

TOPIC COLLECTION: GESTATIONAL DIABETES, PREGNANCY COMPLICATIONS, AND LONG-TERM HEALTH RISKS

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Letter from the NEJM Group Guest Editor

The Centers for Disease Control and Prevention reported that in 2016 the national prevalence of gestational diabetes mellitus (GDM) was 6% among women with live births. Based on this estimate, among the 3.75 million births in the United States in 2019, there were approximately 225,000 pregnancies complicated by GDM.

GDM is a strong risk factor for the later development of type 2 diabetes mellitus (T2DM). A recent meta-analysis by Vounzoulaki and colleagues reported that GDM markedly increased the risk for developing T2DM (relative risk 9.5, 95% confidence interval 7.14–12.67, $P < 0.001$). Among women with a history of GDM, over 16 years of follow-up, T2DM was diagnosed in 16.2%, compared with 1.9% of control women. The American Diabetes Association recommends that women with GDM should have a 75-gram, 2-hour glucose tolerance test 4 to 12 weeks after delivery. This test can both detect frank T2DM and assess the risk for conversion to T2DM. For women with GDM, breast-feeding has been shown to reduce the risk for transitioning to T2DM. In addition, exercise, weight loss, and metformin treatment reduce the rate of transition to T2DM among women with a history of GDM.

GDM increases the pregnant woman's risk for developing one or more adverse pregnancy outcomes (APOs), including preeclampsia, gestational hypertension, polyhydramnios, and stillbirth. In turn, APOs are associated with an increased future risk for cardiovascular disease. In a meta-analysis, Okoth and colleagues reported that GDM increased the risk for ischemic heart disease (RR 2.09, 95% CI 1.56–2.80) and stroke (RR 1.25, 95% CI 1.07–1.48). In this study, breast-feeding reduced the risk for ischemic heart disease and stroke. For women with an APO, breast-feeding may be especially important.

The fetus of a woman with GDM is at an increased risk for being large for gestational age and experiencing a traumatic birth, including brachial plexus nerve injury. Children born to mothers with GDM are at risk for developing obesity, glucose intolerance, and diabetes. In the study by Lowe and colleagues, among children (mean age 11.4 years) of mothers with and without GDM, the prevalence of obesity was 19.1% and 9.9%, respectively. Adjusted for maternal body-mass index during pregnancy, the odds ratio for developing obesity among children born to mothers with GDM compared with those whose mothers did not have GDM was 1.58 (95% CI 1.24–2.01).

The U.S. Preventive Services Task Force recommends that pregnant women should be screened for GDM after 24 weeks' gestation (B rating). For screening, the American College of Obstetricians and Gynecologists recommends a two-step approach and the International Association of the Diabetes and Pregnancy Study Groups recommends a one-step approach. In the study by Hillier and colleagues published in the *New England Journal of Medicine*, the two approaches were directly compared. For the one-step and two-step approaches, gestational diabetes was diagnosed in 16.5% and 8.5% of pregnant women, respectively. For both groups, treatment of gestational diabetes included medical nutrition guidance, frequent glucose measurements, and insulin therapy if needed. For the one-step



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and two-step approaches there were no significant differences in the following pregnancy outcomes: large-for-gestational-age infants (8.9% and 9.2%), perinatal composite outcome (3.1% and 3.0%), gestational hypertension or preeclampsia (13.6% and 13.5%), and primary cesarean delivery (24.0% and 24.6%). Based on this and other studies, I recommend the two-step approach to screening for GDM.

Robert L. Barbieri, MD

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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 as a Growing Risk Factor for Type 2 Diabetes

Women with a history of GDM face a T2DM prevalence as high as 16% after 16 years.

Trends toward older age at conception as well as obesity both influence likelihood of developing type 2 diabetes mellitus (T2DM) subsequent to gestational diabetes mellitus (GDM). Investigators performed a systematic review and meta-analysis of 20 studies in several countries to estimate risk for developing T2DM among women with a history of GDM (68,000 women) compared with those with normal glucose testing during pregnancy (controls; 1,300,000 women).

Pooled relative risk for developing T2DM was 9.5 for women with a history of GDM compared with controls. In a subanalysis of seven studies (mean follow-up, 16 years), T2DM was diagnosed in 16.2% of women with GDM and 1.9% of controls. In six studies (mean follow-up, 7 years), among white women, T2DM was diagnosed in 9.9% of those with GDM and 0.6% of controls. In four studies (mean follow-up, 6 years), among nonwhite women, T2DM was diagnosed in 15.6% of those with GDM and 2.0% of controls.

COMMENT

Although it's well known that a history of GDM is a major risk factor for developing T2DM, this meta-analysis provides more precise estimates of absolute and relative risk. Preventing GDM requires attention to diet and exercise to optimize body-mass index before and after conception. If GDM is diagnosed, postpartum testing for diabetes should occur within 3 months of delivery and at regular intervals thereafter. For women with a history of GDM, breast-feeding, exercise, dietary modification, and metformin therapy all can reduce risk for developing T2DM.

— **Robert L. Barbieri, MD**

Dr. Barbieri is Kate Macy Ladd Distinguished Professor of Obstetrics, Gynecology, and Reproductive Biology and Chief of Obstetrics, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School.

