From:	David Simmons
To:	Committee, Health (REPS)
Subject:	RE: [SEC=OFFICIAL] Inquiry into diabetes - Invitation to give evidence at public hearing on 17 November 2023
Date:	Sunday, 19 November 2023 8:36:29 PM
Attachments:	NEJMoa2214956.pdf NEJMoa2214956_appendix.pdf GEMS NEJM paper NEJMoa2204091 paper.pdf nejmoa2204091_appendix gems full.pdf 23tlde0183_Simmons final.pdf Diabetic Medicine - 2023 - Meek - Timing of gestational diabetes diagnosis A novel precision approach to hyperglycaemia in.pdf

OFFICIAL

Hi Kate

Many thanks for your help and that of your team on Friday

Please find the TOBOGM RCT and GEMS RCT papers

With NEJMed Papers in particular, ilt is really important to look closely at the appendices-they have important stuff in-esp for GEMS!

Please also find an editorial in the Lancet DE re:GDM is not just about cutoffs

And an editorial about early GDM and precision medicine

Please do let me know if there is anything else I can do to help

If any further papets come out of interest I will forward them to you

Kind regards

David

Professor David Simmons | Professor of Medicine
Distinguished Professor
School of Medicine |Director, Diabetes Obesity and Metabolism Translational Research Unit
Head of Department, Macarthur Diabetes Endocrinology and Metabolism Services (MDEMS), Campbelltown/Camden Hospitals
Located on Dharawal Country

SWSLHD Diabetes Advisor
President, Australasian Diabetes in Pregnancy Society
Patron, Diabetes Foundation Aotearoa

westernsydney.edu.au

Please note
I only work at Campbelltown Hospital/SWSLHD Monday and Thursday

Doctopic: Analysis and Interpretation
THELANCETDE-D-23-00183
PII
Embargo: [add date when known]
Linked to 22tlde0949 Twig

Defining gestational diabetes: not just about cutoffs

Md Babul Hosen/Getty Images

Lancet Diabetes Endocrinol 2023

The criteria for diagnosing gestational diabetes, defined as hyperglycaemia less than overt diabetes first detected in pregnancy,[1] vary globally. The International Association of Diabetes in Pregnancy Study Groups (IADPSG), informed by the large international Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study (n=25 505),[2] sought diagnostic consensus in 2010.[1] A global oral glucose tolerance test (OGTT) diagnostic approach was proposed on the basis of the relationship between maternal OGTT glucose values at 24–28 weeks' gestation and perinatal complications. By contrast, the O'Sullivan approach (and its derivative, the Carpenter and Coustan criteria),[3] is based on small studies aligning gestational diabetes prevalence to background diabetes prevalence in the non-pregnant population (n=752). This method was validated with a post-partum follow-up study of the excess maternal risk of future type 2 diabetes (n=1013), which, by 22–25 years' follow-up, reported a relative risk of 6·64 (95% CI 4·19–10·52).[4] Concern over the predicted increase in the number of women diagnosed with gestational diabetes with the IADPSG approach (an increase of 75%[5]) led to continuation of O'Sullivan-derived approaches in many countries. However, the differences between the IADPSG and the O'Sullivan approaches extend beyond the rationale behind diagnosing gestational diabetes (IADPSG for perinatal diabetes *vs* O'Sullivan for future maternal diabetes) and diagnostic glucose cutoffs. There are also major differences in practical application, including glucose load (75 g *vs* 100 g), duration (2 h *vs* 3 h), number of samples needed for diagnosis (one *vs* two), and preceding screening (none *vs* 50 g glucose challenge test [GCT]).

In *The Lancet Diabetes & Endocrinology*, Aya Bardugo and colleagues[6] followed up a large cohort (n=177 241) of women over 10·8 years postpartum after an O'Sullivan-derived approach and reported adjusted hazard ratios (HRs) for type 2 diabetes of 3·39 (95% CI 2·77–4·16; p<0·0001) among women with an abnormal GCT with normal OGTT, 9·11 (7·64–10·86; p<0·0001) among women with one abnormal OGTT value, and 24·84 (21·78–28·34; p<0·0001) among women with gestational diabetes. Importantly, women in all groups had similar BMI at baseline (aged 17 years), which was higher by the time gestational diabetes screening had revealed any elevated glucose value. Along with the high progression rates to type 2 diabetes, these data confirm that preventative lifestyle programmes, or potentially metformin treatment, might be needed beyond women with gestational diabetes to include women with even one elevated glucose value. A previous meta-analysis of 25 studies (n=4466) also showed that even one abnormal value on the O'Sullivan 3 h 100 g OGTT is associated with an increased risk of perinatal complications compared with women with a normal GCT, and similar to women with a diagnosis of gestational diabetes.[7] Although randomised controlled trials of IADPSG versus O'Sullivan-derived approaches have been reported,[8] no randomised controlled trials have been done of the two approaches to evaluate the long-term benefit (eg, time to type 2 diabetes progression). To be consistent with the original O'Sullivan approach by equilibrating with these latest HRs reported by Bardugo and colleagues,[6] the O'Sullivan-derived approach should now move to needing only one positive glucose cutoff for the diagnosis of gestational diabetes. The original reason for the need for two elevated glucose values was the inaccuracy of the laboratory glucose measurements, which is no longer the case with modern pre-analytical glucose standards. Requiring only a single elevated OGTT value will approximately double the number of diagnoses,[6,8] similar to the prevalence of gestational diabetes with the current IADPSG approach, but remains consistent with the original O'Sullivan rationale.

The work by Bardugo and colleagues[6] has confirmed the importance of the isolated fasting glucose value (*vs* the post-glucose load) in the diagnosis of gestational diabetes; in their study it was associated with an increased long-term risk of type 2 diabetes (adjusted HR 11·81 [95% CI 8·58–16·25]; p<0·0001). The importance of the fasting glucose was also shown in the HAPO study in relation to neonatal adverse pregnancy outcomes.[2] The O'Sullivan two step approach uses the GCT to determine which women proceed to an OGTT: an approach that misses around 20–25% of women with gestational diabetes diagnosed with two elevated values[3] and prevents many of those with an isolated high fasting glucose from progressing to an OGTT.

Given the high progression to type 2 diabetes with just one abnormal value or an isolated elevated fasting glucose on the OGTT, along with the known high rates

of nausea and vomiting with the 100 g glucose load[8] and the ethnic variation in glucose profile on the OGTT,[9] the study by Bardugo and colleagues[6] raises important questions over the consistency, validity, and patient-centredness of the O'Sullivan-derived approaches to the diagnosis of gestational diabetes. With the upcoming findings from studies of diagnosing gestational diabetes before 24–28 weeks' gestation,[10] we must review all the current diagnostic approaches to gestational diabetes and determine a common approach to diagnosing hyperglycaemia in pregnancy.

We declare no competing interests.

David Simmons, Arianne Sweeting
da.simmons@westernsydney.edu.au

Macarthur Clinical School, Western Sydney University, Penrith, NSW, Australia (DS); Royal Prince Alfred Hospital, The University of Sydney, Sydney, NSW, Australia (AS)

1 International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; **33:** 676–82.

2 HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; **358:** 1991–2002.

3 Sweeting A, Wong J, Murphy HR, Ross GP. A clinical update on gestational diabetes mellitus. *Endocr Rev* 2022; **43:** 763–93.

4 Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 2009; **373:** 1773–79.

5 Saeedi M, Cao Y, Fadl H, Gustafson H, Simmons D. Increasing prevalence of gestational diabetes mellitus when implementing the IADPSG criteria: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2021; **172:** 108642.

6 Bardugo A, Bendor CD, Rotem RS, et al. Glucose intolerance in pregnancy and risk of early-onset type 2 diabetes: a population based cohort study. *Lancet Diabetes Endocrinol* 2023; published online March 31. https://doi.org/10.1016/S2213-8587(23)00062-1.

7 Roeckner JT, Sanchez-Ramos L, Jijon-Knupp R, et al. Single abnormal value on 3-hour oral glucose tolerance test during pregnancy is associated with adverse maternal and neonatal outcomes: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2016; **215:** 287–97.

8 Carter EB, Powe CE. Gestational diabetes mellitus screening strategies: balancing short-term and long-term risks. *Obstet Gynecol* 2021; **138:** 3–5.

9 Sacks DA, Hadden DR, Maresh M, et al. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes Care* 2012; **35:** 526–28.

10 Simmons D, Hague WM, Teede HJ, et al. Hyperglycaemia in early pregnancy: the Treatment of Booking Gestational diabetes Mellitus (TOBOGM) study. A randomised controlled trial. *Med J Aust* 2018; **209:** 405–06.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 18, 2022 VOL. 387 NO. 7

Lower versus Higher Glycemic Criteria for Diagnosis of Gestational Diabetes

Caroline A. Crowther, M.D., Deborah Samuel, B.Ed., Lesley M.E. McCowan, M.D., Richard Edlin, Ph.D., Thach Tran, Ph.D., and Christopher J. McKinlay, Ph.D., for the GEMS Trial Group*

ABSTRACT

BACKGROUND

Treatment of gestational diabetes improves maternal and infant health, although diagnostic criteria remain unclear.

METHODS

We randomly assigned women at 24 to 32 weeks' gestation in a 1:1 ratio to be evaluated for gestational diabetes with the use of lower or higher glycemic criteria for diagnosis. The lower glycemic criterion was a fasting plasma glucose level of at least 92 mg per deciliter (≥5.1 mmol per liter), a 1-hour level of at least 180 mg per deciliter (≥10.0 mmol per liter), or a 2-hour level of at least 153 mg per deciliter (≥8.5 mmol per liter). The higher glycemic criterion was a fasting plasma glucose level of at least 99 mg per deciliter (≥5.5 mmol per liter) or a 2-hour level of at least 162 mg per deciliter (≥9.0 mmol per liter). The primary outcome was the birth of an infant who was large for gestational age (defined as a birth weight above the 90th percentile according to Fenton–World Health Organization standards). Secondary outcomes were maternal and infant health.

RESULTS

A total of 4061 women underwent randomization. Gestational diabetes was diagnosed in 310 of 2022 women (15.3%) in the lower-glycemic-criteria group and in 124 of 2039 women (6.1%) in the higher-glycemic-criteria group. Among 2019 infants born to women in the lower-glycemic-criteria group, 178 (8.8%) were large for gestational age, and among 2031 infants born to women in the higher-glycemic-criteria group, 181 (8.9%) were large for gestational age (adjusted relative risk, 0.98; 95% confidence interval, 0.80 to 1.19; P=0.82). Induction of labor, use of health services, use of pharmacologic agents, and neonatal hypoglycemia were more common in the lower-glycemic-criteria group than in the higher-glycemic-criteria group. The results for the other secondary outcomes were similar in the two trial groups, and there were no substantial between-group differences in adverse events. Among the women in both groups who had glucose test results that fell between the lower and higher glycemic criteria, those who were treated for gestational diabetes (195 women), as compared with those who were not (178 women), had maternal and infant health benefits, including fewer large-for-gestational-age infants.

CONCLUSIONS

The use of lower glycemic criteria for the diagnosis of gestational diabetes did not result in a lower risk of a large-for-gestational-age infant than the use of higher glycemic criteria. (Funded by the Health Research Council of New Zealand and others; GEMS Australian New Zealand Clinical Trials Registry number, ACTRN12615000290594.)

From the Liggins Institute (C.A.C., D.S., C.J.M.), the Department of Obstetrics and Gynaecology (L.M.E.M.), and the School of Population Health (R.E.), University of Auckland, Auckland, New Zealand; and Osteoporosis and Bone Biology, Garvan Institute of Medical Research, Sydney (T.T.). Dr. Crowther can be contacted at c.crowther@auckland.ac.nz or at the Liggins Institute, University of Auckland, Bldg. 503, Level 2, 85 Park Rd., Auckland 1142, New Zealand.

*The members of the GEMS Trial Group are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2022;387:587-98.
DOI: 10.1056/NEJMoa2204091

A Quick Take is available at NEJM.org

Gestational diabetes mellitus is a major worldwide health problem[1] with immediate[2] and lifelong implications for the affected woman[3,4] and her infant.[5] Pregnancy-related risks include high rates of induced labor, cesarean delivery, preeclampsia, and birth of a large-for-gestational-age infant.[2]

Gestational diabetes exposes the unborn baby to an abnormal metabolic environment with excessive nutrient availability,[6] which may lead to fetal overgrowth. Infants are more likely to be born large for gestational age and have an increased risk of operative birth, shoulder dystocia, and birth injuries. Other neonatal complications include lung disease, jaundice, and hypoglycemia.[7,8]

Management of gestational diabetes that includes nutritional therapy, blood glucose monitoring, and as-needed pharmacologic treatment reduces the risk of a serious perinatal outcome, birth of a large-for-gestational-age infant, shoulder dystocia, and preeclampsia.[7,8] However, there is worldwide controversy concerning the degree of maternal hyperglycemia needed to diagnose gestational diabetes, and diagnostic criteria vary globally.[9-16]

The criteria recommended for the diagnosis of gestational diabetes in New Zealand[17] were developed by the Australasian Diabetes in Pregnancy Society through a consensus process.[10] After the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) cohort study,[18] the International Association of Diabetes in Pregnancy Study Groups (IADPSG) recommended new diagnostic criteria — also developed through a consensus process — with a lower glycemic threshold for gestational diabetes.[15] Professional organizations vary in their adoption of these lower glycemic criteria, with some in favor[11,15,16] and others not[14,17,19,20] or in favor of the new criteria but supporting additional criteria as well.[9,13] Many organizations have suggested that further randomized trials are warranted to assess the effect of using lower glycemic criteria for the diagnosis of gestational diabetes.[16,17,19-22]

Lower glycemic criteria for the diagnosis of gestational diabetes[15,16] would detect more women with milder disease than the diagnostic criteria with a higher glycemic threshold currently in use.[10,17] We now report the primary results of the Gestational Diabetes Mellitus Trial of Diagnostic Detection Thresholds (GEMS), which was conducted to assess whether the detection of gestational diabetes with the use of the lower glycemic criteria, with subsequent treatment, would lead to lower perinatal morbidity without higher maternal health-related risk than such detection and treatment with the higher glycemic criteria; an additional objective was to determine differences in the use of health services between the two trial groups.

