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A Pragmatic, Randomized Clinical Trial of Gestational Diabetes Screening

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ABSTRACT

BACKGROUND

Gestational diabetes mellitus is common and is associated with an increased risk of adverse maternal and perinatal outcomes. Although experts recommend universal screening for gestational diabetes, consensus is lacking about which of two recommended screening approaches should be used.

METHODS

We performed a pragmatic, randomized trial comparing one-step screening (i.e., a glucose-tolerance test in which the blood glucose level was obtained after the oral administration of a 75-g glucose load in the fasting state) with two-step screening (a glucose challenge test in which the blood glucose level was obtained after the oral administration of a 50-g glucose load in the nonfasting state, followed, if positive, by an oral glucose-tolerance test with a 100-g glucose load in the fasting state) in all pregnant women who received care in two health systems. Guidelines for the treatment of gestational diabetes were consistent with the two screening approaches. The primary outcomes were a diagnosis of gestational diabetes, large-for-gestational-age infants, a perinatal composite outcome (stillbirth, neonatal death, shoulder dystocia, bone fracture, or any arm or hand nerve palsy related to birth injury), gestational hypertension or preeclampsia, and primary cesarean section.

RESULTS

A total of 23,792 women underwent randomization; women with more than one pregnancy during the trial could have been assigned to more than one type of screening. A total of 66% of the women in the one-step group and 92% of those in the two-step group adhered to the assigned screening. Gestational diabetes was diagnosed in 16.5% of the women assigned to the one-step approach and in 8.5% of those assigned to the two-step approach (unadjusted relative risk, 1.94; 97.5% confidence interval [CI], 1.79 to 2.11). In intention-to-treat analyses, the respective incidences of the other primary outcomes were as follows: large-for-gestational-age infants, 8.9% and 9.2% (relative risk, 0.95; 97.5% CI, 0.87 to 1.05); perinatal composite outcome, 3.1% and 3.0% (relative risk, 1.04; 97.5% CI, 0.88 to 1.23); gestational hypertension or preeclampsia, 13.6% and 13.5% (relative risk, 1.00; 97.5% CI, 0.93 to 1.08); and primary cesarean section, 24.0% and 24.6% (relative risk, 0.98; 97.5% CI, 0.93 to 1.02). The results were materially unchanged in intention-to-treat analyses with inverse probability weighting to account for differential adherence to the screening approaches.

CONCLUSIONS

Despite more diagnoses of gestational diabetes with the one-step approach than with the two-step approach, there were no significant between-group differences in the risks of the primary outcomes relating to perinatal and maternal complications. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development; ScreenR2GDM ClinicalTrials.gov number, NCT02266758.)

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Gestational diabetes mellitus, one of the most common complications of pregnancy,[1,2] affects 6 to 25% of pregnant women (depending on diagnostic criteria)[3,4] and is associated with increased risks of stillbirth and neonatal death, as well as multiple serious conditions in both mothers and babies.[1] Fetal overgrowth, a complication of gestational diabetes, is associated with an increased risk of birth trauma (e.g., brachial plexus injury or clavicular fracture) and of cesarean section to avoid such trauma.[1,5] Universal gestational diabetes screening is recommended at 24 to 28 weeks of gestation,[6] since data from randomized, controlled trials show that treatment of gestational diabetes improves maternal and perinatal outcomes.[7,8]

There is no scientific consensus on how best to diagnose gestational diabetes. Expert professional organizations acknowledge two acceptable options: the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) one-step screening approach (currently preferred by the American Diabetes Association) and the two-step Carpenter–Coustan screening approach (recommended by the American College of Obstetricians and Gynecologists); both organizations note the need for additional evidence related to outcomes.[1,9]

Each approach has advantages and disadvantages.[1,9] The one-step approach involves a 2-hour oral glucose-tolerance test for all participants. Although screening and diagnosis can be completed in a single visit, all women must fast before screening and make time for a 2-hour visit. The two-step approach includes an initial nonfasting 1-hour glucose challenge test, which is logistically simpler for women and can easily be performed as part of a scheduled prenatal visit; most women do not require further screening. However, approximately 20% of women who undergo this screening are found to have high blood glucose levels and must return for a 3-hour fasting diagnostic oral glucose-tolerance test.[10,11]

The two screening methods also have different diagnostic cutoff thresholds. The one-step approach identifies women with milder hyperglycemia as having gestational diabetes. Although there is a clear linear relationship between maternal hyperglycemia and maternal and perinatal outcomes,[12] the effects of identifying and treating milder cases of gestational diabetes on these outcomes are not known.[1,2,10]

The National Institutes of Health Consensus Development Conference on diagnosing gestational diabetes mellitus recommended that a randomized trial compare these approaches with respect to clinically important outcomes.[10] We conducted ScreenR2GDM, a pragmatic, randomized clinical trial involving pregnant women who were receiving care at Kaiser Permanente Northwest and Kaiser Permanente Hawaii to compare the one-step approach with the two-step approach to screening and diagnosis of gestational diabetes with respect to maternal and neonatal outcomes.