Vounzoulaki E et al. Progression to type 2 diabetes in women with a known history of gestational diabetes: Systematic review and meta-analysis. *BMJ* 2020 May 13; 369:m1361. (<https://doi.org/10.1136/bmj.m1361>)

Women's Reproductive History and Future Cardiovascular Risk

Preeclampsia consistently carries heightened risks, oral contraceptives carry risks for some outcomes, and longer breast-feeding is associated with lower risk for some outcomes.

Factors related to women's reproductive history have been linked to future cardiovascular risk. These authors performed an umbrella review of 24 meta-analyses and 8 systematic reviews (median follow-up: fertility factors, 8 years; pregnancy factors, 10 years), assessing the association of female-specific factors with future cardiovascular risks (ischemic heart disease, heart failure,

peripheral artery disease, stroke, and their composite) in women of reproductive age.

Significant findings were as follows:

Composite cardiovascular outcome

- Preeclampsia, gestational diabetes, stillbirth, and preterm birth, ≥ 2 -fold increased risk
- Gestational hypertension, placental abruption, and premature ovarian failure, 1.5- to 1.9-fold increased risk
- Early menarche, polycystic ovary syndrome (PCOS), ever parity, and early menopause, < 1.5 -fold increased risk
- Longer length of breast-feeding, *reduced* risk

Ischemic heart disease

- Preeclampsia, recurrent preeclampsia, and gestational diabetes, ≥ 2 -fold increased risk
- Current use of combined oral contraceptives (estrogen + progesterone), recurrent miscarriage, premature ovarian failure, and early menopause, 1.5- to 1.9-fold increased risk
- Miscarriage, PCOS, preterm birth, and menopausal symptoms, < 1.5 -fold increased risk

Stroke

- Current use of any oral contraceptive, and preeclampsia, ≥ 2 -fold increased risk
- Current use of combined oral contraceptives, recurrent preeclampsia, and preterm birth, 1.5- to 1.9-fold increased risk
- PCOS and gestational diabetes, < 1.5 -fold increased risk
- Heart failure
- Recurrent preeclampsia, almost 3-fold increased risk

No cardiovascular outcomes were associated with fertility treatment, current use of progesterone-only contraceptives, or use of non-oral hormonal contraceptives.

COMMENT

This study confirms prior associations of reproductive factors and future cardiovascular risk in women. Pregnancy-related outcomes such as preeclampsia, preterm birth, and stillbirth are consistently associated with the greatest risk, but non-pregnancy-related factors such as premature ovarian failure, early menopause, PCOS, and oral contraceptive use were also associated with greater risk. Longer length of breast-feeding was associated with reduced risk. These data support incorporating reproductive history into risk assessment for women. — **Karol E. Watson, MD, PhD, FACC**

Dr. Watson is Director of the UCLA Barbra Streisand Women's Heart Health Program, Codirector of the UCLA Program in Preventive Cardiology, and Director of the UCLA Cardiology Fellowship.

Okoth K et al. Association between the reproductive health of young women and cardiovascular disease in later life: Umbrella review. *BMJ* 2020 Oct 7; 371:m3502. (<https://doi.org/10.1136/bmj.m3502>)

The Lingering Effects of Gestational Diabetes

Women with GDM undiagnosed by current criteria are at excess risk for disorders of glucose metabolism a decade later.

Compared with the Carpenter-Coustan criteria commonly used in the U.S. for diagnosing gestational diabetes (GDM), criteria established by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) result in a two- to threefold higher prevalence of GDM. Concerns about the ramifications of this discrepancy have limited the uptake of IADPSG criteria in the U.S. Now, investigators for the Hyperglycemia and Adverse Pregnancy Outcomes study (which has already revealed excess risk for adverse pregnancy outcomes among women with GDM diagnosed by IADPSG — but not Carpenter-Coustan — criteria) sought to determine the long-term maternal and pediatric consequences of untreated GDM diagnosed with the more-liberal criteria.

Among almost 5000 mother-child pairs, GDM was diagnosed in 14% of women through post-hoc application of IADPSG criteria. Half of these women went on to have disorders of glucose metabolism (type 2 diabetes or prediabetes) over a mean 11.4 years of follow-up (odds ratio, 3.6, compared with women without GDM). Compared with women who did not have GDM, those with

IADPSG-diagnosed GDM were more likely to have children who were obese.

COMMENT

The value of applying the IADPSG criteria (along with an additional burden of diagnosis and treatment) has been debated in the U.S. Although this study does not demonstrate — or even suggest — that treatment of women with GDM will mitigate longer-term harm, we must consider the benefits of a diagnostic tool that can identify families at risk during the captive healthcare period that pregnancy represents. At a minimum, for my patients with evidence of glucose intolerance according to current screening methods, I will share my concerns with them (and their other providers) about their future health so as to enable appropriate screening, lifestyle modification (including breast-feeding), and other treatments during the months and years beyond pregnancy.

— Allison Bryant, MD, MPH

Dr. Bryant is Assistant in Gynecology and Obstetrics, Division of Maternal Fetal Medicine, Massachusetts General Hospital; Assistant Professor of Obstetrics, Gynecology, and Reproductive Biology, Harvard Medical School, Boston.

Lowe WL Jr et al. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. *JAMA* 2018 Sep 11; 320:1005. (<https://doi.org/10.1001/jama.2018.11628>)