Gestational Diabetes Screening, Risk factors and National Evidence of Iran

Samira Behboudi-Gandevani, PhD

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NORD universitet

پژوهشکده علوم غدد درون‌ریز و متابولیسم

Disclosure

- Assistant Professor at reproductive Endocrinology Research Center until, 2019.
- A collaborator of Gulf study

Outline

- Definition
- Importance
- Screening methods
- Risk factors
- National findings, the GULF study

Pregnancy, a Diabetic States

- Pregnancy is generally a state of insulin resistance, mediated primarily by placental secretion of diabetogenic hormones

- These and other metabolic changes, which are most prominent in the Second and third trimesters, ensure that the fetus has an ample supply of glucose and some other nutrients

- GDM develops in pregnant women whose pancreatic function is insufficient to overcome the insulin resistance associated with the pregnant state.

TERMINOLOGY

- GDM Traditionally referred to any pregnant person in whom abnormal glucose tolerance was first recognized at any time during pregnancy,

  - American Diabetes Association (ADA)-2023
  - The American College of Obstetricians and Gynecologists (ACOG)-2018

American Diabetes Association (ADA)-2023

- GDM is diabetes diagnosed in the second or third trimester that was not clearly present prior to conception.

  - This definition excludes patients diagnosed in the first trimester because they likely have previously undiagnosed type 2 diabetes. The term "overt diabetes" is sometimes used to describe the diabetes status of these individuals during pregnancy; a formal diagnosis of type 2 diabetes can be made when the diagnosis is confirmed in the nonpregnant state.

Review > Diabetes Care. 2023 Jan 1;46(Suppl 1):S19-S40. doi: 10.2337/dc23-S002.

2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes–2023

The American College of Obstetricians and Gynecologists (ACOG)-2018

- continues to define GDM as "a condition in which carbohydrate intolerance develops during pregnancy

Practice Guideline > Obstet Gynecol. 2018 Feb;131(2):e49-e64.
doi: 10.1097/AOG.0000000000002501.

ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus

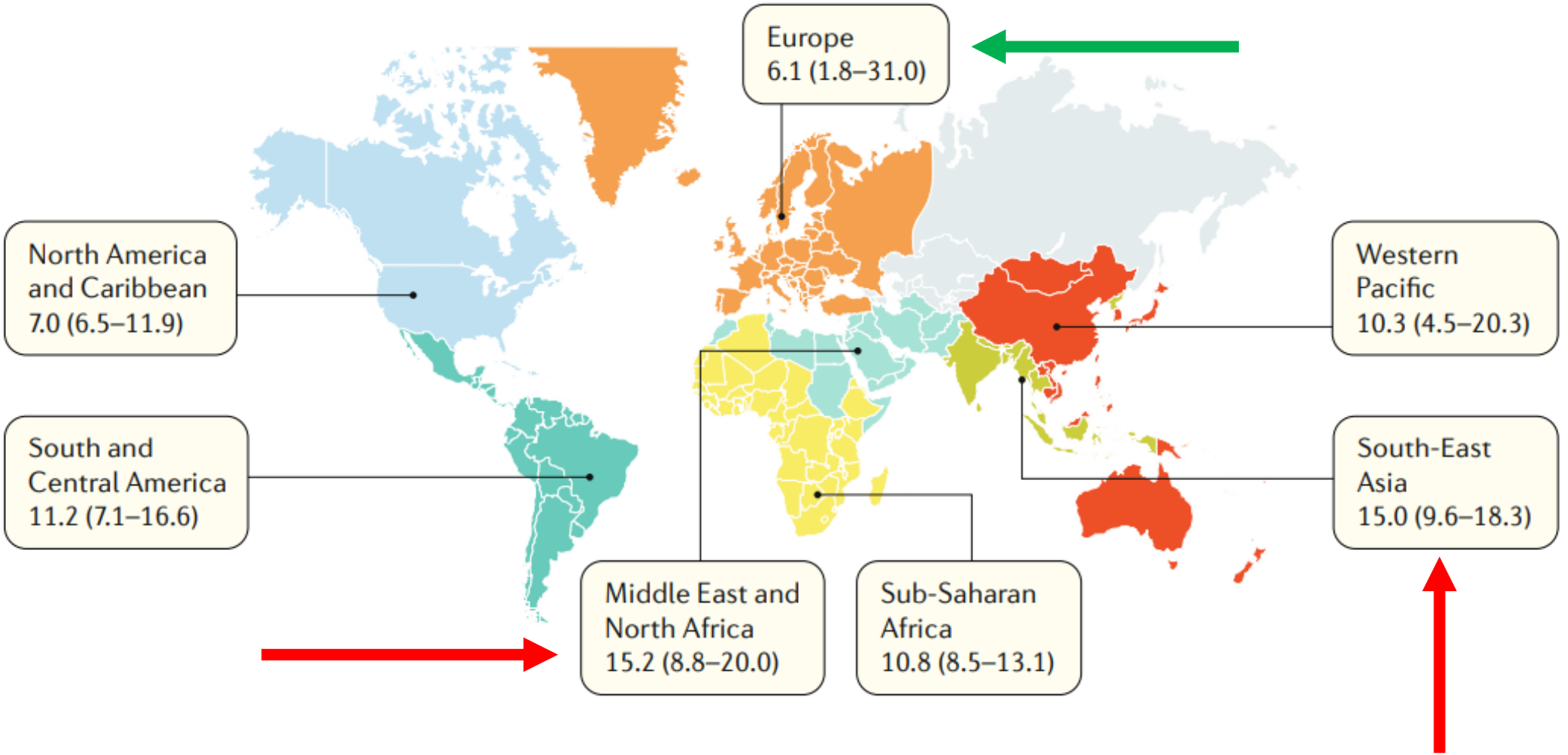
No authors listed

PMID: 29370047 DOI: 10.1097/AOG.0000000000002501

Prevalence of GDM

- Worldwide prevalence varies, due to:
  - differences in population characteristics (eg, average maternal age and BMI)
  - choice of screening and diagnostic criteria.

- Using the 2010 International Association of Diabetes and Pregnancy Study Groups (IADPSG) screening:
  - the global estimates of: 17 percent
  - regional estimates of:
    - 25 % in Southeast Asia
    - 10 % in North America and
    - 10.9% in Europe
    - 13.3% in Iran (based on national-Gulf Study)
    - 8% in Northern Europe



McIntyre, H.D., Catalano, P., Zhang, C. et al. Gestational diabetes mellitus. Nat Rev Dis Primers 5, 47 (2019). https://doi.org/10.1038/s41572-019-0098-8

Canada. 2010-2017

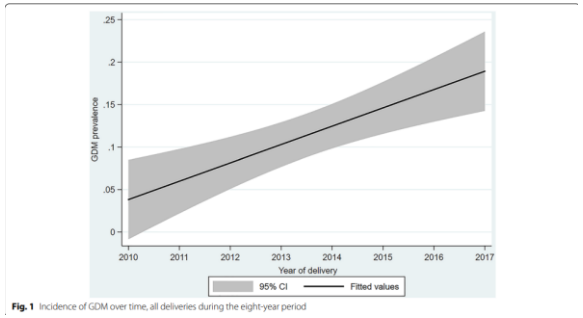
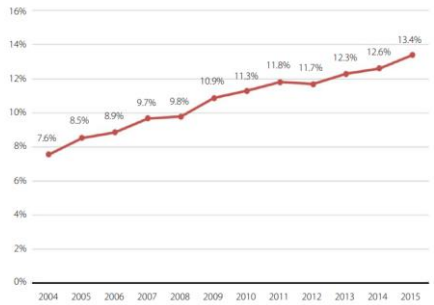


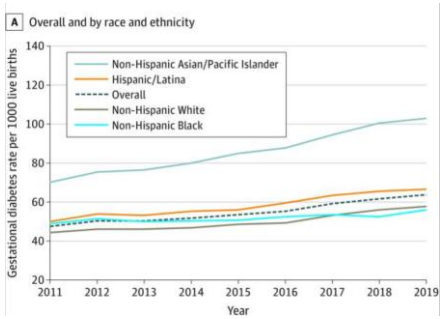
Fig. 1 Incidence of GDM over time, all deliveries during the eight-year period