Methods

Trial Design and Oversight

Details regarding the design of the ScreenR2GDM trial and the characteristics of the trial population have been published previously.[13] All pregnant women who were receiving care at Kaiser Permanente Northwest and Kaiser Permanente Hawaii were randomly assigned to undergo either one-step or two-step screening for the diagnosis of gestational diabetes. Institutional review boards at both institutions approved the randomized clinical trial and waivers for individual consent; the rationale was that both screening approaches are associated with minimal risk and are clinically recommended, and thus waiving consent would not adversely affect patients' rights or welfare, as long as providers could retain clinical judgment to decide whether to adhere to randomization. A data and safety monitoring board provided trial oversight (see Section S2.1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) and conducted one midtrial data review.[13]

The first and second authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The statistical analysis plan is provided with the protocol at NEJM.org. Neither the funding source nor the authors' institutions (where the trial was conducted) had any involvement in the trial design; the collection, analysis, or interpretation of the data; the writing of the report; or the decision to submit the article for publication.

Randomization

All the women were randomly assigned, in a 1:1 ratio, to the one-step or two-step screening approach at their first prenatal visit with the use of

an electronically generated random-assignment procedure. The provider was notified of this assignment in the electronic medical record when gestational diabetes screening was ordered (typically at 24 to 28 weeks of gestation).[13] If screening was ordered more than once, providers were notified of the same assigned test each time. Randomization was conducted independently within the electronic medical record system of each region and was implemented on May 28, 2014, in Kaiser Permanente Northwest (the first woman was enrolled on June 3, 2014) and on July 7, 2014, in Kaiser Permanente Hawaii. Randomization continued in both regions through December 31, 2017; data on outcomes were collected through delivery of neonates (from 2014 through 2018).

Owing to the pragmatic trial design, the providers were aware of the trial-group assignments. All the investigators and trial staff, except the statisticians, were unaware of all the trial data except for the data on overall adherence until all the women had undergone randomization.

APPROACHES TO GESTATIONAL DIABETES SCREENING AND DIAGNOSIS

The one-step approach consisted of a 2-hour oral glucose-tolerance test (i.e., the blood glucose level was obtained 2 hours after the oral administration of a 75-g glucose load in the fasting state). Women received a diagnosis of gestational diabetes if the fasting blood glucose level was at least 92 mg per deciliter (5.1 mmol per liter), the timed glucose measurement was at least 180 mg per deciliter (10.0 mmol per liter) at 1 hour, or the timed measurement was at least 153 mg per deciliter (8.5 mmol per liter) at 2 hours.[9]

In the two-step approach, the first (screening) step was a 1-hour glucose challenge test in which the blood glucose level was obtained after the oral administration of a 50-g glucose load in the nonfasting state.[1] Women with a blood glucose level of at least 200 mg per deciliter (11.1 mmol per liter) on the challenge test were considered to have gestational diabetes and did not undergo further testing.[11] Women who had a positive glucose challenge test with a blood glucose level below 200 mg per deciliter (and ≥130 mg per deciliter [≥7.2 mmol per liter] at Kaiser Permanente Northwest and ≥140 mg per deciliter [≥7.8 mmol per liter] at Kaiser Permanente Hawaii) underwent a diagnostic fasting 3-hour oral glucose-tolerance test in which the blood glucose level was obtained after the oral administration of a 100-g glucose load. Gestational diabetes was diagnosed if two or more of four glucose thresholds were met: a fasting level of at least 95 mg per deciliter (≥5.3 mmol per liter), at least 180 mg per deciliter at 1 hour, at least 155 mg per deciliter (≥8.6 mmol per liter) at 2 hours, or at least 140 mg per deciliter at 3 hours.[1] Treatment for gestational diabetes was based on the same national practice guidelines, regardless of the screening approach[1,14] (Section S2.5).

TRIAL OUTCOMES

We prespecified five primary outcomes on the basis of previous research.[7,8,12] These outcomes, which are not listed in order of importance, were a diagnosis of gestational diabetes, large-for-gestational-age infants (birth weight >90th percentile),[7,8,12,15] a composite measure of perinatal outcomes (stillbirth, neonatal death, shoulder dystocia, bone fracture, or any arm or hand nerve palsy related to birth injury),[8] primary cesarean section,[7,8,12] and gestational hypertension or preeclampsia.[1,7,8,16] Definitions of these outcomes are provided in Table S1.