Methods

Trial Design and Oversight

This randomized trial was conducted within the area of two district health boards that provide primary to tertiary maternity care in New Zealand — Counties Manukau Health and Auckland District Health Board. The trial protocol was approved by the Northern B Health and Disability Ethics Committee and is available with the full text of this article at NEJM.org. The steering group designed and oversaw the trial. An independent data monitoring committee reviewed trial safety and progress. No interim analyses were undertaken. Neither the funding sources nor the author-affiliated institutions had any role in the design of the trial; the collection, analysis, and interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. The penultimate author analyzed the data, and the first and penultimate authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first author wrote the first draft of the manuscript, and all the authors reviewed the drafts and made the decision to submit the manuscript for publication.

Participants

Women with a singleton pregnancy receiving antenatal care within the two district health boards were eligible if they had a 75-g oral glucose-tolerance test (OGTT) for gestational diabetes at 24 to 32 weeks' gestation and provided written informed consent. Women with diabetes mellitus or a history of gestational diabetes were ineligible. Caregivers and researchers provided trial information to potentially eligible women in midpregnancy when testing for gestational diabetes was considered.

Randomization and Treatment Strategies

Eligible women were randomly assigned in a 1:1 ratio to be evaluated for gestational diabetes with lower or higher glycemic criteria for diagnosis.

The lower glycemic criterion was a fasting plasma glucose level of at least 92 mg per deciliter (≥5.1 mmol per liter), a 1-hour level of at least 180 mg per deciliter (≥10.0 mmol per liter), or a 2-hour level of at least 153 mg per deciliter (≥8.5 mmol per liter).[15,16] The higher glycemic criterion was a fasting plasma glucose level of at least 99 mg per deciliter (≥5.5 mmol per liter) or a 2-hour level of at least 162 mg per deciliter (≥9.0 mmol per liter).[10,17] Randomization was performed through a central computerized system, and the randomization sequence, prepared by a nonclinical researcher, used balanced variable blocks with stratification according to district health board and body-mass index (the weight in kilograms divided by the square of the height in meters; <25 or ≥25).

Women with OGTT results that did not indicate gestational diabetes according to the diagnostic criteria to which they were assigned were informed that they did not have the condition and received routine pregnancy care. Women with OGTT results that indicated gestational diabetes according to the diagnostic criteria to which they were assigned were informed that they had the condition and received usual care for gestational diabetes that included nutritional therapy, blood glucose monitoring, and as-needed pharmacologic treatment.[17] After birth, each infant received care according to the protocol of the given hospital. Research personnel collected data from health records. The trial participants, caregivers, and researchers were unaware of the trial-group assignments.

TRIAL OUTCOMES

The primary outcome was the birth of an infant who was large for gestational age (defined as a birth weight above the 90th percentile according to Fenton–World Health Organization standards).[23] Prespecified secondary outcomes for the infant before hospital discharge were other anthropometric measures at birth (weight, length, head circumference, and associated z scores for each; large-for-gestational-age status according to customized New Zealand standards[24]; small-for-gestational-age status [birth weight below the 10th percentile according to population[23] and customized New Zealand standards[24]]; and macrosomia [birth weight, ≥4 kg]); gestational age at birth; preterm birth (<37 weeks' gestation); a composite of serious health outcomes (perinatal death, birth trauma [nerve palsy or bone fracture], or shoulder dystocia)[7]; an Apgar score of less than 4 at 5 minutes; other infant-related complications including type and severity of lung disease, use of respiratory support, hypoglycemia warranting treatment (defined as a blood glucose level of <47 mg per deciliter [<2.6 mmol per liter]), hyperbilirubinemia warranting phototherapy (as determined by the treating clinician), documented systemic infection in the first 48 hours after birth, seizures occurring in the first 24 hours after birth or leading to the use of two or more drugs for control, tube feeding for more than 4 days, and neonatal encephalopathy[25]; and use of health services including admission to an intensive care unit and duration and length of postnatal stay. Prespecified secondary outcomes for the participating women were a composite of serious health outcomes up to postnatal hospital discharge[26]; preeclampsia; induction of labor; mode of birth; postpartum hemorrhage (≥500 ml); gestational weight gain; pharmacologic treatment for gestational diabetes; maternal infectious complications including chorioamnionitis that led to the use of antibiotics during labor and puerperal sepsis that led to the use of antibiotics; breastfeeding at hospital discharge; and use of health services, including health professional visits, specialist care for diabetes, antenatal admission to a hospital and length of stay, and length of postnatal stay.

STATISTICAL ANALYSIS

Assuming a 10% loss to follow-up, we estimated that 4158 women were needed to provide the trial with 90% power to detect an absolute between-group difference of 2.9 percentage points in the incidence of a primary-outcome event, on the basis of projected incidences of 12.9% in the higher-glycemic-criteria group[10,17] and 10.0% in the lower-glycemic-criteria group,[15,16] at a two-sided significance level of 5%.[7,15] Statistical analyses, conducted in accordance with the prespecified statistical analysis plan (available with the protocol), were based on an intention-to-treat approach and were performed by an independent statistician using SAS software, version 9.4 (SAS Institute). We used log-binomial regression to analyze binary outcomes and reported the relative risk with the 95% confidence interval, or we used exact logistic regression when the number of participants with a particular outcome was small and reported the exact odds ratio with the 95% confidence interval. Continuous outcomes were analyzed with the use of linear regression to obtain

the mean difference with the 95% confidence interval. We analyzed count outcomes that had evidence of data overdispersion using a negative binomial regression and reported the ratio of means with the 95% confidence interval. Ordinal outcomes were analyzed with the use of a proportional odds model or separate log-binomial regression with predefined thresholds if the proportional odds assumption was not met. Both unadjusted and adjusted analyses were conducted. The adjusted analyses were adjusted for the two stratification factors of district health board and body-mass index and for the prespecified covariates of maternal age and gestation at randomization.

Secondary outcomes were reported as point estimates with 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity, and thus the inferences drawn may not be reproducible. Among the women who would have or not have received a diagnosis of gestational diabetes had they been assigned to the other trial group, a single, prespecified subgroup analysis was performed in which those who received treatment for gestational diabetes were compared with those who did not.

RESULTS

TRIAL PARTICIPANTS

From April 2015 through the end of the recruitment period in August 2020, a total of 5662 women were assessed for eligibility, among whom 4061 underwent randomization; 2022 (49.8%)

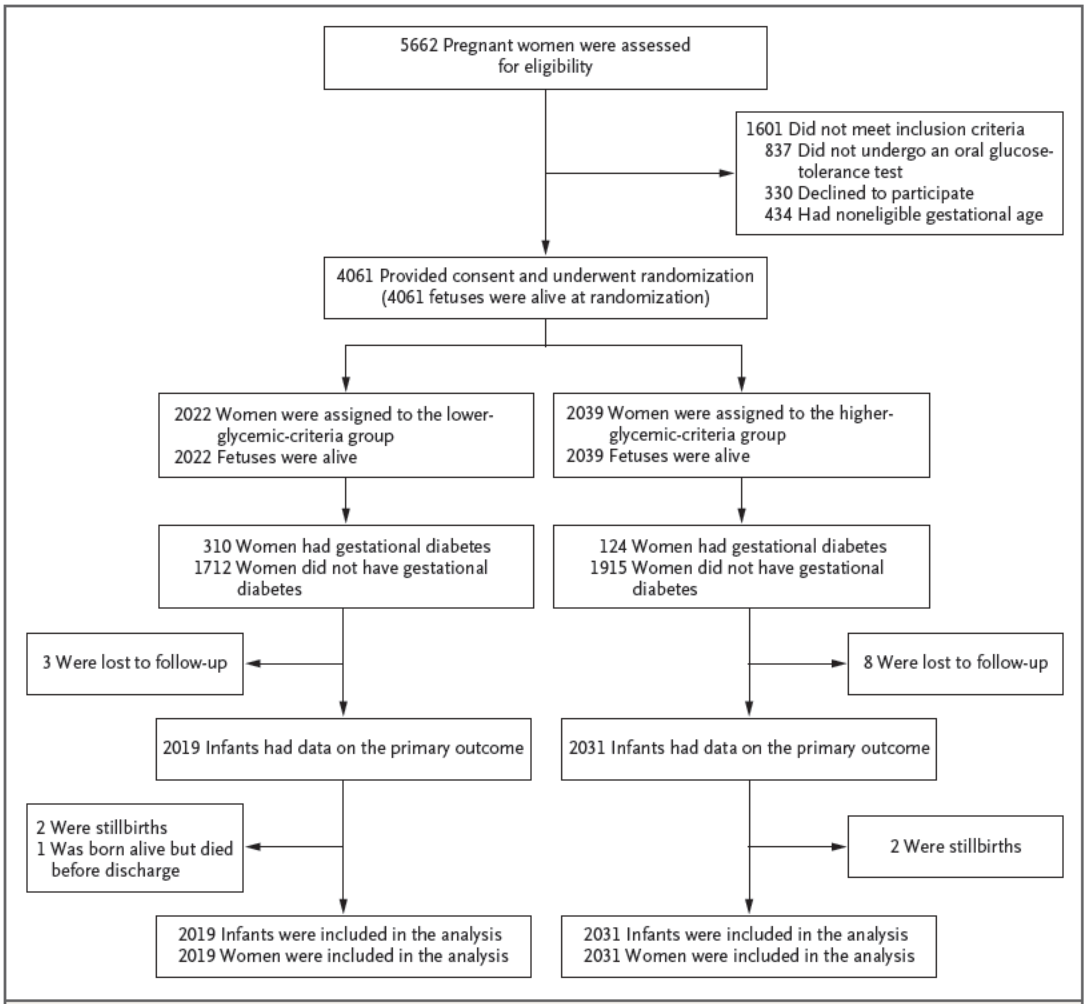

Figure 1. Randomization, Treatment, and Follow-up.

were assigned to the lower-glycemic-criteria group, and 2039 (50.2%) to the higher-glycemic-criteria group (Fig. 1). A total of 4050 women (99.7%) and their infants completed follow-up to the time of hospital discharge after birth (Fig. 1). At the time of trial entry, the characteristics of women in the two trial groups were similar (Table 1). Asian, European, and Pacific populations were well represented, but Maori women were underrepresented among pregnant women in New Zealand (Table S1 in the Supplementary Appendix, available at NEJM.org). Gestational diabetes was diagnosed in 310 women (15.3%) in the lower-glycemic-criteria group and in 124 women (6.1%) in the higher-glycemic-criteria group.

PRIMARY OUTCOME

Large-for-gestational-age infants were born to 178 of 2019 women (8.8%) in the lower-glycemic-criteria group and to 181 of 2031 women (8.9%) in the higher-glycemic-criteria group (unadjusted relative risk, 0.99; 95% confidence interval [CI], 0.81 to 1.21; P=0.91) (Table 2). The risk of a large-for-gestational-age infant was similar in the adjusted analyses (adjusted relative risk, 0.98; 95% CI, 0.80 to 1.19; P=0.82).

SECONDARY INFANT OUTCOMES

Other infant anthropometric measures at birth (weight, length, head circumference, and associated z scores for each; small-for-gestational-age status according to population standards; macrosomia; and large- or small-for-gestational-age status according to customized New Zealand standards) showed no substantial between-group differences, findings that support those of our primary analysis (Table 2). Gestational age at birth and the incidence of preterm birth were similar in the two trial groups. Hypoglycemia was detected and treated more frequently among the infants in the lower-glycemic-criteria group than among those in the higher-glycemic-criteria

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Lower-Glycemic-Criteria Group (N=2022)	Higher-Glycemic-Criteria Group (N=2039)
Maternal age — yr	31.4±5.1	31.5±5.2
Primiparous — no. (%)	998 (49.4)	970 (47.6)
Median gestation at OGTT (IQR) — wk	27.3 (26.3–28.3)	27.3 (26.3–28.3)
24 to <28 wk — no. (%)	1334 (66.0)	1350 (66.2)
28 to <32 wk — no. (%)	688 (34.0)	689 (33.8)
Median body-mass index (IQR)	26.6 (23.4–31.0)	26.5 (23.4–30.8)
Race or ethnic group — no. (%)†		
White	807 (39.9)	821 (40.3)
Pacific	316 (15.6)	304 (14.9)
Maori	105 (5.2)	120 (5.9)
Asian	678 (33.5)	665 (32.6)
Other	116 (5.7)	129 (6.3)
Previous perinatal death — no./total no. (%)	30/1024 (2.9)	42/1069 (3.9)
Chronic hypertension — no. (%)	77 (3.8)	78 (3.8)
Family history of diabetes — no. (%)	723 (35.8)	688 (33.7)
Median OGTT result (IQR) — mg/dl		
Fasting plasma glucose level	77.5 (73.9–82.9)	77.5 (73.9–82.9)
1-hr plasma glucose level	135.1 (115.3–153.1)	135.1 (113.4–153.1)
2-hr plasma glucose level	109.9 (93.7–127.9)	109.9 (93.7–127.9)

* Plus–minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.05551. IQR denotes interquartile range, and OGTT oral glucose-tolerance test.
† Race or ethnic group was reported by the participants.