Taiwan. 2004-2015

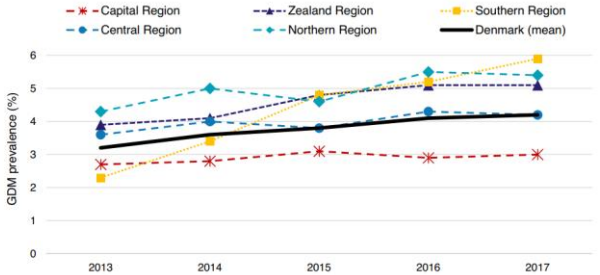


Gestational diabetes mellitus (GDM) is the fastest growing type of diabetes with rates doubling or trebling over the past decades partially explained by rising obesity rates and advanced-maternal age among childbearing women

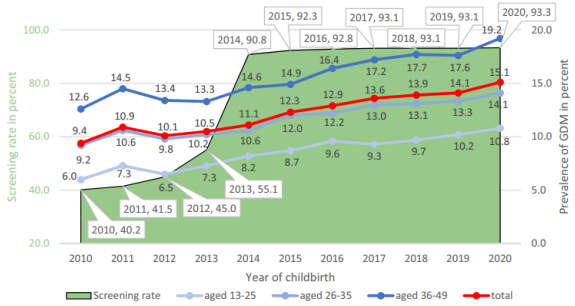
USA. 2011-2019



Denmark. 2013-2017



Germany. 2010-2020



https://doi.org/10.1186/s12884-022-04420-9
https://doi.org/ 10.1111/jdi.13595
https://doi.org/ 10.1001/jama.2021.7217
https://doi.org/ 10.1038/s41598-023-43382-6

Screening *vs.* Diagnostic Tests

- Screening test:

  Differentiates apparently healthy BUT diseased individuals from those that probably do not have the disease

  - Objective: Early detection of a disease condition in apparently healthy individuals

- Diagnostic test:

  Identify and/or confirm a disease condition in individuals

  - Objective: Case finding within a population that is probably "diseased"

WHO principles of early disease detection

Condition

- The condition sought should be an important health problem
- There should be a recognizable latent or early symptomatic stage
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.

Test

- There should be a suitable test or examination.
- The test should be acceptable to the population.

Treatment

- There should be an accepted treatment for patients with recognized disease.

Screening program

- Facilities for diagnosis and treatment should be available.
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-finding should be a continuing process and not a “once and for all” project.

Screening of GDM

- Detecting GDM is important because perinatal complications and stillbirth risk are greatly reduced by treatment
- There is no universally accepted standard regarding screening for or diagnosis of GDM. Practitioners tend to follow the guidance of their national medical organizations.
- There is strong controversy over:
  - Screening approaches? (universal or targeted)
  - Time of screening? (early gestation or second trimester)
  - Screening methods? (fasting plasma glucose, random glucose and oral glucose challenge), diagnostic criteria (one steps or two, amount of the 75 g or 100 g glucose load, the duration of the test for 2 or 3 h, as well as the glucose threshold values, and whether 1 or 2 high glucose values are all used)
  - Obstetricians and Endocrine societies recommendation?
-

Screening approach: who should be screened?

Universal Screening:

- All of pregnant women are screen for GDM.
- This is a common practice in many parts of the world

Targeted Screening:

- Those women with risk factors are screen.
- Many European countries still use this approach

Risk factors for GDM

- Personal history of any of the following:
  - GDM in a previous pregnancy (associated with a 40 % risk of recurrence)
  - Impaired glucose tolerance
  - Pre-pregnancy A1C ≥5.7 percent
  - Elevated fasting glucose
- Family history of diabetes, especially in a first-degree relative.
- Pre-pregnancy BMI ≥30 kg/m^2, significant weight gain in early adulthood or between pregnancies, or excessive gestational weight gain during the first 18 to 24 weeks of pregnancy.
- Previous birth of an infant ≥4000 g.
- Medical condition/setting associated with development of diabetes (eg, polycystic ovary syndrome).
- Older maternal age (≥35 years of age)
- Member of one of the following groups, which have a high prevalence of type 2 diabetes: Hispanic American; Native American, Alaska native, or Native Hawaiian; South or East Asian, Pacific Islander. The prevalence is less in non-Hispanic White and non-Hispanic Black people