Secondary outcomes were the incidence of macrosomia (birth weight >4000 g),[7,8] small-for-gestational-age infants (birth weight ≤10th percentile),[7,8,15] maternal gestational diabetes for which insulin or oral hypoglycemic treatment was warranted,[1] neonatal respiratory distress,[7,8] neonatal jaundice for which treatment was warranted,[7] neonatal hypoglycemia,[7,8] and the individual components of the composite perinatal outcome.[8] Screening practices for neonatal hypoglycemia were consistent with the American Academy of Pediatrics guidelines, which recommend screening neonates with risk factors for hypoglycemia within 24 hours after birth.[17,18] In both trial regions, newborn screening is performed by a heel stick, with point-of-care glucose testing in the delivery room or nursery. Safety outcomes were neonatal sepsis, admission to a neonatal intensive care unit, preterm birth (at <37 weeks of gestation as well as at <32 weeks of gestation), and induction of labor. Primary, secondary, and safety outcomes were assessed for subgroups of participants with a diagnosis of gestational diabetes (prespecified) and participants who were not screened (post hoc analyses).

STATISTICAL ANALYSIS

We originally estimated that a sample size of 17,626 pregnancies would provide 80% power to detect a relative between-group difference of 20% for all primary outcomes except the composite perinatal outcome, for which the trial would be powered to detect a 40% difference, at a two-sided significance level of 0.05. However, early monitoring of fidelity to the randomized screening revealed that at both sites, a higher percentage of the women who were randomly assigned to one-step screening received two-step screening than the reverse.[13] Providers reported that this imbalance was partly due to efforts to ensure screening by conducting the nonfasting two-step glucose challenge test at a prenatal visit. Given the pragmatic nature of this trial, the research team was unable to enforce strict adherence to randomization. Accordingly, we modified our protocol to continue the trial until an adequate sample size had been achieved among women receiving the one-step approach[13] and to include additional statistical analyses to account for nonadherence (see below and Section S2.11.1).[13,19,20]

We estimated the relative risks of each primary outcome between the two trial groups using generalized linear log-binomial models with adjustment for correlated errors owing to multiple pregnancies per woman. The quasi-likelihood information criterion was used to confirm working correlation structure and variable selection.[21]

In planned intention-to-treat analyses, we used an unadjusted model comparing pregnancy outcomes between the randomly assigned groups as well as models adjusted for the diagnosis of gestational diabetes, group-by-diagnosis interaction, and other covariates that may have modified the relationship of the group with each outcome. These covariates included excessive gestational weight gain, as defined according to the National Academy of Medicine guidelines,[22,23] since this covariate is independently related to several outcomes.[24-26] The interaction between gestational diabetes and group assignment was not significant for any outcome. Thus, final adjusted models included gestational diabetes, prespecified covariates, and factors related to nonadherence. To further account for nonadherence to the randomized assignment, we conducted intention-to-treat analyses with inverse probability weighting[19,20]; in these analyses, pregnancies were assigned stabilized weights that were based on the modeled probability of adherence to the assigned screening approach (Fig. 1).[13]

We also conducted sensitivity analyses, including multiple imputation, to account for missing data (Section S2.11.3 and Tables S3 and S4). Our statistical analysis plan prespecified 97.5% confidence intervals for relative risks of primary outcomes; these are reported here. For secondary or other outcomes, we report 95% confidence intervals. Because the widths of the confidence intervals have not been adjusted to account for the multiplicity of outcomes assessed, they should not be used to infer definitive effects of one screening approach over the other. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

TRIAL POPULATION

Overall, 23,792 eligible pregnant women were randomly assigned to one-step or two-step screening for gestational diabetes; women with more than one pregnancy during the trial could have been assigned to more than one type of screening (see Fig. 1). A total of 94% of the eligible women completed screening, and 66% of the women in the one-step group and 92% of those in the two-step group adhered to the assigned screening approach. The characteristics of the women in the two groups are presented in Table 1.

PRIMARY OUTCOMES

Gestational diabetes was diagnosed in 16.5% of the pregnant women who were assigned to the one-step approach and in 8.5% of those assigned to the two-step approach (relative risk, 1.94; 97.5% confidence interval [CI], 1.79 to 2.11). Intention-to-treat analyses showed no significant differences between the one-step group and the two-step group in the incidences or the unadjusted risks of the other primary outcomes. These outcomes were large-for-gestational-age infants (in 8.9% of the pregnancies in the one-step group and 9.2% of those in the two-step group; relative risk, 0.95; 97.5% CI, 0.87 to 1.05); the perinatal composite outcome (in 3.1% and 3.0%, respectively; relative risk, 1.04; 97.5% CI, 0.88 to 1.23); gestational hypertension or preeclampsia (in 13.6% and 13.5%; relative risk, 1.00; 97.5% CI, 0.93 to 1.08); and primary cesarean section (in 24.0% and 24.6%; relative risk, 0.98; 97.5%

CI, 0.93 to 1.02). After adjustment for gestational diabetes and other prespecified covariates, including those related to adherence, there were still no significant between-group differences for all the primary outcomes with the exception of the diagnosis of gestational diabetes (Table 2). The results of the analyses with inverse probability weighting were similar to those of the intention-to-treat analyses (Table 2).