Table 2. Primary and Secondary Infant Outcomes.*

Outcome	Lower-Glycemic-Criteria Group	Higher-Glycemic-Criteria Group	Unadjusted Treatment Effect (95% CI)†	Adjusted Treatment Effect (95% CI)†‡
Primary outcome: large-for-gestational-age infant — no./total no. (%)	178/2019 (8.8)	181/2031 (8.9)	0.99 (0.81 to 1.21)	0.98 (0.80 to 1.19)
Other birth-related anthropometric outcomes				
Birth weight — g	3389±545	3402±548	−13.43 (−47.08 to 20.23)§	−13.77 (−47.18 to 19.64)§
Birth-weight z score¶	0.00±0.93	0.04±0.95	−0.04 (−0.10 to 0.02)§	−0.04 (−0.09 to 0.02)§
Birth length — cm	51.0±2.7	51.0±2.7	0.01 (−0.16 to 0.18)§	0.01 (−0.16 to 0.17)§
Birth-length z score¶	0.35±1.01	0.36±1.02	−0.01 (−0.07 to 0.06)§	−0.01 (−0.07 to 0.05)§
Birth head circumference — cm	34.8±1.7	34.8±1.7	0.00 (−0.10 to 0.11)§	0.00 (−0.10 to 0.11)§
Birth-head-circumference z score¶	0.18±1.09	0.18±1.14	−0.00 (−0.07 to 0.07)§	−0.00 (−0.07 to 0.07)§
Large for gestational age according to customized New Zealand standards — no. (%)	190/2019 (9.4)	206/2031 (10.1)	0.93 (0.77 to 1.12)	0.93 (0.77 to 1.12)
Small for gestational age — no. (%)	168/2019 (8.3)	157/2031 (7.7)	1.08 (0.87 to 1.33)	1.08 (0.87 to 1.33)
Small for gestational age according to customized New Zealand standards — no. (%)	258/2019 (12.8)	262/2031 (12.9)	0.99 (0.84 to 1.16)	0.99 (0.84 to 1.16)
Macrosomia — no. (%)	238/2019 (11.8)	250/2031 (12.3)	0.96 (0.81 to 1.13)	0.95 (0.81 to 1.12)
Gestational age at birth — wk	39.3±1.6	39.3±1.6	0.01 (−0.09 to 0.11)§	0.01 (−0.09 to 0.11)§
Preterm birth, <37 wk of gestation — no. (%)	109/2019 (5.4)	106/2031 (5.2)	1.03 (0.80 to 1.34)	1.03 (0.80 to 1.34)
Serious health outcome — no./total no. (%)				
Composite of stillbirth, death of live-born infant before discharge, birth trauma, or shoulder dystocia	50/2019 (2.5)	45/2031 (2.2)	1.12 (0.75 to 1.66)	1.11 (0.75 to 1.65)
Stillbirth	2/2019 (0.1)	2/2031 (0.1)	1.01 (0.07 to 13.89)‖	1.00 (0.07 to 13.87)‖
Death of live-born infant before discharge	1/2017 (<0.1)	0/2029	NA**	NA**
Birth trauma	1/2017 (<0.1)	4/2029 (0.2)	0.25 (0.01 to 2.54)‖	0.25 (0.01 to 2.55)‖
Shoulder dystocia	46/2017 (2.3)	41/2029 (2.0)	1.13 (0.74 to 1.71)	1.12 (0.74 to 1.70)
Apgar score <4 at 5 min — no./total no. (%)	3/2017 (0.1)	8/2029 (0.4)	0.45 (0.10 to 1.60)‖	0.45 (0.10 to 1.61)‖
Any neonatal lung disease — no./total no. (%)	71/2017 (3.5)	56/2029 (2.8)	1.28 (0.90 to 1.80)	1.26 (0.90 to 1.78)

Severity of any lung disease — no./total no. (%)				
Mild	52/2017 (2.6)	39/2029 (1.9)	1.28 (0.90 to 1.80)††	1.26 (0.90 to 1.78)††
Moderate	18/2017 (0.9)	16/2029 (0.8)	1.12 (0.59 to 2.16)††	1.11 (0.58 to 2.13)††
Severe	1/2017 (<0.1)	1/2029 (<0.1)	1.01 (0.01 to 79.00)‖	1.00 (0.01 to 78.26)‖
Use of respiratory support — no./total no. (%)	143/2017 (7.1)	119/2029 (5.9)	1.21 (0.96 to 1.53)	1.20 (0.95 to 1.51)
Hypoglycemia warranting treatment — no./total no. (%)	215/2017 (10.7)	170/2029 (8.4)	1.27 (1.05 to 1.54)	1.27 (1.05 to 1.54)
Hyperbilirubinemia warranting phototherapy — no./total no. (%)	69/2017 (3.4)	66/2029 (3.3)	1.05 (0.75 to 1.47)	1.05 (0.75 to 1.46)
Proven systemic infection in the first 48 hours after birth — no./total no. (%)	3/2017 (0.1)	6/2029 (0.3)	0.50 (0.08 to 2.36)‖	0.50 (0.08 to 2.35)‖
Seizure in first 24 hr after birth or that led to the use of ≥2 drugs to control — no./total no. (%)	2/2017 (0.1)	1/2029 (<0.1)	2.01 (0.10 to 118.81)‖	2.01 (0.10 to 118.72)‖
Tube feeding for >4 days — no./total no. (%)	59/2017 (2.9)	61/2029 (3.0)	0.97 (0.68 to 1.38)	0.97 (0.68 to 1.38)
Neonatal encephalopathy — no./total no. (%)	2/2017 (0.1)	2/2029 (0.1)	1.01 (0.07 to 13.89)‖	1.01 (0.07 to 13.99)‖
Admission to neonatal intensive care unit — no./total no. (%)	93/2017 (4.6)	73/2029 (3.6)	1.28 (0.95 to 1.73)	1.27 (0.94 to 1.71)
Stay in neonatal intensive care unit — days	0.4±3.2	0.5±4.5	0.59 (0.30 to 1.17)‡‡	0.91 (0.49 to 1.70)‡‡
Length of postnatal stay — days	4.4±6.4	4.3±5.7	1.02 (0.97 to 1.07)§§	1.02 (0.97 to 1.07)§§

* Plus–minus values are means ±SD. NA denotes not applicable because no event was reported.
† Treatment effects are given as the relative risk, unless otherwise indicated.
‡ The treatment effect was adjusted for body-mass index, planned birthing institution, and maternal age and gestation at the time of randomization.
§ The treatment effect is given as the mean difference, as estimated from a linear-regression model.
¶ The z scores were estimated with the use of the Fenton–World Health Organization growth references.[24]
‖ The treatment effect is given as the exact odds ratio, as estimated from an exact logistic-regression model; in the adjusted analysis, the treatment effect was adjusted for body-mass index and planned birthing institution.
** The effect size was judged to be clinically not interpretable (i.e., median exact odds ratio, 1.01; 95% CI, 0.05 to infinity).
†† The treatment effect is given as the relative risk, as estimated from a separate log-binomial regression model (mild or greater severity vs. no lung disease; moderate or greater severity vs. mild or no lung disease; severe vs. moderate, mild, or no lung disease), since the proportional odds assumption was not met.
‡‡ The treatment effect is given as the ratio of means, as estimated from a zero-inflated negative binomial-regression model.
§§ The treatment effect is given as the ratio of means, as estimated from a negative binomial-regression model.

Table 3. Maternal Outcomes Assessed before Hospital Discharge after Birth.*

Outcome	Lower-Glycemic-Criteria Group (N = 2019)	Higher-Glycemic-Criteria Group (N = 2031)	Unadjusted Treatment Effect (95% CI)†	Adjusted Treatment Effect (95% CI)†‡
Serious health outcome — no. (%)§	83 (4.1)	76 (3.7)	1.10 (0.81 to 1.49)	1.10 (0.81 to 1.49)
Maternal death	0	0	NA	NA
Acute pulmonary edema	0	2 (0.1)	NA¶	NA¶
Eclampsia	2 (0.1)	3 (0.1)	0.67 (0.06 to 5.86)¶	0.68 (0.06 to 5.92)¶
Respiratory distress syndrome	0	2 (0.1)	NA¶	NA¶
Cardiac arrest	0	0	NA	NA
Placental abruption	7 (0.3)	8 (0.4)	0.88 (0.32 to 2.42)	0.88 (0.32 to 2.42)
Hemolysis	0	0	NA	NA
Coagulopathy	12 (0.6)	11 (0.5)	1.10 (0.49 to 2.48)	1.08 (0.48 to 2.45)
Major postpartum hemorrhage of ≥1500 ml	59 (2.9)	49 (2.4)	1.21 (0.83 to 1.76)	1.21 (0.83 to 1.76)
DVT or PE	3 (0.1)	6 (0.3)	0.50 (0.08 to 2.36)‖	0.50 (0.08 to 2.34)‖
Pneumonia	2 (0.1)	1 (<0.1)	2.01 (0.10 to 118.81)‖	2.01 (0.10 to 118.73)‖
Preeclampsia — no. (%)	74 (3.7)	76 (3.7)	0.98 (0.72 to 1.34)	0.97 (0.71 to 1.33)
Induction of labor — no. (%)	681 (33.7)	613 (30.2)	1.12 (1.02 to 1.22)	1.12 (1.02 to 1.22)
Cesarean section — no. (%)	711 (35.2)	771 (38.0)	0.93 (0.86 to 1.01)	0.93 (0.86 to 1.01)
Elective	266 (13.2)	303 (14.9)	0.88 (0.76 to 1.03)	0.91 (0.78 to 1.05)
Emergency	445 (22.0)	468 (23.0)	0.96 (0.85 to 1.07)	0.96 (0.85 to 1.07)
Postpartum hemorrhage — no. (%)	566 (28.0)	598 (29.4)	0.95 (0.86 to 1.05)	0.95 (0.86 to 1.04)
Gestational weight gain — kg**	11.5±6.9	11.4±7.0	0.13 (–0.37 to 0.63)	0.12 (–0.37 to 0.61)
Chorioamnionitis that led to use of antibiotics — no. (%)	21 (1.0)	11 (0.5)	1.92 (0.93 to 3.97)	1.92 (0.93 to 3.96)
Maternal infectious complication — no. (%)	268 (13.3)	280 (13.8)	0.96 (0.82 to 1.13)	0.96 (0.82 to 1.12)
Breast-feeding at discharge — no./total no. (%)	1977/2016 (98.1)	1993/2029 (98.2)	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)
Pharmacologic treatment for gestational diabetes — no. (%)	221 (10.9)	94 (4.6)	2.37 (1.87 to 2.99)	2.40 (1.90 to 3.03)
Use of insulin	116 (5.7)	49 (2.4)	2.38 (1.72 to 3.31)	2.41 (1.74 to 3.34)
Use of oral hypoglycemic drugs	175 (8.7)	78 (3.8)	2.26 (1.74 to 2.93)	2.28 (1.76 to 2.95)
Insulin and oral hypoglycemic drugs	70 (3.5)	33 (1.6)	2.13 (1.42 to 3.21)	2.15 (1.43 to 3.23)
Antenatal hospitalization — no. (%)	235 (11.6)	242 (11.9)	0.98 (0.83 to 1.16)	0.97 (0.82 to 1.15)

Antenatal hospital stay — days	0.4±2.1	0.4±2.1	0.99 (0.70 to 1.40)††	1.03 (0.76 to 1.40)††
Diabetes service visits — no.	0.6±1.6	0.2±1.0	2.61 (1.94 to 3.52)‡‡	2.42 (1.80 to 3.26)‡‡
Diabetes medical specialist visits since OGTT — no.	0.3±0.9	0.1±0.6	2.48 (1.87 to 3.30)‡‡	2.39 (1.80 to 3.18)‡‡
Diabetes nurse visits — no.	0.4±1.2	0.2±0.8	2.47 (1.85 to 3.30)‡‡	2.41 (1.80 to 3.21)‡‡
Dietitian visits — no.	0.1±0.3	<0.1±0.3	2.27 (1.73 to 2.96)‡‡	2.26 (1.73 to 2.95)‡‡
Postnatal stay — days	3.0±2.1	3.0±2.1	0.98 (0.94 to 1.02)‡‡	0.98 (0.94 to 1.02)‡‡

* Plus–minus values are means ±SD. DVT denotes deep-vein thrombosis, NA not applicable because no event was reported, and PE pulmonary embolism.
† Treatment effects are given as the relative risk, unless otherwise indicated.
‡ The treatment effect was adjusted for body-mass index, planned birthing institution, and maternal age and gestational age at randomization.
§ A woman could have more than one serious health outcome.
¶ The effect size was judged to be clinically not interpretable (i.e., median exact odds ratio, 0.42; 95% CI, 0.00 to 3.49).
‖ The treatment effect is given as the exact odds ratio, as estimated from an exact logistic-regression model; in the adjusted analysis, the treatment effect was adjusted for body-mass index and planned birthing institution.
** The treatment effect is given as the mean difference, as estimated from a linear-regression model.
†† The treatment effect is given as the ratio of means, as estimated from a zero-inflated negative binomial-regression model.
‡‡ The treatment effect is given as the ratio of means, as estimated from a negative binomial-regression model.

group (215 [10.7%] vs. 170 [8.4%]; adjusted relative risk, 1.27; 95% CI, 1.05 to 1.54). Other secondary infant health outcomes, including the use of health services, were similar in the two groups (Table 2).