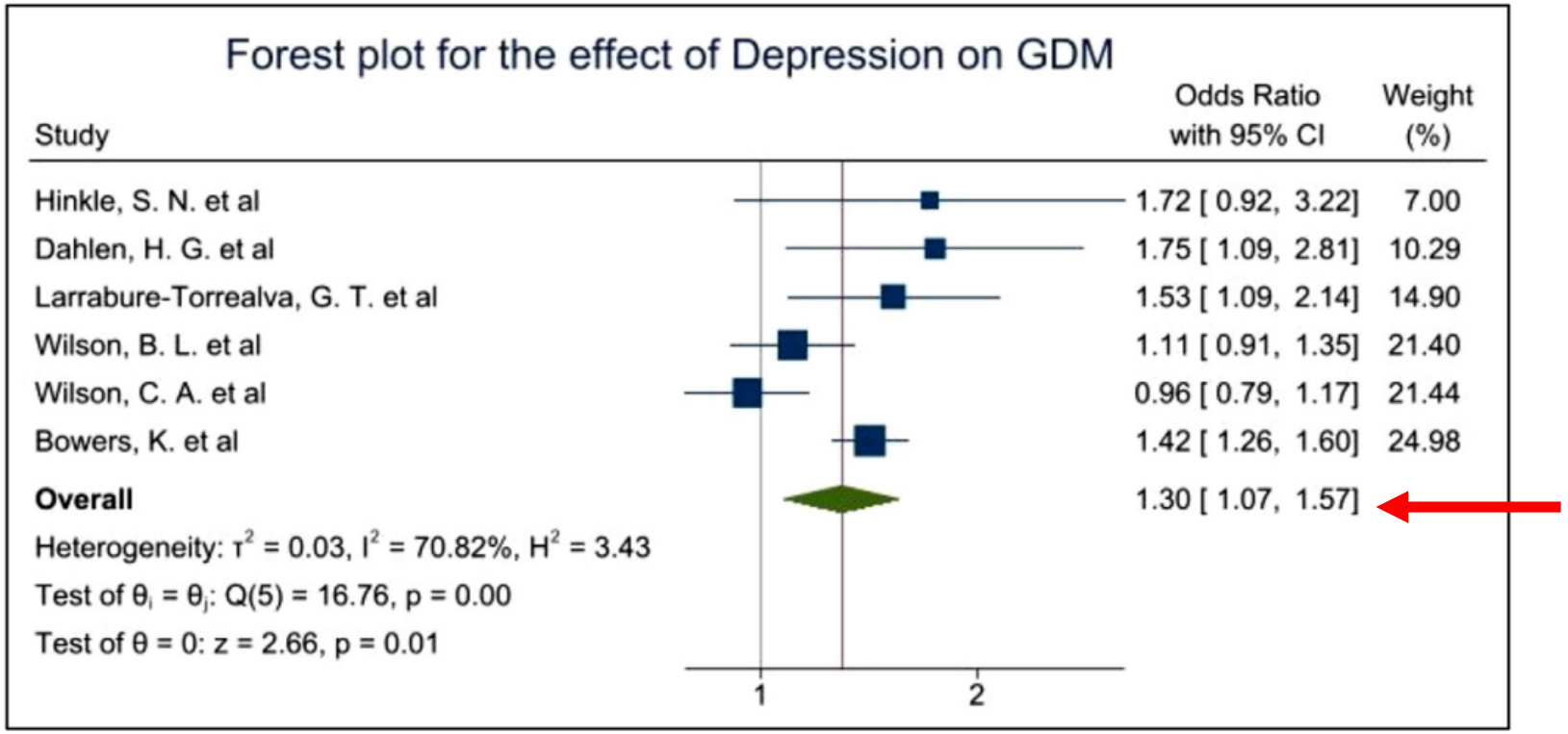
ADA, 2023. and Getahun D, Fassett MJ, Jacobsen SJ. Gestational diabetes: risk of recurrence in subsequent pregnancies. Am J Obstet Gynecol 2010; 203:467.e1.