SECONDARY, SAFETY, AND SUBGROUP OUTCOMES

The results for the secondary outcomes and the safety outcomes were similar in the two groups (Table 3). In a prespecified analysis that was limited to women with a diagnosis of gestational diabetes, the incidences of the trial outcomes were similar between the groups (Table S7). In 39% of the women assigned to one-step screening for gestational diabetes, the diagnosis was based on the isolated fasting plasma glucose level alone, and half these women met the criteria for gestational diabetes with an isolated fasting plasma glucose level in the range of 92 to 94 mg per deciliter (5.1 to 5.2 mmol per liter); thus, their glucose levels at diagnosis were already within the target range for treatment (fasting plasma glucose level <95 mg per deciliter).[1] Among the women with gestational diabetes, the percentages of those who received insulin or hypoglycemic medication were similar in the one-step and two-step groups (42.6% and 45.6%, respectively) (Table 3). Baseline information and the outcomes of pregnancies in women who did not undergo screening for gestational diabetes (a post hoc subgroup involving 1450 women) are provided in Tables S8 and S9.

DISCUSSION

This pragmatic, head-to-head, randomized clinical trial of the two clinically recommended approaches to screening for gestational diabetes,[1,9] showed no significant differences in maternal and perinatal outcomes among 23,792 pregnant women who were randomly assigned to undergo one-step screening or two-step screening as part of their clinical care, even though twice as many women in the one-step group received a diagnosis of gestational diabetes. There was lower adherence to screening with the fasting one-step approach, but the results were similar in analyses that accounted for differences in adherence.

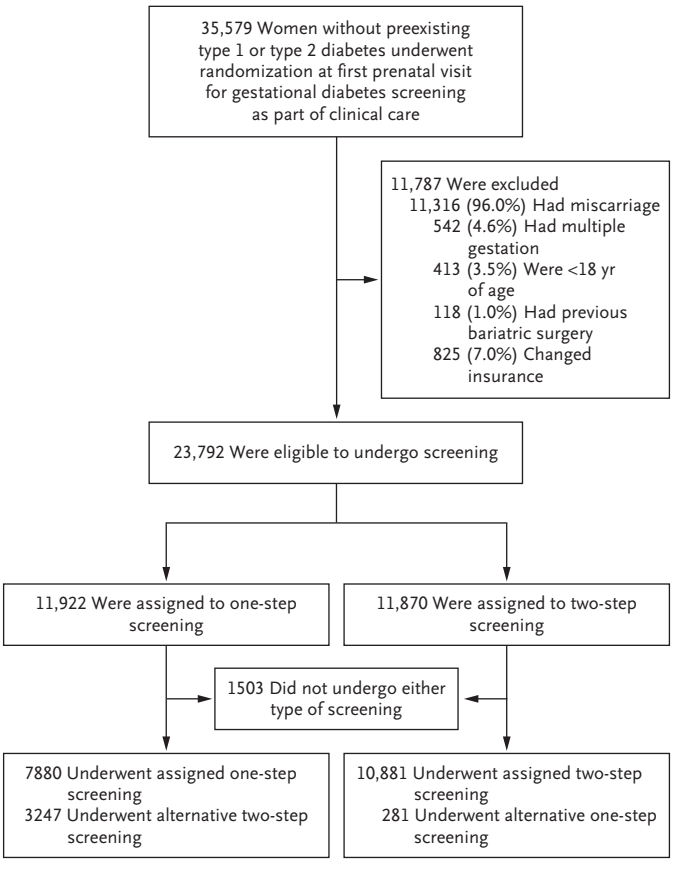

Figure 1. Randomization and Screening.

Percentages for exclusion do not total 100% because some pregnancies met multiple exclusion criteria. The major reason for exclusion was miscarriage (because randomization occurred at the first prenatal visit, and in many cases this visit also determined nonviability, or miscarriage, on the same day of randomization and before any screening for gestational diabetes was ordered). Terminations were also included in this exclusion category. A change of insurance during pregnancy was a criterion for exclusion because the investigators were unable to evaluate outcomes in these pregnancies. Intention-to-treat analyses were planned. Because of the unanticipated lower adherence to the fasting one-step screening at both sites, randomization was continued until enough pregnant women had been enrolled with one-step screening to achieve adequate statistical power, and additional analyses were conducted, including an intention-to-treat analyses with inverse probability weighting, both with and without adjustment for factors related to nonadherence.[13,19,20] Factors related to lower adherence included both maternal and provider characteristics as well as provider reliance on nonfasting tests to ensure that gestational diabetes screening was completed at a visit.[13] These pragmatic barriers to adherence could not be adequately addressed without putting women at risk for not receiving gestational diabetes screening. A total of 1450 of 23,792 women (6.1%) did not undergo screening (778 in the one-step group and 672 in the two-step group), and these women presented on average at a mean of 18.9 weeks of gestation, as compared with 10.5 weeks for women who underwent screening. In addition, 53 women underwent screening in the first trimester (e.g., by measurement of a glycated hemoglobin level)[9] but did not undergo screening with either randomized gestational diabetes screening strategy.