SECONDARY MATERNAL OUTCOMES

Labor was more likely to be induced among the women in the lower-glycemic-criteria group than among those in the higher-glycemic-criteria group (681 [33.7%] vs. 613 [30.2%]; adjusted relative risk, 1.12; 95% CI, 1.02 to 1.22) (Table 3), and the use of pharmacologic treatment for gestational diabetes was more common among the women in the lower-glycemic-criteria group (221 [10.9%] vs. 94 [4.6%]; adjusted relative risk, 2.40; 95% CI, 1.90 to 3.03). Pharmacologic treatment included the use of the oral hypoglycemic drug metformin, insulin, and both metformin as an oral hypoglycemic drug and insulin. The use of health services was greater among the women in the lower-glycemic-criteria group than among those in the higher-glycemic-criteria group, as reflected by the participants having more visits to the diabetes service, diabetes specialist, diabetes nurse, and dietitian. Other maternal outcomes were similar in the two trial groups (Table 3).

PRESPECIFIED SUBGROUP ANALYSIS

In the prespecified subgroup analysis that included women in both groups whose OGTT results fell between the lower and higher glycemic criteria, the outcomes of 195 women who received treatment for gestational diabetes were compared with those of 178 women who did not (Table S2). The characteristics of the women who received treatment were similar to those who did not (Table S3).

Among the women included in the subgroup analysis, those in the lower-glycemic-criteria group gave birth to fewer large-for-gestational-age infants than those in the higher-glycemic-criteria group (12 of 195 [6.2%] vs. 32 of 178 [18.0%]; adjusted relative risk, 0.33; 95% CI, 0.18 to 0.62). The adjusted number of women needed to diagnose and treat gestational diabetes in order to prevent one large-for-gestational-age infant in this subgroup was 4 (95% CI, 2 to 17). Other infant anthropometric measurements, including the incidence of macrosomia, were lower in the lower-glycemic-criteria group than in the higher-glycemic-criteria group, and the mean gestational age

at birth was slightly lower in the lower-glycemic-criteria group, although the percentage of small-for-gestational-age infants was higher in the lower-glycemic-criteria group than in the higher-glycemic-criteria group according to Fenton–World Health Organization standards[23] but not according to customized New Zealand standards.[24] A serious health outcome occurred in 1 of 195 infants (0.5%) in the lower-glycemic-criteria group and in 7 of 178 infants (3.9%) in the higher-glycemic-criteria group. There were no substantial between-group differences in the incidence of stillbirth, death of a live-born infant before discharge, or birth trauma, but shoulder dystocia was less common in the lower-glycemic-criteria group than in the higher-glycemic-criteria group. Neonatal hypoglycemia was detected and treated more frequently in the lower-glycemic-criteria group than in the higher-glycemic-criteria group (53 of 195 [27.2%] vs. 16 of 178 [9.0%]). Other secondary infant health outcomes and the use of health services were similar in the two trial groups.

In the subgroup analysis, mothers in the lower-glycemic-criteria group had less gestational weight gain than those in the higher-glycemic-criteria group (10.0 kg vs. 11.9 kg), as well as a lower incidence of preeclampsia (1 of 195 [0.5%] vs. 10 of 178 [5.6%]), more instances of induced labor (111 of 195 [56.9%] vs. 54 of 178 [30.3%]), and a higher prevalence of breast-feeding at hospital discharge (194 of 195 [99.5%] vs. 169 of 178 [94.9%]). Pharmacologic treatment for gestational diabetes was much more common among the women in the lower-glycemic-criteria group than among those in the higher-glycemic-criteria group (124 of 195 [63.6%] vs. 4 of 178 [2.3%]). The use of health services was greater among the women in the lower-glycemic-criteria group, who had more visits to the diabetes service, diabetes specialist, diabetes nurse, and dietician. Other maternal outcomes did not differ substantially between the two groups. The results of post hoc exploratory analyses that additionally adjusted for parity were consistent with the primary results.

DISCUSSION

In this randomized trial comparing two recommended criteria[17,18] for the diagnosis of gestational diabetes among 4061 women, we found that those who had been assigned to the lower-glycemic-criteria group were more than 2.5 times as likely to receive a diagnosis of and treatment for gestational diabetes as those assigned to the higher-glycemic-criteria group when tested in midpregnancy. Greater proportions of women receiving a diagnosis of gestational diabetes through the use of the lower glycemic criteria of the IADPSG than through the use of the current higher glycemic criteria[27-29] and other criteria[30] have been reported.

Although use of the lower glycemic criteria led to a greater proportion of women receiving a diagnosis of gestational diabetes and treatment than did use of the higher glycemic criteria, it did not lead to apparent health benefits; however, use of the lower glycemic criteria led to greater use of health services. We found no significant difference in the incidence of birth of a large-for-gestational-age infant (the primary outcome) between the two trial groups. However, more infants with hypoglycemia warranting treatment were identified in the lower-glycemic-criteria group than in the higher-glycemic-criteria group, a finding that is most likely due to the higher percentage of infants born to a mother with a diagnosis of gestational diabetes who were therefore identified as requiring screening for hypoglycemia according to the hospital protocol. Some infants born to mothers in the higher-glycemic-criteria group may have had undetected hypoglycemia that was not treated. Neonatal hypoglycemia is associated with later adverse neurodevelopment,[31,32] so follow-up will be needed in order to know whether this detection and treatment lead to later benefits or harms.

No health benefits were observed among the women in our trial population; the risk of preeclampsia was similar in the trial groups, as was the mode of birth. Women assigned to the lower-glycemic-criteria group were more likely to have their labor induced than those in the higher-glycemic-criteria group. Induction of labor by 40 weeks' gestation is recommended for women with well-controlled gestational diabetes, and earlier induction of labor is recommended for women receiving pharmacologic treatment for hyperglycemia or if there are maternal or infant complications.[14,17,33] The use of health services was greater among the women in the lower-glycemic-criteria group than among those in the higher-glycemic-criteria group; more women in the lower-glycemic-criteria group visited the dia-

betes service, the diabetes specialist, the diabetes nurse, and the dietitian[17] and received pharmacologic treatments for blood glucose control. We found no evidence that this greater use of health services led to maternal benefits.

In our trial, we were able to assess not only the effects of diagnosis and treatment on the mother and her infant at the population level when using the lower glycemic criteria for the diagnosis of gestational diabetes, but also the effects of diagnosis and treatment for milder disease — an evidence gap identified by professional bodies[9] and other researchers.[21,22] Almost 63% of the women in the lower-glycemic-criteria group who received a diagnosis of gestational diabetes and treatment would not have been identified as having gestational diabetes if they had been assigned to the higher-glycemic-criteria group and therefore would not have received treatment.

Our subgroup analysis suggests clinically important, short-term maternal and infant health benefits for the women who received a diagnosis of a milder degree of gestational diabetes and also received treatment, as compared with those who did not receive a diagnosis of a milder degree of gestational diabetes and therefore did not receive treatment; these health benefits include, for the infant, a lower risk of being large for gestational age and, for the woman, a lower risk of preeclampsia. The number needed to treat to prevent one large-for-gestational-age infant in this subgroup of women with OGTT results that fell between the lower and higher glycemic criteria was only 4. Our findings in this subgroup may be relevant for pregnant women, clinicians, and service providers. Health economic analyses will be needed to aid decision making. Infants born large for gestational age have higher risks of obesity, hypertension, and diabetes[5] in later life, so follow-up will be needed to assess whether the differences in body size observed at birth influence later health. Gestational diabetes is a known risk factor for later cardiometabolic problems in women[4,34]; thus, further follow-up of the mothers is needed to assess whether treating women with mild gestational diabetes has later maternal cardiometabolic benefits.[9,35]

Two previous randomized trials have compared the IADPSG criteria with the Carpenter–Coustan screening criteria[36,37] (Table S4), but data from trials comparing the IADPSG criteria[15] with the criteria currently recommended for use in New Zealand are lacking.[10] Both previous trials showed that there were more women who received a diagnosis of gestational diabetes with the IADPSG criteria than with the Carpenter–Coustan screening criteria but that there was no improvement in perinatal health.

In the current randomized trial, use of the lower glycemic criteria, as expected, led to a higher percentage of women receiving a diagnosis of gestational diabetes than use of the higher glycemic criteria; therefore, use of health services, which included induction of labor, care for diabetes, pharmacotherapy for blood glucose control, and treatment for neonatal hypoglycemia, was greater in the lower-glycemic-criteria group. Overall, the risks of giving birth to a large-for-gestational-age infant and of other infant or maternal complications were not lower with the lower glycemic criteria than with the higher glycemic criteria.

Supported by a 3-year project grant (ID14/104) from the Health Research Council of New Zealand, and grants from Counties Manukau Health Tupu Fund, the Liggins Institute Philanthropic Fund, and the New Zealand Society for the Study of Diabetes.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the women and infants who participated in this trial, the midwives and medical staff who counseled eligible women, and the staff who conducted the trial at each of the sites.

REFERENCES

1. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. Curr Diab Rep 2016;16:7.
2. Dodd JM, Crowther CA, Antoniou G, Baghurst P, Robinson JS. Screening for gestational diabetes: the effect of varying blood glucose definitions in the prediction of adverse maternal and infant health outcomes. Aust N Z J Obstet Gynaecol 2007;47:307-12.
3. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. BMJ 2020;369:m1361.
4. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia 2019;62:905-14.
5. Vohr BR, Boney CM. Gestational diabetes: the forerunner for the development of maternal and childhood obesity and metabolic syndrome? J Matern Fetal Neonatal Med 2008;21:149-57.
6. Catalano PM, Kirwan JP, Haugel-de Mouzon S, King J. Gestational diabetes and insulin resistance: role in short- and long-term implications for mother and fetus. J Nutr 2003;133:Suppl 2:1674S-1683S.
7. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS; Australian Carbohydrate Intolerance Study in

Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477-86.
8. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339-48.
9. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes. Diabetes Care 2021;44:Suppl 1:S15-S33.
10. Hoffman L, Nolan C, Wilson JD, Oats JJ, Simmons D. Gestational diabetes mellitus — management guidelines. Med J Aust 1998;169:93-7.
11. Nankervis A, McIntyre HD, Moses R, et al. ADIPS consensus guidelines for the testing and diagnosis of hyperglycaemia in pregnancy in Australia and New Zealand. Australasian Diabetes in Pregnancy Society, November 2014 (https://www.adips.org/downloads/2014ADIPSGDMGuidelinesV18.11.2014.pdf).
12. American College of Obstetricians and Gynecologists. Practice bulletin no. 137: gestational diabetes mellitus. Obstet Gynecol 2013;122:406-16.
13. Thompson D, Berger H, Feig D, et al. Diabetes and pregnancy. Can J Diabetes 2013;37:Suppl 1:S168-S183.
14. National Institute for Health and Care Excellence. Diabetes in pregnancy: management from preconception to the postnatal period. February 25, 2015 (https://www.nice.org.uk/guidance/ng3).
15. Metzger BE, Gabbe SG, Persson B, et al. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676-82.
16. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. 2013 (https://apps.who.int/iris/handle/10665/85975).
17. New Zealand Ministry of Health. Screening, diagnosis and management of gestational diabetes in New Zealand: a clinical practice guideline. 2014 (https://www.health.govt.nz/system/files/documents/publications/screening-diagnosis-management-of-gestational-diabetes-in-nz-clinical-practive-guideline-dec14-v2.pdf).
18. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991-2002.
19. Vandorsten JP, Dodson WC, Espeland MA, et al. NIH consensus development conference: diagnosing gestational diabetes mellitus. NIH Consens State Sci Statements 2013;29:1-31.
20. Davidson KW, Barry MJ, Mangione CM, et al. Screening for gestational diabetes: US Preventive Services Task Force recommendation statement. JAMA 2021;326:531-8.
21. Waters TP, Dyer AR, Scholtens DM, et al. Maternal and neonatal morbidity for women who would be added to the diagnosis of GDM using IADPSG criteria: a secondary analysis of the Hyperglycemia and Adverse Pregnancy Outcome study. Diabetes Care 2016;39:2204-10.
22. Sacks DA, Black MH, Li X, Montoro MN, Lawrence JM. Adverse pregnancy outcomes using the International Association of the Diabetes and Pregnancy Study Groups criteria: glycemic thresholds and associated risks. Obstet Gynecol 2015;126:67-73.
23. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.
24. Anderson NH, Sadler LC, Stewart AW, Fyfe EM, McCowan LM. Ethnicity, body mass index and risk of pre-eclampsia in a multiethnic New Zealand population. Aust N Z J Obstet Gynaecol 2012;52:552-8.
25. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. Arch Neurol 1976;33:696-705.
26. Rumbold AR, Crowther CA, Haslam RR, Dekker GA, Robinson JS; ACTS Study Group. Vitamins C and E and the risks of preeclampsia and perinatal complications. N Engl J Med 2006;354:1796-806.
27. Wong VW, Lin A, Russell H. Adopting the new World Health Organization diagnostic criteria for gestational diabetes: how the prevalence changes in a high-risk region in Australia. Diabetes Res Clin Pract 2017;129:148-53.
28. Moses RG, Morris GJ, Petocz P, San Gil F, Garg D. The impact of potential new diagnostic criteria on the prevalence of gestational diabetes mellitus in Australia. Med J Aust 2011;194:338-40.
29. Ekeroma AJ, Chandran GS, McCowan L, Ansell D, Eagleton C, Kenealy T. Impact of using the International Association of Diabetes and Pregnancy Study Groups criteria in South Auckland: prevalence, interventions and outcomes. Aust N Z J Obstet Gynaecol 2015;55:34-41.
30. Saeedi M, Cao Y, Fadl H, Gustafson H, Simmons D. Increasing prevalence of gestational diabetes mellitus when implementing the IADPSG criteria: a systematic review and meta-analysis. Diabetes Res Clin Pract 2021;172:108642.
31. McKinlay CJD, Alsweiler JM, Anstice NS, et al. Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years. JAMA Pediatr 2017;171:972-83.
32. Kaiser JR, Bai S, Gibson N, et al. Association between transient newborn hypoglycemia and fourth-grade achievement test proficiency: a population-based study. JAMA Pediatr 2015;169:913-21.
33. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 190: gestational diabetes mellitus. Obstet Gynecol 2018;131(2):e49-e64.
34. Lowe WL Jr, Scholtens DM, Lowe LP, et al. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. JAMA 2018;320:1005-16.
35. Bilous RW, Jacklin PB, Maresh MJ, Sacks DA. Resolving the gestational diabetes diagnosis conundrum: the need for a randomized controlled trial of treatment. Diabetes Care 2021;44:858-64.
36. Hillier TA, Pedula KL, Ogasawara KK, et al. A pragmatic, randomized trial of gestational diabetes screening. N Engl J Med 2021;384:895-904.
37. Davis EM, Abebe KZ, Simhan HN, et al. Perinatal outcomes of two screening strategies for gestational diabetes mellitus: a randomized controlled trial. Obstet Gynecol 2021;138:6-15.

