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Lower versus Higher Glycemic Criteria for Diagnosis of Gestational Diabetes

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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.)

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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%)

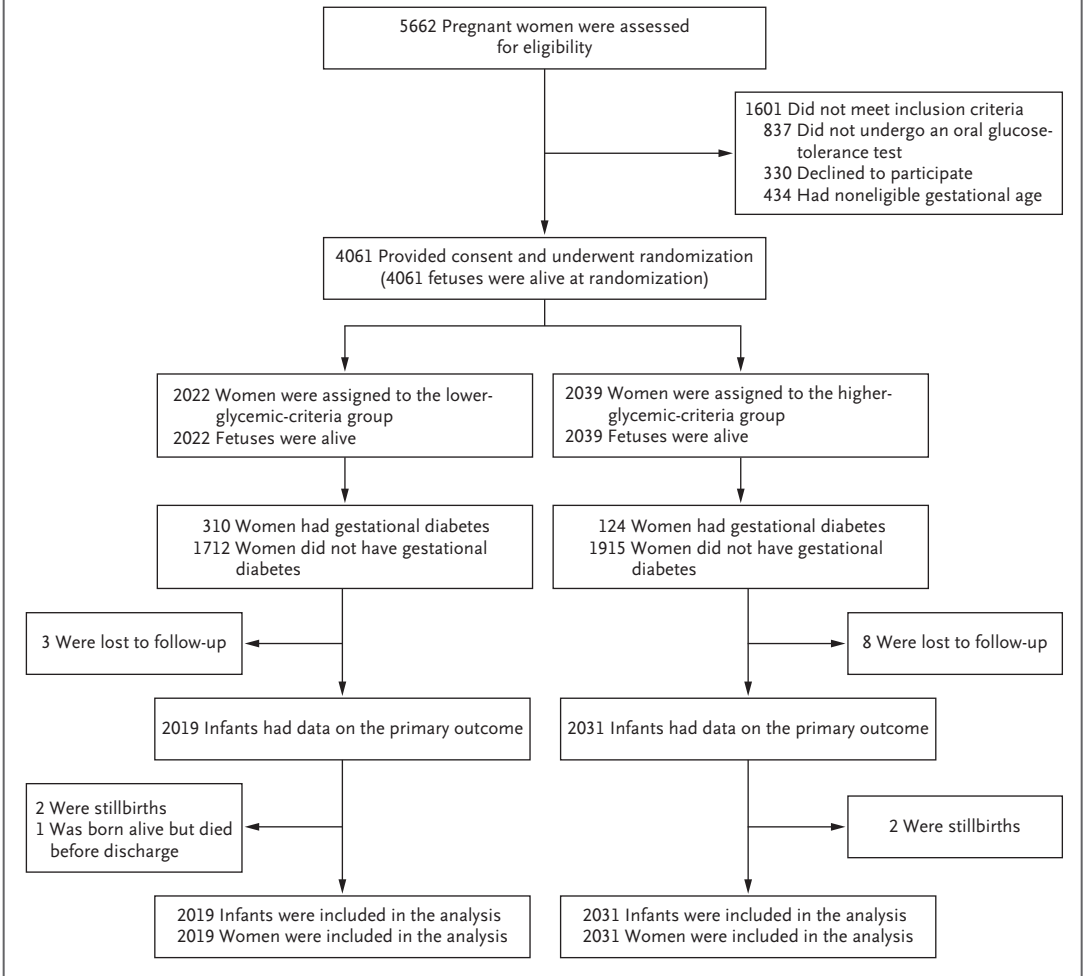

Figure 1. Randomization, Treatment, and Follow-up.

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.

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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.

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