Table 1. Characteristics of the Trial Population.*

Characteristic	One-Step Screening (N=11,922)	Two-Step Screening (N=11,870)
Maternal age — yr	29.4±5.5	29.3±5.5
BMI at first prenatal visit†	27.4±6.7	27.6±7.0
Prepregnancy obesity — no./total no. (%)†	2527/9504 (26.6)	2615/9429 (27.7)
Medicaid recipient — no. (%)	1914 (16.1)	1810 (15.2)
Race or ethnic group — no. (%)‡		
White	6608 (55.4)	6586 (55.5)
Asian	1789 (15.0)	1782 (15.0)
Native Hawaiian or Pacific Islander	623 (5.2)	619 (5.2)
Black	329 (2.8)	328 (2.8)
American Indian	49 (0.4)	50 (0.4)
Multiple races	1317 (11.0)	1310 (11.0)
Other	40 (0.3)	42 (0.4)
Unknown	1167 (9.8)	1153 (9.7)
Trial-site region — no. (%)		
Northwest	8203 (68.8)	8140 (68.6)
Hawaii	3719 (31.2)	3730 (31.4)
Nulliparous — no. (%)	3642 (30.5)	3616 (30.5)
Previous hypertension — no. (%)	948 (8.0)	976 (8.2)
Previous gestational diabetes — no. (%)	636 (5.3)	637 (5.4)
Gestational weight gain exceeding NAM guidelines — no./total no. (%)§	4160/9239 (45.0)	4255/9133 (46.6)

* Plus–minus values are means ±SD. NAM denotes National Academy of Medicine.
† Body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) was assessed at the first obstetrical visit (mean gestation, 10.9 weeks); 6 women did not have these measurements. Prepregnancy obesity was defined as a BMI of at least 30. The prepregnancy weight was the most recent weight measurement obtained up to 3 months before the estimated date of conception or (if not available) the earliest weight measurement obtained during pregnancy (≤12 weeks of gestation).
‡ Race or ethnic group was reported by the women. Hispanic ethnic group is not presented here because it was commonly reported in combination with other races or ethnic groups. Of the 11,859 women for whom Hispanic ethnic group status was known, 1343 of 5993 women (22.4%) in the one-step group and 1280 of 5866 women (21.8%) in the two-step group reported that they were Hispanic.
§ The prepregnancy weight or the weight at delivery needed to calculate this measure was missing for 5420 women.

Our finding that 16.5% of the women received a diagnosis of gestational diabetes with the one-step approach is consistent with previous research using the same criteria.[4,9] Data from randomized clinical trials showing a benefit of treatment for gestational diabetes are limited to trials using the two-step approach[7,8]; studies to address whether or not the treatment of more women on the basis of the one-step approach yields better outcomes are lacking. Although we did not find increased harms associated with the diagnosis and treatment of gestational diabetes in many more women with the one-step approach, some retrospective observational cohort studies have shown higher incidences of primary cesarean delivery[27] and neonatal hypoglycemia[28] with one-step screening after conversion from two-step protocols, with no substantive improvement in outcomes.[27-29] Other considerations relevant to one-step screening include the burden on individual women of receiving a diagnosis of gestational diabetes on the basis of these milder criteria and the burden on the system of treating many more women. However, some studies have shown that maternal gestational diabetes may be a risk factor for childhood obesity and metabolic sequelae, so treating more women could have long-term benefits.[30-32] Other studies have

Table 2. Primary Outcomes, According to One-Step or Two-Step Screening for Gestational Diabetes.*