Risk factors for GDM

- Adults with overweight (BMI ≥25 kg/m2 or ≥23 kg/m2 in Asian American individuals) (OR: 2.637, 95% CI: (1.561, 4.453)
- Stillbirth (OR: 2.341, 95% CI: (1.435, 3.819),
- pregestational smoking (OR: 2.322, 95% CI: (1.359, 3.967)
- Mental health (Depression, Anxiety abd stress): (OR: 2.30, 95% CI: (1.07, 1.57)
- history of abortion 22% (95% CI:16–27)
- pregnancy-induced hypertension (OR 3.20, 95% CI 2.19–4.68)
- Grand multiparity ≥5 (OR 1.37, 95% CI 1.24–1.52)
- history of preterm delivery (OR 1.93, 95% CI 1.21–3.07)
- Hypothyroidism
- Iatrogenic: glucocorticoids and antipsychotic medication
- Immigration: (OR 1.32, 95% CI 1.21–3.05)

- Giannakou K, Evangelou E, Yiallouros P, Christophi CA, Middleton N, Papatheodorou E, Papatheodorou SI. Risk factors for gestational diabetes: An umbrella review of meta-analyses of observational studies. PLoS One. 2019 Apr 19;14(4):e0215372. doi: 10.1371/journal.pone.0215372.
- Lee KW, Ching SM, Ramachandran V, Yee A, Hoo FK, Chia YC, Wan Sulaiman WA, Suppiah S, Mohamed MH, Veettil SK. Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2018 Dec 14;18(1):494. doi: 10.1186/s12884-018-2131-4.
- Sweeting A, Wong J, Murphy HR, Ross GP. A Clinical Update on Gestational Diabetes Mellitus. Endocr Rev. 2022 Sep 26;43(5):763-793. doi: 10.1210/endrev/bnac003.

Mental health (Depression, (OR: 2.30, 95% CI: (1.07, 1.57)



Arafa A, Dong JY. Depression and risk of gestational diabetes: A meta-analysis of cohort studies. Diabetes Res Clin Pract. 2019 Oct;156:107826. doi: 10.1016/j.diabres.2019.107826. Epub 2019 Aug 23. PMID: 31449873.

Individuals at low risk of GDM

The risk of developing GDM is low in

- younger (<25 years of age)
- non-Hispanic White people,
- with normal BMI (<25 kg/m2 , <23 kg/m2 in Asian people),
- no history of previous glucose intolerance or adverse pregnancy outcomes associated with GDM,
- no first-degree relative with diabetes.

Only 10 percent of the general obstetric population in the United States meets all of these criteria for low risk of developing GDM, which is the basis for universal rather than selective screening

- Being primigravida ? (OR: 0.752, 95% CI: (0.698, 0.810)
- Smoking cessation? (cessation has multiple maternal and fetal benefits but weight gain;)
- History of congenital anomaly, and HIV status?

Zhang Y, Xiao CM, Zhang Y, Chen Q, Zhang XQ, Li XF, Shao RY, Gao YM. Factors Associated with Gestational Diabetes Mellitus: A Meta-Analysis. J Diabetes Res. 2021 May 10;2021:6692695. doi: 10.1155/2021/6692695.

Universal screening VS. risk profiles screening

- Two trials that randomized 4523 women and their infants.

- Both trials were conducted in Ireland.
- One trial (which quasi-randomized 3742 women, and analyzed 3152 women) compared universal screening versus risk factor-based screening, and one trial (which randomized 781 women, and analyzed 690 women).

- Overall, there was moderate to high risk of bias due to one trial being quasi-randomized, inadequate blinding, and incomplete outcome data in both trials

Clinical Trial > Diabet Med. 2000 Jan;17(1):26-32. doi: 10.1046/j.1464-5491.2000.00214.x.

Universal vs. risk factor-based screening for gestational diabetes mellitus: detection rates, gestation at diagnosis and outcome

M E Griffin [1], M Coffey, H Johnson, P Scanlon, M Foley, J Stronge, N M O'Meara, R G Firth

Affiliations + expand

PMID: 10691156 DOI: 10.1046/j.1464-5491.2000.00214.x

Randomized Controlled Trial > Trials. 2014 Jan 17:15:27. doi: 10.1186/1745-6215-15-27.

