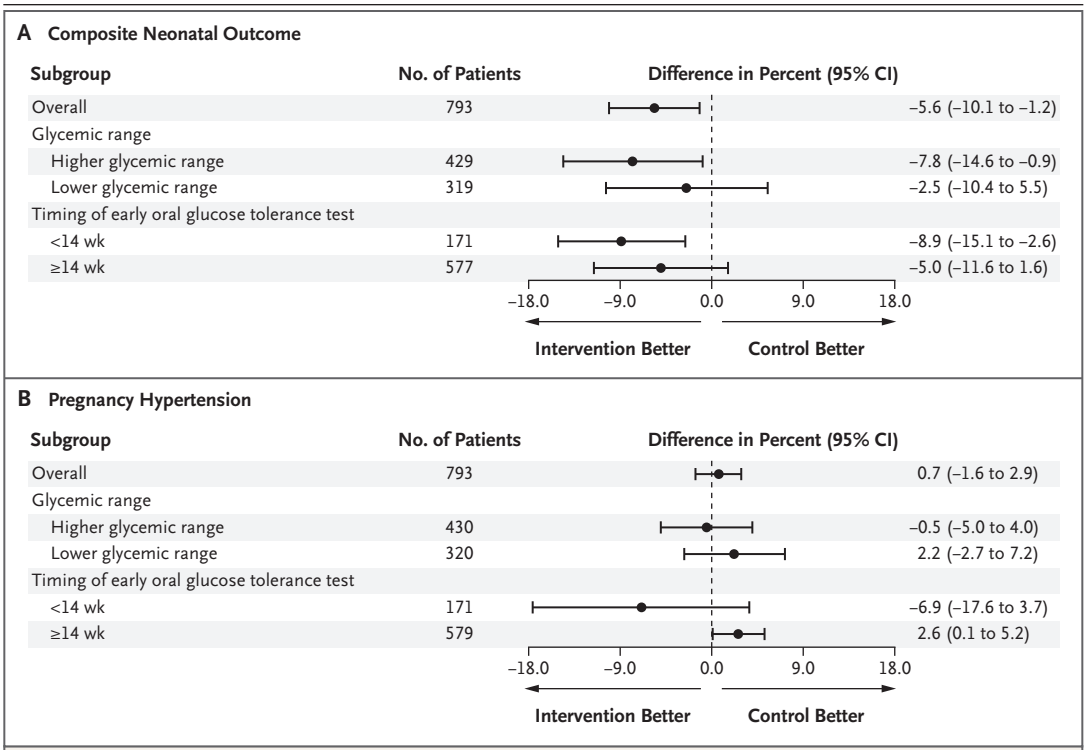

Figure 2. Primary Outcomes Overall and within Prespecified Subgroups.

Panel A shows the results of the analyses of the composite adverse neonatal outcome (the first primary outcome), a composite of birth before 37 weeks' gestation, birth weight of 4500 g or greater, birth trauma,[16] neonatal respiratory distress (i.e., distress warranting ≥4 hours of respiratory support with supplemental oxygen, continuous positive airway pressure, or intermittent positive-pressure ventilation [or combinations thereof] during the 24 hours after birth), phototherapy, stillbirth or neonatal death, or shoulder dystocia (vaginal birth in which additional obstetrical maneuvers were performed to deliver the fetus after delivery of the head and failed gentle traction). Panel B shows the results of the analyses of pregnancy-related hypertension (the secondary primary outcome), a composite of preeclampsia, eclampsia, or gestational hypertension. Women with chronic hypertension were excluded from the analysis of this outcome.

sis of gestational diabetes during this period. The results of our trial support the observation that hyperglycemia often occurs before 24 to 28 weeks' gestation in women with risk factors for gestational diabetes, but further research is needed with regard to the extent to which this observation reflects women with preexisting mild hyperglycemia[29-31]; the women in our trial were unlikely to have had preexisting, undiagnosed diabetes, given the glycemic exclusion criteria.

Limitations of our trial include the nonstandardized approach to treatment for gestational diabetes and the use of treatment targets that

had been established for the third trimester of pregnancy and had not been tested in early pregnancy. We specifically recruited women with risk factors for hyperglycemia, rather than broadly screening for early-pregnancy hyperglycemia; hence, the results may not be applicable to women without these risk factors. Although our trial was conducted in a multiethnic sample, it included limited numbers of Black or Hispanic women, few of whom live in the trial recruitment countries (Table S16). The percentage of women who received pharmacotherapy was high (67.4% in the immediate-treatment group and 45.8% in the control group) but within the range seen across Australia among women with gestational diabetes.[32]

In this trial involving pregnant women who had a risk factor for hyperglycemia, immediate treatment of gestational diabetes before 20 weeks' gestation led to a modestly lower incidence of a composite of severe adverse neonatal outcomes than no immediate treatment. However, between-group differences with respect to pregnancy-related hypertension and neonatal lean body mass were not significant.

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APPENDIX

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