Outcome	Randomized Group		Preplanned Intention-to-Treat Analyses†			Intention-to-Treat Analyses with Inverse Probability Weighting‡
	One-Step Screening (N=11,922)	Two-Step Screening (N=11,870)	Unadjusted Relative Risk (97.5% CI)§	Relative Risk, Adjusted for Gestational Diabetes (97.5% CI)§	Relative Risk, Adjusted for Gestational Diabetes, Prespecified Covariates, and Nonadherence‡ (97.5% CI)§	Relative Risk, Adjusted for Gestational Diabetes, Prespecified Covariates, and Nonadherence‡ (97.5% CI)§
	no./total no. (%)					
Gestational diabetes¶	1837/11,127 (16.5)	945/11,162 (8.5)	1.94 (1.79–2.11)	NA	1.93 (1.77–2.11)	1.93 (1.76–2.12)
Large-for-gestational-age infants	977/11,028 (8.9)	1015/10,986 (9.2)	0.95 (0.87–1.05)	0.93 (0.84–1.03)	0.94 (0.85–1.04)	0.92 (0.83–1.02)
Perinatal composite outcome‖	351/11,281 (3.1)	337/11,213 (3.0)	1.04 (0.88–1.23)	1.08 (0.90–1.30)	1.08 (0.89–1.31)	1.10 (0.91–1.35)
Gestational hypertension or preeclampsia	1490/10,974 (13.6)	1472/10,894 (13.5)	1.00 (0.93–1.08)	0.96 (0.88–1.03)	0.98 (0.90–1.06)	0.98 (0.90–1.06)
Primary cesarean section	2826/11,755 (24.0)	2887/11,714 (24.6)	0.98 (0.93–1.02)	0.95 (0.91–1.00)	0.96 (0.91–1.02)	0.96 (0.91–1.02)

* The denominators vary according to the ascertainment method for each outcome. For the gestational diabetes outcome, only the women who underwent one of the two types of screening were included. The maternal outcome of gestational hypertension or preeclampsia excluded women with preexisting hypertension before pregnancy. Primary cesarean section excluded women who left the health plan before delivery (167 women in the one-step screening group and 156 women in the two-step screening group). The perinatal outcomes included pregnancies for which information was available in the maternal record (stillbirth and shoulder dystocia) or in newborn records that were matched to maternal records. Reasons for unmatched newborn records include adopted infants, deliveries within and outside the health plan in which the newborn was covered by other insurance, deliveries outside the health plan for which no reimbursement for newborn care was requested, and instances in which the mother left the health plan before delivery and no information was available for the newborn. There were 702 unmatched newborn records in the one-step screening group and 709 unmatched newborn records in the two-step screening group. In 30 pregnancies in the one-step group and 21 pregnancies in the two-step group, there was a diagnosis of shoulder dystocia in the maternal record but no matching newborn record. In 32 pregnancies in the one-step group and 31 pregnancies in the two-step group, there was a diagnosis of stillbirth in the maternal record but no matching newborn record. For the outcome of large-for-gestational-age infants, unmatched newborn records were excluded, and birth weight was not available for 192 pregnancies in the one-step group and 175 pregnancies in the two-step group. CI denotes confidence interval, and NA not applicable.

† The intention-to-treat analysis compared pregnant women who were randomly assigned to one-step screening with those who were randomly assigned to two-step screening.

‡ Analyses with inverse probability weighting were conducted to account for nonadherence to the randomized screening test. Stabilized weights were derived from modeling the probability of adhering to the randomly assigned screening test (details are provided in Section S2.11 in the Supplementary Appendix).

§ Prespecified covariates included race or ethnic group, prepregnancy obesity, and weight exceeding National Academy of Medicine weight-gain guidelines.[22,23] Factors related to nonadherence included maternal age, nulliparity, race or ethnic group, Medicaid insurance, previous gestational diabetes, preexisting hypertension, trial site, maternal obesity at the first prenatal visit, provider type, and randomized group. The widths of the confidence intervals have not been adjusted to account for multiplicity and cannot be used to infer treatment effects.

¶ A total of 795 women who were assigned to one-step screening and 708 women who were assigned to two-step screening did not undergo either type of screening.

‖ The perinatal composite outcome was any of the following: stillbirth, neonatal death, shoulder dystocia, bone fracture, or any arm or hand nerve palsy related to birth injury.[8]

Table 3. Preplanned Secondary and Safety Outcomes.*

Outcome	One-Step Screening	Two-Step Screening	Relative Risk (95% CI)†
	no./total no. (%)		
Secondary outcomes			
Macrosomia, birth weight >4000 g	1178/10,312 (11.4)	1186/10,275 (11.5)	0.99 (0.91–1.06)
Small-for-gestational-age infants	937/11,028 (8.5)	892/10,986 (8.1)	1.05 (0.96–1.14)
Maternal gestational diabetes for which insulin or oral hypoglycemic treatment warranted‡	783/1837 (42.6)	431/945 (45.6)	0.93 (0.87–1.03)
Neonatal respiratory distress	225/11,220 (2.0)	227/11,161 (2.0)	0.99 (0.82–1.18)
Neonatal jaundice for which treatment warranted	478/11,220 (4.3)	476/11,161 (4.3)	1.00 (0.88–1.13)
Neonatal hypoglycemia	1034/11,220 (9.2)	838/11,161 (7.5)	1.23 (1.12–1.34)
Components of perinatal composite outcome			
Stillbirth	56/11,252 (0.5)	64/11,192 (0.6)	0.87 (0.61–1.25)
Neonatal death	7/11,220 (0.1)	12/11,161 (0.1)	0.58 (0.23–1.47)
Shoulder dystocia	239/11,250 (2.1)	223/11,182 (2.0)	1.07 (0.89–1.28)
Bone fracture	59/11,220 (0.5)	42/11,161 (0.4)	1.40 (0.94–2.07)
Nerve palsy	14/11,220 (0.1)	15/11,161 (0.1)	0.93 (0.45–1.92)
Safety outcomes			
Neonatal sepsis	46/11,220 (0.4)	38/11,161 (0.3)	1.20 (0.78–1.85)
Admission to NICU	526/11,220 (4.7)	473/11,161 (4.2)	1.11 (0.98–1.25)
Preterm birth <37 wk of gestation	716/11,220 (6.4)	711/11,161 (6.4)	1.00 (0.91–1.11)
Preterm birth <32 wk of gestation	118/11,220 (1.1)	125/11,161 (1.1)	0.94 (0.73–1.21)
Induction of labor	3675/11,755 (31.3)	3670/11,714 (31.3)	1.00 (0.96–1.04)