Screening uptake rates and the clinical and cost effectiveness of screening for gestational diabetes mellitus in primary versus secondary care: study protocol for a randomised controlled trial

Angela O'Dea [1], Jennifer J Infanti, Paddy Gillespie, Olga Tummon, Samuel Fanous, Liam G Glynn, Brian E McGuire, John Newell, Fidelma P Dunne

Affiliations + expand

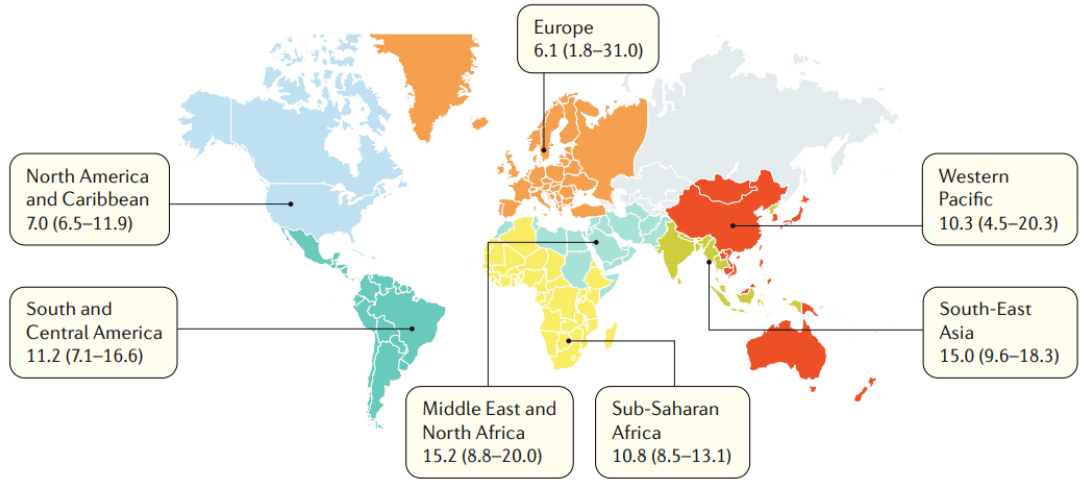
PMID: 24438478 PMCID: PMC3899741 DOI: 10.1186/1745-6215-15-27

Results

There are insufficient randomized controlled trial data evaluating the effects of screening for GDM based on different risk profiles and settings on maternal and infant outcomes. Low-quality evidence suggests universal screening compared with risk factor-based screening leads to more women being diagnosed with GDM. Low to very low-quality evidence suggests no clear differences between primary care and secondary care screening, for outcomes: GDM, hypertension, pre-eclampsia, caesarean birth, large-for-gestational age, neonatal complications composite, and hypoglycaemia.