Supplementary Appendix

Supplement to: Crowther CA, Samuel D, McCowan LME, et al. Lower versus higher glycemic criteria for diagnosis of gestational diabetes. N Engl J Med 2022;387:587-98. DOI: 10.1056/NEJMoa2204091

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

Supplement to: Crowther C, Samuel D, McCowan L, et al. Lower versus higher diagnostic criteria for detecting gestational diabetes.

This appendix has been provided by the authors to give readers additional information about their work.

Table of Contents **Page**

List of Investigators

The Steering Group

C. Crowther, Liggins Institute, University of Auckland, Auckland, New Zealand.

L. McCowan, Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand.

J. Rowan, Department of Obstetrics, National Women's Health, Auckland City Hospital, Auckland, New Zealand.

R. Edlin, School of Population Health, University of Auckland, Auckland, New Zealand.

C. McKinlay, Liggins Institute, University of Auckland, Auckland, New Zealand.

The GEMS Trial Group

GEMS Data Management Team Liggins Institute, University of Auckland, Auckland, New Zealand: D. Samuel, J. Yates, S. Philipsen, C. Paine, R. Hasan, V. Ball, S. Zhang, S. Khan, C. Crowther, T. Tran (statistician).

Data and Safety Monitoring Committees: P. Middleton, Healthy Mothers, Babies and Children, South Australian Health and Medical Research Institute, North Adelaide, South Australia. K. Groom, Liggins Institute, University of Auckland, Auckland, New Zealand. F. Bloomfield, Liggins Institute, University of Auckland, Auckland, New Zealand. G. Gamble, Liggins Institute, University of Auckland, Auckland, New Zealand. J. Alsweiler, Department of Paediatrics: Child and Youth Health, The University of Auckland, Auckland, New Zealand, R. Martis, Liggins Institute, University of Auckland, Auckland, New Zealand. M. Wise, Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand.

Research Team Liggins Institute, University of Auckland, Auckland, New Zealand: D. Samuel, H. Hauch, V. Rose, R. Edwards, S. Masomi, D. West, J. Barrowclough, G. Maree, K. Manerkar, C. Overfield, S. Said, F. Keen, B. Morison, S. Lu, M. Li, C. Goodson, S. Edwards, O. Hofer.

Participating Institutions:

Auckland District Health Board, Auckland, New Zealand: S. Fleming, J. McDougall, C. McLintock, C. Marnoch, L. McCowan, L. Mackey, K. Upton, A. Siegers, A. Budden.

Counties Manukau Health, Auckland, New Zealand: K. Okesene-Gafa, J. Griffiths, T. Thompson, S. Tout, D. Fenton, A. Hinks, G. McIver, S. Wadsworth, G. Parry, I. Smart, H. Walker, R. Hubbard, L. Austerberry, W. Davison, J. Graham, M. Fakasilea, L. Mravicich, N. Williams, J. Giles, N. Trainor, L. Maclennan.

Prespecified study outcome definitions.*

Type	Outcome
Infant	Large for gestational age defined as a birth weight >90th percentile by population standards[1]
	Birth weight
	Birth length
	Birth head circumference
	Birth weight z-score
	Birth length z-score
	Birth head circumference z-score
	Large for gestational age by customized standards[2]
	Small for gestational age defined as a birth weight <10th percentile by Fenton-World Health Organization standards[1]
	Small for gestational age defined as a birth weight <10th percentile by customized New Zealand standards[2]
	Macrosomia defined as birth weight ≥4 kg
	Gestational age at birth
	Preterm birth birth defined as <37 weeks' gestation
	Serious health outcomes defined as perinatal death or birth trauma (nerve palsy or bone fracture) or shoulder dystocia.[3]
	Apgar score <4 at 5 minutes
	Type of lung disease
	Severity of lung disease
	Use of respiratory support
	Hypoglycemia requiring treatment defined as blood glucose concentration <2.6 mmol/L
	Hyperbilirubinaemia requiring phototherapy
	Proven systemic infection in first 48 hours of life
	Seizures at <24 hours age or requiring two or more drugs to control
	Tube feeding >4 days
	Neonatal encephalopathy[4]
	Neonatal intensive care admission
	Length of stay in neonatal intensive care
	Length of postnatal stay.
Type	**Outcome**
Women	Composite of serious health outcomes up to the time of primary hospital discharge after the birth defined by one or more of maternal death, pulmonary oedema, eclampsia, stroke, adult respiratory distress syndrome, cardiac arrest, respiratory arrest, placental abruption, haemolysis, coagulopathy, major postpartum haemorrhage, deep vein thrombosis or pulmonary embolism requiring anticoagulant therapy[5]
	Preeclampsia
	Induction of labor
	Mode of birth

Postpartum hemorrhage (≥500 ml)

Gestational weight gain

Use of pharmacologic treatment for gestational diabetes

Chorioamnionitis requiring antibiotics during labor

Maternal infectious morbidity including puerperal sepsis requiring antibiotics.

Breast feeding at hospital discharge

Health service utilization defined as health professional visits

Specialist diabetes care

Need for antenatal admission

Length of antenatal admission

Length of postnatal stay.

* Defined in the GEMS statistical analysis plan.

Table S1: Representativeness of Study Participants.

Category	
Disease, problem, or condition under investigation	Gestational diabetes.
Special considerations related to:	
Sex and Gender	Only pregnant women can develop gestational diabetes.
Age	There is a linear increase in the risk of gestational diabetes with advancing maternal age with older women of child bearing age are at greatest risk.[6]
Race or ethnic group	In New Zealand 44.6% of recent mothers identify as European, 25.0% as Māori, 17.7% as Asian (including Indian), 10.1% as Pacific peoples and 2.6% as other ethnicities.[7] In New Zealand, gestational diabetes disproportionately affects ethnic groups being most prevalent amongst Asian, Indian women then Pacific peoples, Māori and European.
Geography	Rates of gestational diabetes are rising throughout the world linked to the increasing obesity rates.[8] Rates vary between countries and availability of resources may impact the ability to screen for and diagnose gestational diabetes and to provide care for women with gestational diabetes and their infants.[9] South-East Asia has the highest prevalence with Middle East and North Africa the lowest.[9]
Overall representativeness of this trial	The trial population had a median gestational age at entry of 27.3 weeks. Amongst the participants the proportion of ethnicities were 40% European, 33.1% Asian, 15 3% Pacific peoples, 5 5% Māori, and 6.0% other. Asian, Pacific people and European were well representative whilst Māori under representative of women in the New Zealand population giving birth.[7] All participants in this study were enrolled in New Zealand.

Footnote: A search of PubMed was undertaken to assess how gestational diabetes affects women of different ages and ethnicities.

Table S2. Maternal and Infant Outcomes for Women with OGTT Fasting Plasma Glucose Concentration 5.1 to <5.5 mmol/l, and/or 1 hour >10.0 mmol/l and/or 2-hour 8.5 to <9.0 mmol/l by Criteria Group for the Pre-specified Subgroup.*

Outcomes	Lower-Glycemic-Criteria Group (N=195)	Higher-Glycemic-Criteria Group (N=178)	Unadjusted treatment effect (95% CI)†	Adjusted treatment effect (95% CI)†‡
Infant Outcomes				
Primary outcome: large-for-gestational age infant – no. (%)	12 (6.2)	32 (18.0)	0.34 (0.18 to 0.64)	0.33 (0.18 to 0.62)
Other birth-related anthropometry outcomes				
Birth weight – g	3254 ±445	3507 ±565	-253.49 (-355.95 to -151.03)§	-265.56 (-367.57 to -163.55)§
Birth weight z-scores¶	-0.06 ±0.87	0.32 ±1.04	-0.39 (-0.58 to -0.19)§	-0.40 (-0.59 to -0.20)§
Birth length – cm	50.4 ±2.4	51.2 ±2.8	-0.78 (-1.31 to -0.26)§	-0.84 (-1.36 to -0.32)§
Birth length z-scores¶	0.26 ±1.0	0.49 ±1.1	-0.23 (-0.44 to -0.02)§	-0.24 (-0.45 to -0.03)§
Birth head circumference – cm	34.5 ±1.4	34.8 ±1.7	-0.31 (-0.62 to 0.01)§	-0.36 (-0.67 to -0.04)§
Birth head circumference z-scores¶	0.21 ±1.02	0.33 ±1.16	-0.11 (-0.34 to 0.11)§	-0.13 (-0.35 to 0.09)§
Large for gestational age according to customized New Zealand standards) – no. (%)	18 (9.2)	35 (19.7)	0.47 (0.28 to 0.80)	0.49 (0.29 to 0.83)
Small for gestational age – no. (%)	19 (9.7)	7 (3.9)	2.48 (1.07 to 5.75)	2.64 (1.13 to 6.16)
Small for gestational age according to customized New Zealand standards – no. (%)	26 (13.3)	16 (9.0)	1.48 (0.82 to 2.67)	1.49 (0.82 to 2.69)
Macrosomia – no. (%)	8 (4.1)	29 (16.3)	0.25 (0.12 to 0.54)	0.24 (0.11 to 0.52)
Gestational age at birth – wk	38.8 ±1.0	39.1 ±1.6	-0.37 (-0.63 to -0.10)§	-0.39 (-0.66 to -0.13)§
Preterm birth, <37 wk of gestation – no. (%)	9 (4.6)	10 (5.6)	0.82 (0.34 to 1.98)	0.86 (0.36 to 2.07)
Serious health outcome – no. (%)				
Composite of stillbirth, death of liveborn infant before discharge, birth trauma, or shoulder dystocia	1 (0.5)	7 (3.9)	0.13 (0.003 to 1.00)‖	0.13 (0.003 to 1.05)‖
Stillbirth	0 (0.0)	0 (0.0)	NA	NA
Death of liveborn prior to discharge	0 (0.0)	0 (0.0)	NA	NA
Birth trauma	0 (0.0)	1 (0.6)	NA**	NA**
Shoulder dystocia	1 (0.5)	7 (3.9)	0.13 (0.003 to 1.00)‖	0.13 (0.004 to 1.05)‖
Apgar score <4 at 5 min – no. (%)	0 (0.0)	0 (0.0)	NA	NA
Any neonatal lung disease – no. (%)	3 (1.5)	5 (2.8)	0.54 (0.08 to 2.83)‖	0.52 (0.08 to 2.75)‖
Use of respiratory support – no. (%)	10 (5.1)	10 (5.6)	0.91 (0.39 to 2.14)	0.89 (0.39 to 2.06)
Hypoglycemia warranting treatment – no. (%)	53 (27.2)	16 (9.0)	3.02 (1.80 to 5.09)	3.09 (1.83 to 5.21)
Hyperbilirubinemia warranting phototherapy – no. (%)	7 (3.6)	4 (2.3)	1.62 (0.40 to 7.67)‖	1.66 (0.41 to 7.91)‖