* The denominators vary according to the ascertainment method used for each outcome. The perinatal outcomes included pregnancies for which information was available in the maternal record (stillbirth and shoulder dystocia) or in newborn records that were matched to maternal records. Reasons for unmatched newborn records include adopted infants, deliveries within and outside the health plan in which the newborn was covered by other insurance, deliveries outside the health plan and for which no reimbursement for newborn care was requested, and instances in which the mother left the health plan before delivery and no information was available for the newborn. There were 702 unmatched newborn records in the one-step screening group and 709 unmatched newborn records in the two-step screening group. In 30 pregnancies in the one-step group and 21 pregnancies in the two-step group, there was a diagnosis of shoulder dystocia in the maternal record but no matching newborn record. In 32 pregnancies in the one-step group and 31 pregnancies in the two-step group, there was a diagnosis of stillbirth in the maternal record but no matching newborn record. For the outcomes of macrosomia and small-for-gestational-age infants, unmatched newborn records were excluded, and birth weight was not available for 192 pregnancies in the one-step group and 175 pregnancies in the two-step group. Furthermore, macrosomia was estimated in newborns with a gestational age of more than 36 weeks. Maternal gestational diabetes for which insulin was warranted included only women who had gestational diabetes. Induction of labor excluded women who left the health plan before delivery (167 women in the one-step group and 156 in the two-step group). NICU denotes neonatal intensive care unit.

† Relative risks are for the one-step group as compared with the two-step group. The widths of the confidence intervals have not been adjusted to account for multiplicity and cannot be used to infer treatment effects.

‡ Of the 1214 pregnant women with class A2 gestational diabetes for which medication was warranted, 1092 (90.0%) received insulin and 64 (5.3%) received oral medication; 58 women (4.8%) received both.

not shown associations between maternal gestational diabetes and long-term child outcomes.[33,34]

Outcomes of the 6% of pregnancies in women who did not undergo screening appeared to be worse than those in either of the screened groups. However, these findings are probably explained at least in part by other differences between women who adhered to recommended screening and those who did not.

Our trial has some limitations. The lower adherence to the one-step approach biased the findings toward the planned intention-to-treat analyses.[13] To address this, we extended the trial and conducted additional intention-to-treat analy-

ses with inverse probability weighting[19,20]; our identification of prognostic factors associated with adherence would be expected to increase the validity of the these analyses. However, these statistical methods may not fully account for potential differences resulting from nonadherence. Another potential limitation of our trial is that the sites used slightly different thresholds for the glucose challenge test to determine whether women in the two-step group should receive an oral glucose-tolerance test; both blood glucose level thresholds (130 mg per deciliter and 140 mg per deciliter) are clinically recommended.[1,9]

We randomized assignment to a screening approach as part of clinical care. Our research team did not have control over what occurred after the assignment was presented to the clinical provider, including whether the provider would order the test and what clinical care women would receive after screening; however, the same guidelines for the treatment of gestational diabetes were used in both randomized groups. This head-to-head design compared outcomes in a "real-world" clinical setting in which virtually the entire population at these trial sites was included, and we would expect results to be generalizable to similar settings. Owing to the overall racial or ethnic makeup of these regions, Black and American Indian women were not well represented in the trial sample. Given the pragmatic nature of the trial, the providers were aware of the approach to screening and diagnosis, and we cannot rule out the possibility that provider awareness of the approach affected some outcomes. An ongoing randomized trial (ClinicalTrials.gov number, NCT02309138) involves 921 women with a diagnosis of gestational diabetes according to either IADPSG or Carpenter–Coustan criteria. That trial, in which providers remain unaware of the criteria used, is under way to provide more information on outcomes according to diagnostic criteria for gestational diabetes.[35]

In our large randomized trial, one-step screening, as compared with two-step screening, doubled the incidence of the diagnosis of gestational diabetes but did not affect the risks of large-for-gestational-age infants, adverse perinatal outcomes, primary cesarean section, or gestational hypertension or preeclampsia.