Outcomes	Lower-Glycemic-Criteria Group (N=195)	Higher-Glycemic-Criteria Group (N=178)	Unadjusted treatment effect (95% CI)†	Adjusted treatment effect (95% CI)†‡
Proven systemic infection in the first <48 hours after birth – no. (%)	0 (0.0)	1 (0.6)	NA**	NA**
Seizure at <24 hours or that led to the use of ≥2 drugs to control – no. (%)	0 (0.0)	0 (0.0)	NA	NA
Tube feeding >4 days – no. (%)	2 (1.0)	4 (2.3)	0.45 (0.04 to 3.20)‖	0.51 (0.04 to 3.81)‖
Neonatal encephalopathy – no. (%)	0 (0.0)	0 (0.0)	NA	NA
Admission to neonatal intensive care unit – no. (%)	7 (3.6)	4 (2.3)	1.62 (0.40 to 7.67)‖	1.78 (0.44 to 8.55)‖
Stay in neonatal intensive care unit – days	0.2 ±2.0	0.5 ±5.2	0.16 (0.01 to 2.66)††	0.23 (0.01 to 4.62)††
Length of postnatal stay – days	4.0 ±3.2	4.5 ±6.9	0.89 (0.77 to 1.03)‡‡	0.93 (0.80 to 1.08)‡‡
Maternal outcomes				
Serious maternal health outcomes – no. (%)	8 (4.1)	8 (4.5)	0.91 (0.35 to 2.38)	0.85 (0.33 to 2.21)
Preeclampsia – no. (%)	1 (0.5)	10 (5.6)	0.09 (0.002 to 0.62)‖	0.08 (0.002 to 0.60)‖
Induction of labor – no. (%)	111 (56.9)	54 (30.3)	1.88 (1.46 to 2.42)	1.89 (1.47 to 2.43)
Cesarean section – no. (%)	77 (39.5)	86 (48.3)	0.82 (0.65 to 1.03)	0.82 (0.65 to 1.02)
Elective – no. (%)	26 (13.3)	32 (18.0)	0.74 (0.46 to 1.19)	0.75 (0.47 to 1.19)
Emergency – no. (%)	51 (26.2)	54 (30.3)	0.86 (0.62 to 1.19)	0.87 (0.63 to 1.21)
Postpartum haemorrhage – no./total (%)	54/191 (28.3)	57/174 (32.8)	0.86 (0.63 to 1.18)	0.85 (0.63 to 1.16)
Gestational weight gain – kg	10.0 ±7.1	11.9 ±6.8	-1.89 (-3.36 to -0.42)§	-1.99 (-3.45 to -0.54)§
Chorioamnionitis that led to the use of antibiotics – no. (%)	1 (0.5)	2 (1.1)	0.45 (0.01 to 8.80)‖	0.49 (0.01 to 9.57)‖
Maternal infectious complication – no. (%)	24 (12.3)	22 (12.4)	1.00 (0.58 to 1.71)	1.00 (0.59 to 1.71)
Breastfeeding at hospital discharge – no. (%)	194 (99.5)	169 (94.9)	1.05 (1.01 to 1.08)	1.05 (1.01 to 1.09)
Pharmacologic treatment for gestational diabetes – no. (%)	124 (63.6)	4 (2.3)	75.03 (27.03 to 290 34)‖	84.22 (29.64 to 332.23)‖
Use of Insulin – no. (%)	57 (29.2)	3 (1.7)	23.94 (7 53 to 122.07)‖	24.42 (7.61 to 125.35)‖
Use of oral hypoglycaemic metformin – no. (%)	102 (52.3)	4 (2.3)	47.26 (17.09 to 182 34)‖	47.81 (17.21 to 185.15)‖
Insulin and oral hypoglycemic metformin – no. (%)	35 (17.9)	3 (1.7)	12.70 (3.89 to 65.76)‖	12.44 (3.80 to 64.59)‖
Antenatal hospitalization – no. (%)	26 (13.3)	27 (15.2)	0.88 (0.53 to 1.45)	0.90 (0.54 to 1.48)
Antenatal hospital stay – days	0.3 ±1.0	0.5 ±3.1	0.55 (0.26 to 1.16)‡‡	0.55 (0.26 to 1.17)‡‡
Diabetic service visits – no.	3.6 ±2.6	0.1 ±0.8	26.85 (17.51 to 41.17)‡‡	26.44 (17.26 to 40.49)‡‡
Diabetes medical specialist visits since OGTT – no.	1.7 ±1.5	0.1 ±0.4	24.87 (13.80 to 44.83)‡‡	25.30 (14.04 to 45.60)‡‡
Diabetes nurse visits – no.	2.4 ±2.2	0.03 ±0.2	71.66 (31.65 to 162 24)‡‡	71.41 (31.55 to 161.63)‡‡

Outcomes	Lower-Glycemic-Criteria Group (N=195)	Higher-Glycemic-Criteria Group (N=178)	Unadjusted treatment effect (95% CI)†	Adjusted treatment effect (95% CI)†‡
Dietitian visits – no.	0.6 ±0.6	0.02 ±0.2	28.30 (14 30 to 55.98)‡‡	28.71 (14.56 to 56.61)‡‡
Postnatal stay – days	3.1 ±2.5	3.0 ±2.0	1.04 (0.91 to 1.19)‡‡	1.03 (0.90 to 1.18)‡‡

OGTT fasting plasma glucose concentration was 5.1 to <5.5 mmol/l, and/or 1 hour >10.0 mmol/l and/or their 2-hour plasma glucose concentration was 8.5 to <9.0 mmol/l for women in both criteria groups.

* Plus–minus values are means ±SD. NA denotes not applicable because no event was reported.

† Treatment effects are given as the relative risk with the 95% confidence interval, unless otherwise indicated.

‡ The treatment effect was adjusted for body-mass index, planned birthing institution, and maternal age and gestational age at the time of randomization.

§ The treatment effect is given as the mean difference with the 95% confidence interval, as estimated from a linear-regression model.

¶ The z scores were estimated with the use of the Fenton–World Health Organization growth references.[1]

‖ The treatment effect is given as the exact odds ratio with the 95% confidence interval, as estimated from an exact logistic-regression model; in the adjusted analysis, the treatment effect was adjusted for body-mass index and planned birthing institution.

** The effect size was judged to be clinically not interpretable (i.e., median exact odds ratio, 0.91; 95% CI, 0.00 to 17.34).

†† The treatment effect is given as the ratio of means with the 95% confidence interval, as estimated from a zero-inflated negative binomial-regression model.

‡‡ The treatment effect is given as the ratio of means with the 95% confidence interval, as estimated from a negative binomial-regression model.

Table S3. Characteristics of the Participants at Trial Entry included in the Pre-specified Subgroup.*

Characteristics	Lower-Glycemic-Criteria Group N = 195	Higher-Glycemic-Criteria Group N = 179
Maternal age – yr	32.3 ± 5.1	32.5 ± 5.5
Primiparous – no. (%)	92 (47.2)	78 (43.6)
Gestational age at OGTT - wk	27.4 (26.3-28.7)	27.1 (26.0-28.3)
24 to < 28 weeks – no. (%)	120 (61 5)	119 (66.5)
28 to < 32 weeks – no. (%)	75 (38.5)	60 (33.5)
Median body mass index (IQR)†	28.2 (25.0-32.5)	27.9 (25.0-33.1)
Race or ethnic group – no. (%)†		
White	58 (29.7)	51 (28.5)
Pacific Islander	24 (12.3)	31 (17.3)
Māori	12 (6.2)	12 (6.7)
Asian	85 (43.6)	72 (40.2)
Other	16 (8.2)	13 (7.3)
Previous prenatal death – no. (%)	4 (3.9)	3 (3.0)
Chronic hypertension – no. (%)	9 (4.6)	6 (3.4)
Family history of diabetes – no. (%)	90 (46.2)	70 (39.1)
Mean OGTT result (IQR) – mg/dl		
Fasting plasma glucose level	88.3 (79.3-93.7)	88.3 (81.1-93.7)
1-hr plasma glucose level	180.2 (153.2-187.4)	176.6 (145.9-187.4)
2-hr plasma glucose level	135.1 (117.1-153.2)	135.1 (117.1-153.2)

* Plus-minus values are means ±SD. To convert glucose to millimoles per liter, multiply by 0.05551.

IQR denotes interquartile range, and OGTT oral glucose-tolerance test.

† Race or ethnic group was reported by the participants.

References

1. Fenton TR and Kim JH. A systematic review and meta-analysis to revise the Fenton growth charts for preterm infants. BMC Pediatrics 2013;13(1):1–13.
2. Anderson NH, Sadler LC, Stewart AW, Fyfe EM, McCowan LM. Ethnicity, body mass index and risk of pre-eclampsia in a multi-ethnic New Zealand population. Aust N Z J Obstet Gynaecol 2012;52(6):552-558.
3. Crowther CA, Hiller JE, Moss JR, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352(24):2477-2486.
4. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol 1976;33(10):696-705.
5. Rumbold AR, Crowther CA, Haslam RR, Dekker GA, Robinson JS. Vitamins C and E and the risks of preeclampsia and perinatal complications. N Engl J Med 2006;27(17):1796-1806.
6. Li Y, Ren X, He L, Li J, Zhang S, Chen W. Maternal age and the risk of gestational diabetes mellitus: A systematic review and meta-analysis of over 120 million participants. Diabetes Research and Clinical Practice, 2020, Volume 162, 108044, doi.org/10.1016/j.diabres.2020.108044.
7. Report on Maternity 2017. Ministry of Health 2019, Wellington, New Zealand.
8. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. Curr Diab Rep 2016;16(1):7.
9. Boyko EJ, Magliano DJ, Karuranga S, et al. International Diabetes Foundation. IDF Diabetes Atlas. 10th edition. International Diabetes Federation; 2021. Brussels, Belgium. ISBN: 978-2-930229-98-0.

ORIGINAL ARTICLE

Treatment of Gestational Diabetes Mellitus Diagnosed Early in Pregnancy

D. Simmons, J. Immanuel, W.M. Hague, H. Teede, C.J. Nolan, M.J. Peek, J.R. Flack, M. McLean, V. Wong, E. Hibbert, A. Kautzky-Willer, J. Harreiter, H. Backman, E. Gianatti, A. Sweeting, V. Mohan, J. Enticott, and N.W. Cheung, for the TOBOGM Research Group*

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.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Simmons can be contacted at da.simmons@westernsydney.edu.au or at the School of Medicine, Western Sydney University, Locked Bag 1797, Campbelltown, NSW 2751, Australia.

*The investigators in the TOBOGM Research Group are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on May 5, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2214956

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

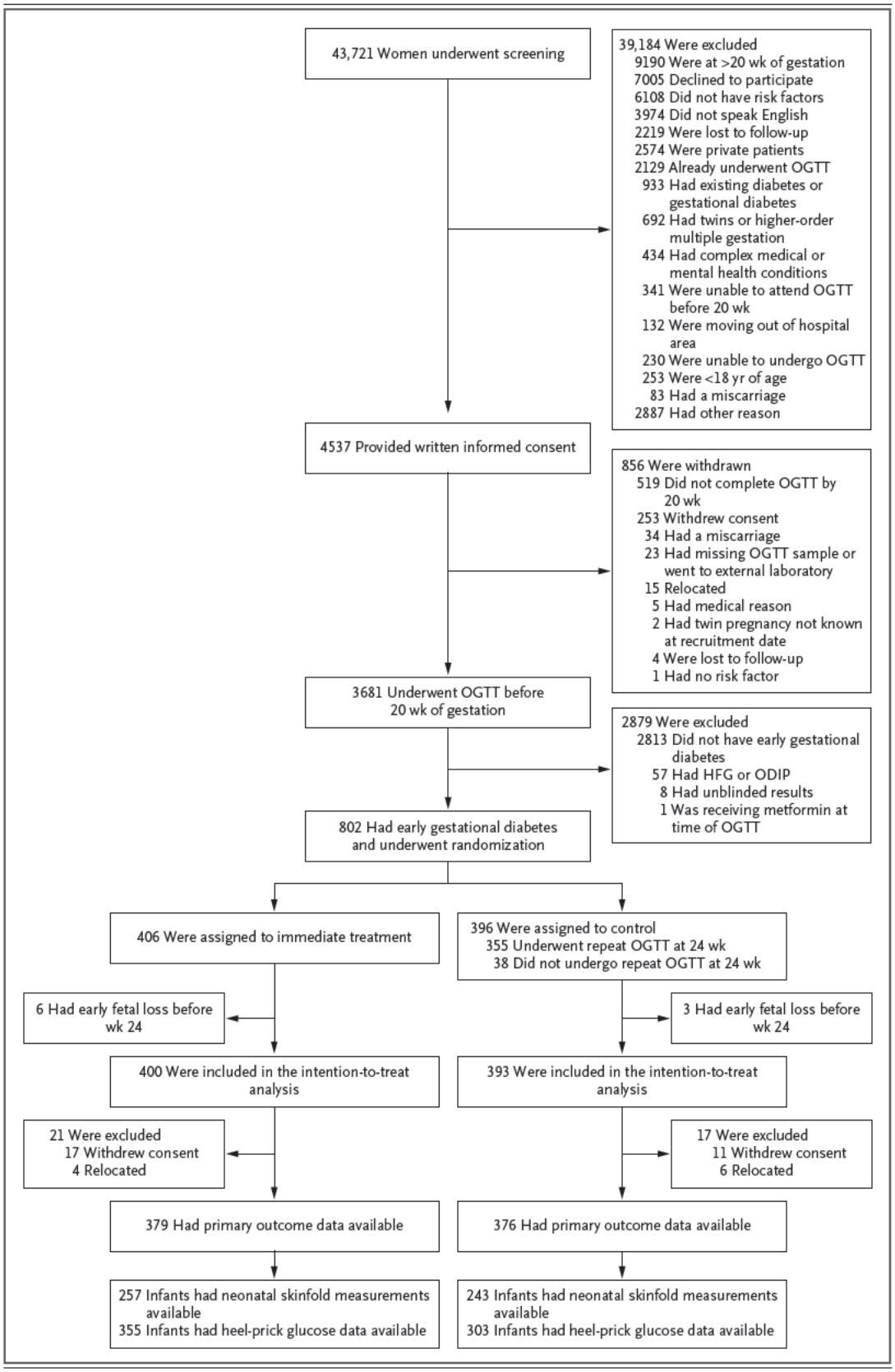
43,721 Women underwent screening
39,184 Were excluded
9190 Were at >20 wk of gestation
7005 Declined to participate
6108 Did not have risk factors
3974 Did not speak English
2219 Were lost to follow-up
2574 Were private patients
2129 Already underwent OGTT
933 Had existing diabetes or gestational diabetes
692 Had twins or higher-order multiple gestation
434 Had complex medical or mental health conditions
341 Were unable to attend OGTT before 20 wk
132 Were moving out of hospital area
230 Were unable to undergo OGTT
253 Were <18 yr of age
83 Had a miscarriage
2887 Had other reason
4537 Provided written informed consent
856 Were withdrawn
519 Did not complete OGTT by 20 wk
253 Withdrew consent
34 Had a miscarriage
23 Had missing OGTT sample or went to external laboratory
15 Relocated
5 Had medical reason
2 Had twin pregnancy not known at recruitment date
4 Were lost to follow-up
1 Had no risk factor
3681 Underwent OGTT before 20 wk of gestation
2879 Were excluded
2813 Did not have early gestational diabetes
57 Had HFG or ODIP
8 Had unblinded results
1 Was receiving metformin at time of OGTT
802 Had early gestational diabetes and underwent randomization
406 Were assigned to immediate treatment
396 Were assigned to control
355 Underwent repeat OGTT at 24 wk
38 Did not undergo repeat OGTT at 24 wk
6 Had early fetal loss before wk 24
3 Had early fetal loss before wk 24
400 Were included in the intention-to-treat analysis
393 Were included in the intention-to-treat analysis
21 Were excluded
17 Withdrew consent
4 Relocated
17 Were excluded
11 Withdrew consent
6 Relocated
379 Had primary outcome data available
376 Had primary outcome data available
257 Infants had neonatal skinfold measurements available
355 Infants had heel-prick glucose data available
243 Infants had neonatal skinfold measurements available
303 Infants had heel-prick glucose data available

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).

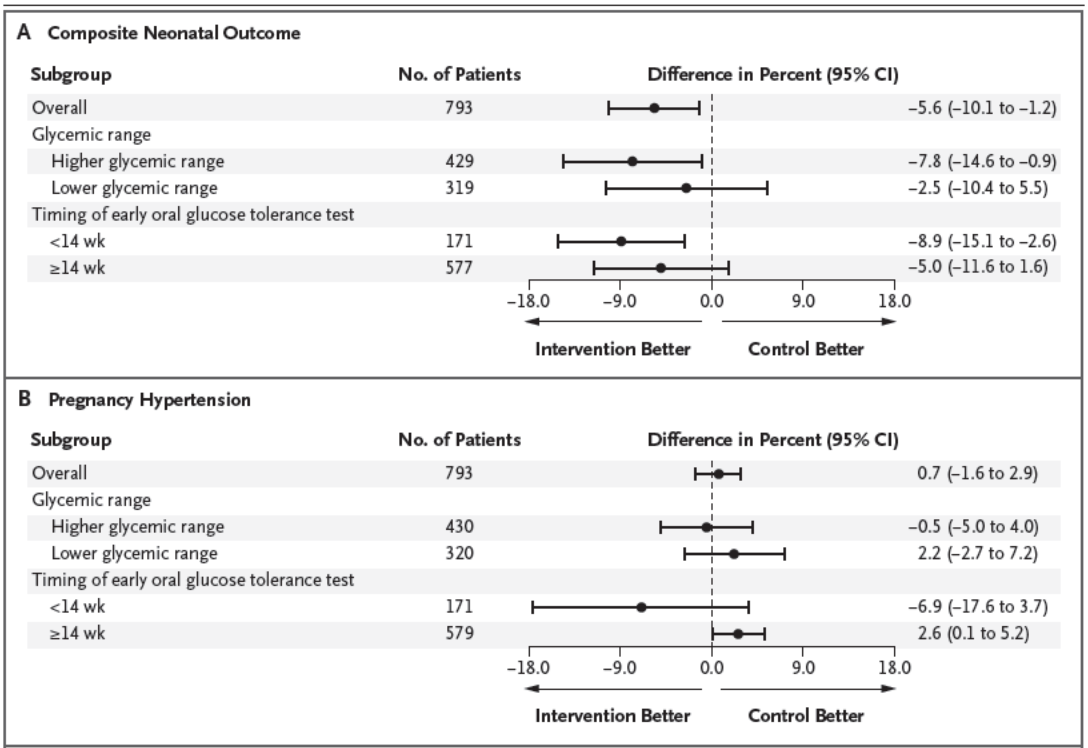

Figure 2. Primary Outcomes Overall and within Prespecified Subgroups.

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.

Supported by the National Health and Medical Research Council (grants 1104231 and 2009326), the Region Örebro Research Committee (grants Dnr OLL-970566 and OLL-942177), Medical Scientific Fund of the Mayor of Vienna (project 15205), the South Western Sydney Local Health District Academic Unit (grant 2016), and a Western Sydney University Ainsworth Trust Grant (2019).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the women who participated in the TOBOGM trial; the trial coordinators, research midwives, and nurses at each site; the maternity service and laboratory staff who assisted the project; the trial coordination staff; and the personnel at Roche for the donation of the glucose-monitoring meters used for the trial participants.

APPENDIX

The authors' full names and academic degrees are as follows: David Simmons, M.D., Jincy Immanuel, Ph.D., William M. Hague, M.D., Helena Teede, Ph.D., Christopher J. Nolan, Ph.D., Michael J. Peek, Ph.D., Jeff R. Flack, M Med., Mark McLean, Ph.D., Vincent Wong, Ph.D., Emily Hibbert, M.Clin.Ed., Alexandra Kautzky-Willer, M.D., Jürgen Harreiter, Ph.D., Helena Backman, Ph.D., Emily Gianatti, Ph.D., Arianne Sweeting, Ph.D., Viswanathan Mohan, D.Sc., Joanne Enticott, Ph.D., and N. Wah Cheung, Ph.D.

The authors' affiliations are as follows: Western Sydney University, Campbelltown, NSW (D.S., J.I.), Robinson Research Institute, University of Adelaide, Adelaide, SA (W M.H.), Monash University, Melbourne, VIC (H.T., J.E.), Canberra Hospital and Australian National University (C.J.N.) and Australian National University (M.J.P.), Canberra, ACT, Bankstown-Lidcombe Hospital (J.R.F.), Blacktown Hospital (M M.), Liverpool Hospital and University of New South Wales (V.W.), Nepean Clinical School, University of Sydney and Nepean Hospital (E.H.), the Department of Endocrinology, Royal Prince Alfred Hospital (A.S.), and Westmead Hospital (N.W.C.), Sydney, and the Department of Endocrinology, Fiona Stanley Hospital, Murdoch, WA (E.G.) — all in Australia; the Gender Medicine Unit, Division of Endocrinology and Metabolism, Department of Medicine III, Medical University of Vienna, Vienna (A.K.-W., J.H.); the Department of Obstetrics and Gynecology, Faculty of Medicine and Health, Örebro University, Orebro, Sweden (H.B.); and Dr. Mohan's Diabetes Specialities Centre and Madras Diabetes Research Foundation, Chennai, India (V M).

REFERENCES

1. ACOG practice bulletin no. 190: gestational diabetes mellitus. Obstet Gynecol 2018;131(2):e49-e64.
2. American Diabetes Association Professional Practice Committee. Management of diabetes in pregnancy: standards of medical care in diabetes — 2022. Diabetes Care 2022;45:Suppl 1:S232-S243.
3. Davidson KW, Barry MJ, Mangione CM, et al. Screening for gestational diabetes: US Preventive Services Task Force recommendation statement. JAMA 2021;326:531-8.
4. Sovio U, Murphy HR, Smith GCS. Accelerated fetal growth prior to diagnosis of gestational diabetes mellitus: a prospective cohort study of nulliparous women. Diabetes Care 2016;39:982-7.
5. Immanuel J, Simmons D. Screening and treatment for early-onset gestational diabetes mellitus: a systematic review and meta-analysis. Curr Diab Rep 2017;17:115.
6. Riskin-Mashiah S, Younes G, Damti A, Auslender R. First-trimester fasting hyperglycemia and adverse pregnancy outcomes. Diabetes Care 2009;32:1639-43.
7. Bhavadharini B, Anjana RM, Deepa M, et al. Association between number of abnormal glucose values and severity of fasting plasma glucose in IADPSG criteria and maternal outcomes in women with gestational diabetes mellitus. Acta Diabetol 2022;59:349-57.
8. Simmons D, Nema J, Parton C, et al. The treatment of booking gestational diabetes mellitus (TOBOGM) pilot randomised controlled trial. BMC Pregnancy Childbirth 2018;18:151.
9. Simmons D, Hague WM, Teede HJ, et al. Hyperglycaemia in early pregnancy: the Treatment of Booking Gestational diabetes Mellitus (TOBOGM) study: a randomised controlled trial. Med J Aust 2018;209:405-6.
10. Nankervis A, McIntyre HD, Moses R, et al. ADIPS consensus guidelines for the testing and diagnosis of hyperglycaemia in pregnancy in Australia and New Zealand. Sydney: Australasian Diabetes in Pregnancy Society, 2014 (http://adips.org/downloads/2014ADIPSGDMGuidelinesV18.11.2014_000.pdf).
11. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. Geneva: World Health Organization, 2013 (http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf).
12. The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991-2002.
13. International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676-82.
14. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treat-

ment for mild gestational diabetes. N Engl J Med 2009;361:1339-48.
15. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477-86.
16. Feig DS, Corcoy R, Jensen DM, et al. Diabetes in pregnancy outcomes: a systematic review and proposed codification of definitions. Diabetes Metab Res Rev 2015;31:680-90.
17. Catalano PM, Thomas AJ, Avallone DA, Amini SB. Anthropometric estimation of neonatal body composition. Am J Obstet Gynecol 1995;173:1176-81.
18. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-43.
19. Food and Drug Administration. Multiple endpoints in clinical trials. October 2022 (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf).
20. Western Sydney University. The Treatment Of BOoking Gestational diabetes Mellitus Study: evaluating the impact on obstetric outcomes of immediate versus delayed care for gestational diabetes diagnosed at booking. Australian New Zealand Clinical Trials Registry number ACTRN12616000924459. September 28, 2022 (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370820&isReview=true).
21. Li Y, Wang W, Zhang D. Maternal diabetes mellitus and risk of neonatal respiratory distress syndrome: a meta-analysis. Acta Diabetol 2019;56:729-40.
22. Harper LM, Jauk V, Longo S, Biggio JR, Szychowski JM, Tita AT. Early gestational diabetes screening in obese women: a randomized controlled trial. Am J Obstet Gynecol 2020;222(5):495.e1-495.e8.
23. Zhu W-W, Yang H-X, Wei Y-M, et al. Evaluation of the value of fasting plasma glucose in the first prenatal visit to diagnose gestational diabetes mellitus in China. Diabetes Care 2013;36:586-90.
24. McIntyre HD, Sacks DA, Barbour LA, et al. Issues with the diagnosis and classification of hyperglycemia in early pregnancy. Diabetes Care 2016;39:53-4.
25. Landon MB, Rice MM, Varner MW, et al. Mild gestational diabetes mellitus and long-term child health. Diabetes Care 2015;38:445-52.
26. Gillman MW, Oakey H, Baghurst PA, Volkmer RE, Robinson JS, Crowther CA. Effect of treatment of gestational diabetes mellitus on obesity in the next generation. Diabetes Care 2010;33:964-8.
27. Mills JL, Jovanovic L, Knopp R, et al. Physiological reduction in fasting plasma glucose concentration in the first trimester of normal pregnancy: the diabetes in early pregnancy study. Metabolism 1998;47:1140-4.
28. Northwestern University. Glycemic Observation and Metabolic Outcomes in Mothers and Offspring (GO MOMs). ClinicalTrials.gov. December 8, 2021 (https://clinicaltrials.gov/ct2/show/NCT04860336).
29. Simmons D. Paradigm shifts in the management of diabetes in pregnancy: the importance of type 2 diabetes and early hyperglycemia in pregnancy: the Norbert Freinkel Award Lecture. Diabetes Care 2021;44:1075-81.
30. Harris MI. Gestational diabetes may represent discovery of preexisting glucose intolerance. Diabetes Care 1988;11:402-11.
31. Jarrett RJ. Gestational diabetes: a nonentity? BMJ 1993;306:37-8.
32. Immanuel J, Flack J, Wong VW, et al. The ADIPS Pilot National Diabetes in Pregnancy Benchmarking Programme. Int J Environ Res Public Health 2021;18:4899.

Received: 14 July 2023 | Accepted: 29 July 2023

DOI: 10.1111/dme.15191

DIABETIC Medicine

COMMENTARY

Timing of gestational diabetes diagnosis: A novel precision approach to hyperglycaemia in pregnancy?

Claire L. Meek[1,2] | **David Simmons**[3]

[1]Wolfson Diabetes & Endocrine Department, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[2]Wellcome-Trust MRC Institute of Metabolic Science Metabolic Research Laboratories, University of Cambridge, Cambridge, UK

[3]Western Sydney University, Penrith, New South Wales, Australia

Correspondence
Claire L. Meek, Wolfson Diabetes & Endocrine Department, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.
Email: clm70@cam.ac.uk

Funding information
Diabetes UK; European Foundation for the Study of Diabetes; National Institute for Health and Care Research; Novo Nordisk Fonden

Keywords: diagnosis, gestational diabetes, pregnancy

1 | INTRODUCTION

Precision medicine has offered new opportunities to improve diagnosis, prognostication and management of type 1 diabetes and type 2 diabetes but is relatively unexplored in gestational diabetes. The results of the recent Treatment of Booking Gestational Diabetes Mellitus (TOBOGM) trial suggests that the timing of diagnosis may identify clinically relevant subtypes of gestational diabetes.[1] We, here, discuss the rationale, practicalities and translational opportunities of a precision approach to gestational diabetes, which incorporates the timing of diagnosis ('early' being before 20–24 weeks; 'late' being after 24 weeks).