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

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REFERENCES

1. Committee on Practice Bulletins — Obstetrics. ACOG practice bulletin no. 190: gestational diabetes mellitus. Obstet Gynecol 2018;131(2):e49-e64.
2. Landon MB. Changing the diagnostic criteria for gestational diabetes mellitus? Obstet Gynecol 2016;127:3-6.
3. Centers for Disease Control and Prevention. Diabetes during pregnancy (https://www.cdc.gov/reproductivehealth/maternalinfanthealth/diabetes-during-pregnancy.htm).
4. 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;35:526-8.
5. Moyer VA. Screening for gestational diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014;160:414-20.
6. U.S. Preventive Services Task Force. Gestational diabetes mellitus, screening. January 14, 2014 (https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/gestational-diabetes-mellitus-screening).
7. 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.
8. 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.
9. American Diabetes Association. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes — 2020.* Diabetes Care 2020;43:Suppl 1:S14-S31.
10. 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.
11. Hillier TA, Ogasawara KK, Pedula KL, Vesco KK. Markedly different rates of incident insulin treatment based on universal gestational diabetes mellitus screening in a diverse HMO population. Am J Obstet Gynecol 2013;209(5):440.e1-440.e9.
12. The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991-2002.
13. Pedula KL, Hillier TA, Ogasawara KK, et al. A randomized pragmatic clinical trial of gestational diabetes screening (ScreenR2GDM): study design, baseline characteristics, and protocol adherence. Contemp Clin Trials 2019;85:105829.

14. American Diabetes Association. 14. Management of diabetes in pregnancy: *Standards of Medical Care in Diabetes — 2020.* Diabetes Care 2020;43:Suppl 1:S183-S192.
15. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatr 2003;3:6.
16. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy: report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122-31.
17. Committee on Fetus and Newborn. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics 2011;127:575-9.
18. American Academy of Pediatrics. AAP publications reaffirmed or retired. Pediatrics 2015;136(3):e730.
19. Hernán MA, Robins JM. Causal inference: what if. Boca Raton, FL: Chapman & Hall/CRC Press, 2020.
20. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550-60.
21. Pan W. Akaike's information criterion in generalized estimating equations. Biometrics 2001;57:120-5.
22. Institute of Medicine, National Research Council. Weight gain during pregnancy: reexamining the guidelines. Washington, DC: National Academies Press, 2009.
23. American College of Obstetricians and Gynecologists. ACOG Committee opinion no. 548: weight gain during pregnancy. Obstet Gynecol 2013;121:210-2.
24. Goldstein RF, Abell SK, Ranasinha S, et al. Association of gestational weight gain with maternal and infant outcomes: a systematic review and meta-analysis. JAMA 2017;317:2207-25.
25. Kominiarek MA, Saade G, Mele L, et al. Association between gestational weight gain and perinatal outcomes. Obstet Gynecol 2018;132:875-81.
26. Rogozińska E, Zamora J, Marlin N, et al. Gestational weight gain outside the Institute of Medicine recommendations and adverse pregnancy outcomes: analysis using individual participant data from randomised trials. BMC Pregnancy Childbirth 2019;19:322.
27. Feldman RK, Tieu RS, Yasumura L. Gestational diabetes screening: the International Association of the Diabetes and Pregnancy Study Groups compared with Carpenter-Coustan screening. Obstet Gynecol 2016;127:10-7.
28. Kong JM, Lim K, Thompson DM. Evaluation of the International Association of the Diabetes In Pregnancy Study Group new criteria: gestational diabetes project. Can J Diabetes 2015;39:128-32.
29. Meloncelli NJL, Barnett AG, D'Emden M, De Jersey SJ. Effects of changing diagnostic criteria for gestational diabetes mellitus in Queensland, Australia. Obstet Gynecol 2020;135:1215-21.
30. Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles M-A, Pettitt DJ. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. Diabetes Care 2007;30:2287-92.
31. Scholtens DM, Kuang A, Lowe LP, et al. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal glycemia and childhood glucose metabolism. Diabetes Care 2019;42:381-92.
32. Lowe WL Jr, Scholtens DM, Kuang A, et al. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal gestational diabetes mellitus and childhood glucose metabolism. Diabetes Care 2019;42:372-80.
33. Landon MB, Mele L, Varner MW, et al. The relationship of maternal glycemia to childhood obesity and metabolic dysfunction‡. J Matern Fetal Neonatal Med 2020;33:33-41.
34. 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.
35. Scifres CM, Abebe K, Simhan HN, et al. 187-OR: randomized clinical trial of the IADPSG vs. Carpenter Coustan criteria for diagnosis of gestational diabetes mellitus. Diabetes 2020;69:Suppl:187. abstract.