2 | THE RATIONALE FOR USING TIME OF DIAGNOSIS AS A PRECISION APPROACH TO GESTATIONAL DIABETES

Gestational diabetes, defined as hyperglycaemia with first onset or recognition in pregnancy, which is less severe than overt diabetes, is fundamentally a heterogeneous group of disorders in both early and late pregnancy.[2,3] First-onset hyperglycaemia describes a pregnancy-induced condition, typically presenting after 24 weeks' gestation, coinciding with increasing insulin resistance of pregnancy. Conversely, first-trimester hyperglycaemia (first recognised in pregnancy) is likely to have existed before pregnancy[4] and is established before period of organogenesis. The lack of widespread glucose testing in early pregnancy prevents differentiation of these subgroups in routine clinical care, but with rising population rates of obesity and dysglycaemia, the proportion of women with hyperglycaemia in early pregnancy will increase markedly. Recent clinical studies have shown that 15–70% of pregnant women have evidence of hyperglycaemia in early pregnancy.[5]

However, it is unclear if 'early' and 'late' subtypes of gestational diabetes reflect true differences in disease pathophysiology or simply differences in the severity of the underlying altered glucose homeostasis. It has been postulated for many years that women with gestational diabetes often have pre-existing glucose intolerance prior to pregnancy.[4] Indeed, early pregnancy measures of glycaemia, body composition, insulin resistance, insulin secretion and metabolites can predict gestational diabetes diagnosed later in pregnancy.[6–9] Women with the most impaired pre-pregnancy glucose handling may have worse pregnancy outcomes[10] and be less likely to benefit from lifestyle interventions in early pregnancy or preconception.[11,12]

3 | TIMING OF DIAGNOSIS—SIMPLY A REFLECTION OF THE IMPORTANCE OF FASTING HYPERGLYCAEMIA?

It is also possible that any pathophysiological differences simply reflect the importance of elevated fasting glucose concentrations, already well established as a strong contributor to fetal growth and suboptimal pregnancy outcomes.[2,10,13–15] Clinical audit data from our centre identified that 10.5% of women with gestational diabetes were diagnosed before 24 weeks and had significantly higher fasting OGTT glucose ($p < 0.01$) and HbA1c ($p < 0.05$; unpublished data; $n = 826$; Cambridge UK). Women with impaired fasting glucose pre-pregnancy will almost inevitably have fasting hyperglycaemia in early pregnancy, resulting in a diagnosis of gestational diabetes according to many criteria internationally.

Some studies have suggested pathophysiological differences in women with fasting hyperglycaemia. For example, Immanuel and colleagues identified that insulin resistance in women with early gestational diabetes was common and strongly associated with pregnancy outcomes.[2] Using data from the UK pregnancies better eating and activity trial (UPBEAT), White and colleagues identified that women with fasting hyperglycaemia had impaired insulin resistance and impaired insulin secretory function.[16] Fasting hyperglycaemia has strong associations with large-for-gestational age compared to postprandial hyperglycaemia.[13,14]

Currently, there are limited data to suggest true differences in disease pathophysiology between 'early' and 'late' subtypes of gestational diabetes,[17,18] but this is an active area of research. Future work in the TOBOGM cohort and other cohorts will identify key characteristics of women with 'early' versus 'late' gestational diabetes; stored samples can be used to assess pathophysiology in more detail.

4 | IMPLICATIONS FOR THE NATURAL HISTORY OF GESTATIONAL DIABETES

The TOBOGM trial also demonstrates that the natural history of gestational diabetes is much more complex than we had previously thought.[1,19] Many women with 'early GDM' had normal glucose tolerance at the time of second testing at 24–28 weeks' gestation, consistent with previous findings.[20] One interpretation of these findings is that resolution of gestational diabetes is possible, providing new opportunities to intervene and prevent the development of 'late' gestational diabetes. However, previous efforts have not shown a consistent effect of early pregnancy interventions in the prevention of gestational diabetes[21–23] while a meta-analysis suggests interventions may be effective, but only if they commenced in the first trimester.[24]

It is also possible that the discordance between 'early' and 'late' OGTT results may simply reflect the known unreliability and lack of reproducibility of the post-load glucose during the OGTT.[25–28] However, regardless of cause, this issue creates substantial logistical problems for defining gestational diabetes consistently throughout pregnancy.

5 | TRANSLATIONAL OPPORTUNITIES

Precision categorisation into 'early' and 'late' gestational diabetes provides opportunities to improve treatment and reduce neonatal complications, in spite of the practical challenges. The TOBOGM trial has identified that treating women with early hyperglycaemia, particularly from the first trimester, results in improved pregnancy outcomes and reduced days in the neonatal intensive care unit (NICU).[1] Although a cost-effectiveness analysis will be crucial to guide implementation in the NHS and elsewhere, the reduction in NICU bed-days and severe perineal tears may show a cost benefit to early treatment, particularly in women with the most severe hyperglycaemia. Future work with the TOBOGM cohort may also identify if the timing of diagnosis can improve prediction of suboptimal pregnancy outcomes or prognostication for risk of postnatal type 2 diabetes, impaired glucose tolerance or impaired fasting glucose.[29]

6 | CONCLUSIONS: HARNESSING A SUCCESSFUL PRECISION APPROACH TO GESTATIONAL DIABETES

There is widespread international disagreement about the optimal type of screening, diagnostic testing and specific thresholds used to diagnose gestational diabetes at 24–28 weeks' gestation.[25] Introducing categories of 'early' and 'late' gestational diabetes risks exacerbating this further and may, or may not, reflect different patho-aetiological processes. However, despite the challenges, the diagnostic pathway needs to evolve to reflect the changing levels of risk in the population that have now been identified. First-trimester hyperglycaemia, including undiagnosed type 2 diabetes in early pregnancy, is more common than ever before and needs careful management to prevent complications. Refocussing the diagnostic pathway for hyperglycaemia in pregnancy to consistently identify the highest

risk pregnancies in the first trimester would be a worthwhile long-term investment.

AUTHOR CONTRIBUTIONS

CLM and DS were responsible for all aspects relating to the conceptualisation and writing of this manuscript. All authors reviewed the manuscript and contributed to the discussion.

ACKNOWLEDGEMENTS

CLM is supported by Diabetes UK (17/0005712) and the European Foundation for the Study of Diabetes - Novo Nordisk Foundation (NNF19SA058974). This research was supported by the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre (IS-BRC-1215-20014). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

FUNDING INFORMATION

This commentary was not supported by specific project funding. CLM is supported by Diabetes UK (17/0005712), the European Foundation for the Study of Diabetes - Novo Nordisk Foundation (NNF19SA058974). This research was supported by the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre (BRC).

CONFLICT OF INTEREST STATEMENT

None of the authors disclosed any financial or non-financial competing interests on this study.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Claire L. Meek https://orcid.org/0000-0002-4176-8329

REFERENCES

1. Simmons D, Immanuel J, Hague WM, et al. Treatment of gestational diabetes mellitus diagnosed early in pregnancy. *N Engl J Med*. 2023;388(23):2132-2144. doi:10.1056/NEJMoa2214956
2. Immanuel J, Simmons D, Harreiter J, et al. Metabolic phenotypes of early gestational diabetes mellitus and their association with adverse pregnancy outcomes. *Diabet Med*. 2021;38(2):e14413. doi:10.1111/dme.14413
3. Powe CE, Allard C, Battista MC, et al. Heterogeneous contribution of insulin sensitivity and secretion defects to gestational diabetes mellitus. *Diabetes Care*. 2016;39(6):1052-1055. doi:10.2337/dc15-2672
4. Harris MI. Gestational diabetes may represent discovery of preexisting glucose intolerance. *Diabetes Care*. 1988;11(5):402-411. doi:10.2337/diacare.11.5.402
5. Immanuel J, Simmons D. Screening and treatment for early-onset gestational diabetes mellitus: a systematic review and meta-analysis. *Curr Diab Rep*. 2017;17(11):115. doi:10.1007/s11892-017-0943-7
6. Powe CE. Early pregnancy biochemical predictors of gestational diabetes mellitus. *Curr Diab Rep*. 2017;17(2):12. doi:10.1007/s11892-017-0834-y
7. White SL, Lawlor DA, Briley AL, et al. Early antenatal prediction of gestational diabetes in obese women: development of prediction tools for targeted intervention. *PloS One*. 2016;11(12):e0167846. doi:10.1371/journal.pone.0167846
8. Mittendorfer B, Patterson BW, Haire-Joshu D, et al. Insulin sensitivity and β-cell function during early and late pregnancy in women with and without gestational diabetes mellitus. *Diabetes Care*. 2023. doi:10.2337/dc22-1894
9. Gerszi D, Orosz G, Török M, et al. Risk estimation of gestational diabetes mellitus in the first trimester. *J Clin Endocrinol Metab*. 2023. doi:10.1210/clinem/dgad301
10. Riskin-Mashiah S, Younes G, Damti A, Auslender R. First-trimester fasting hyperglycemia and adverse pregnancy outcomes. *Diabetes Care*. 2009;32(9):1639-1643. doi:10.2337/dc09-0688
11. Phelan S, Jelalian E, Coustan D, et al. Randomized controlled trial of prepregnancy lifestyle intervention to reduce recurrence of gestational diabetes mellitus. *Am J Obstet Gynecol*. 2023;229:158.e1-158.e14. doi:10.1016/j.ajog.2023.01.037
12. Rönö K, Stach-Lempinen B, Eriksson JG, et al. Prevention of gestational diabetes with a prepregnancy lifestyle intervention—findings from a randomized controlled trial. *Int J Womens Health*. 2018;10:493-501. doi:10.2147/IJWH.S162061
13. Meek CL, Lewis HB, Patient C, Murphy HR, Simmons D. Diagnosis of gestational diabetes mellitus: falling through the net. *Diabetologia*. 2015;58(9):2003-2012. doi:10.1007/s00125-015-3647-z
14. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008;358(19):1991-2002. doi:10.1056/NEJMoa0707943
15. Riskin-Mashiah S, Damti A, Younes G, Auslender R. First trimester fasting hyperglycemia as a predictor for the development of gestational diabetes mellitus. *Eur J Obstet Gynecol Reprod Biol*. 2010;152(2):163-167. doi:10.1016/j.ejogrb.2010.05.036
16. White SL, Koulman A, Ozanne SE, Furse S, Poston L, Meek CL. Towards precision medicine in gestational diabetes: pathophysiology and glycemic patterns in pregnant women with obesity. *J Clin Endocrinol Metab*. 2023. doi:10.1210/clinem/dgad168
17. Harreiter J, Simmons D, Desoye G, et al. IADPSG and WHO 2013 gestational diabetes mellitus criteria identify obese women with marked insulin resistance in early pregnancy. *Diabetes Care*. 2016;39(7):e90-e92. doi:10.2337/dc16-0200
18. Egan AM, Vellinga A, Harreiter J, et al. Epidemiology of gestational diabetes mellitus according to IADPSG/WHO 2013 criteria among obese pregnant women in Europe. *Diabetologia*. 2017;60(10):1913-1921. doi:10.1007/s00125-017-4353-9
19. Simmons D. Paradigm shifts in the Management of Diabetes in pregnancy: the importance of type 2 diabetes and early hyperglycemia in pregnancy: the 2020 Norbert Freinkel award lecture. *Diabetes Care*. 2020;44(5):1075-1081. doi:10.2337/dci20-0055
20. Sacks DA, Chen W, Wolde-Tsadik G, Buchanan TA. Fasting plasma glucose test at the first prenatal visit as a screen for gestational diabetes. *Obstet Gynecol*. 2003;101(6):1197-1203. doi:10.1016/s0029-7844(03)00049-8

21. Simmons D, Devlieger R, van Assche A, et al. Effect of physical activity and/or healthy eating on GDM risk: the DALI lifestyle study. *J Clin Endocrinol Metab*. 2017;102(3):903-913. doi:10.1210/jc.2016-3455
22. Poston L, Bell R, Croker H, et al. Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2015;3(10):767-777. doi:10.1016/S2213-8587(15)00227-2
23. Koivusalo SB, Rönö K, Klemetti MM, et al. Gestational diabetes mellitus can Be prevented by lifestyle intervention: the Finnish gestational diabetes prevention study (RADIEL): a randomized controlled trial. *Diabetes Care*. 2016;39(1):24-30. doi:10.2337/dc15-0511
24. Song C, Li J, Leng J, Ma RC, Yang X. Lifestyle intervention can reduce the risk of gestational diabetes: a meta-analysis of randomized controlled trials. *Obes Rev*. 2016;17(10):960-969. doi:10.1111/obr.12442
25. Meek CL. Natural selection? The evolution of diagnostic criteria for gestational diabetes. *Ann Clin Biochem*. 2017;54(1):33-42. doi:10.1177/0004563216674743
26. Olefsky JM, Reaven GM. Insulin and glucose responses to identical oral glucose tolerance tests performed forty-eight hours apart. *Diabetes*. 1974;23(5):449-453. doi:10.2337/diab.23.5.449
27. Mooy JM, Grootenhuis PA, de Vries H, et al. Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn study. *Diabetologia*. 1996;39(3):298-305. doi:10.1007/bf00418345
28. O'Sullivan JB, Mahan CM. Glucose tolerance test. Variability in pregnant and nonpregnant women. *Am J Clin Nutr*. 1966;19(5):345-351. doi:10.1093/ajcn/19.5.345
29. Chivese T, Hoegfeldt CA, Werfalli M, et al. IDF diabetes atlas: the prevalence of pre-existing diabetes in pregnancy—a systematic reviewand meta-analysis of studies published during 2010-2020. *Diabetes Res Clin Pract*. 2022;183:109049. doi:10.1016/j.diabres.2021.109049

How to cite this article: Meek CL, Simmons D. Timing of gestational diabetes diagnosis: A novel precision approach to hyperglycaemia in pregnancy? *Diabet Med*. 2023;40:e15191. doi:10.1111/dme.15191