The risk of developing GDM is low in

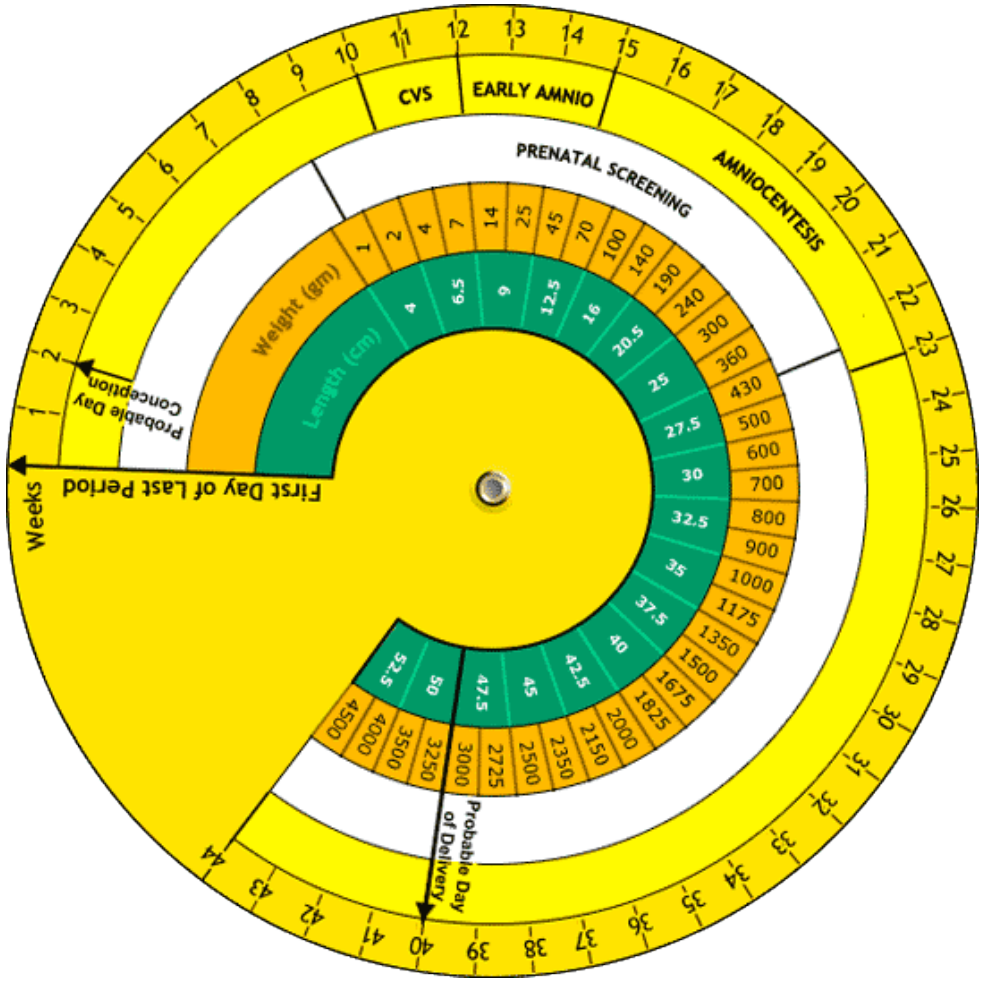
- younger (<25 years of age)
- non-Hispanic White people,
- with normal BMI,
- no history of previous glucose intolerance or adverse pregnancy outcomes associated with GDM,
- no first-degree relative with diabetes.



- It is estimated that Only 10 percent of the general obstetric population in the United States and many parts of the world meets all of these criteria for low risk of developing GDM, which is the basis for universal rather than selective screening

- General low prevalence of GDM and health economic analyses are the basis for selective rather than universal screening in European countries

Time of screening (early gestation or second trimester)



Early screening

- Currently, there is no consensus on universal or targeted screening in the first trimester.
- Currently, there is no consensus on the preferred testing approach or diagnostic glycemic thresholds for early GDM.
- Currently, there is no consensus on the approach for the management of GDM diagnosed early in gestation
- Most international guidelines now recommend early antenatal testing for women at high risk to identify women with diabetes mellitus in pregnancy (DIP). This has resulted in increased detection of milder degrees of hyperglycemia below the threshold of DIP, referred to as GDM diagnosed prior to 24 weeks' gestation or early GDM. *(Risk assessment for GDM should be undertaken at the first prenatal visit, Women with clinical characteristics consistent with a high risk of GDM should undergo glucose testing as soon as feasible)*

International criteria for testing of gestational diabetes mellitus in early pregnancy

Organization	Early pregnancy testing	Method of testing	Diagnostic test	Criteria for diagnosing early GDM (mmol/L)
IADPSG	Yes	Selective—women at risk of overt diabetes during pregnancy[a]	Fasting glucose[b]	≥5.1
WHO	Not specified[c]		75-g 2-hour OGTT	Fasting 5.1-6.9 *or* 1-hour ≥ 10.0 *or* 2-hour 8.5-11.0
ADIPS	Yes	Selective—women at risk of hyperglycemia in pregnancy[d]	75-g 2-hour OGTT	Fasting 5.1-6.9 *or* 1-hour ≥ 10.0 *or* 2-hour 8.5-11.0
ADA	Yes	Selective—women with risk factors for undiagnosed type 2 diabetes[e]	One-step: 75-g 2-hour OGTT Two-step: 50-g GCT 100-g 3-hour OGTT	Fasting 5.1-6.9 *or* 1-hour ≥ 10.0 *or* 2-hour 8.5-11.0 ≥7.2 to 7.8 Carpenter and Coustan NDDG Fasting ≥ 5.3 ≥ 5.8 1-hour ≥ 10.0 ≥ 10.6 2-hour ≥ 8.6 ≥ 9.2 3-hour ≥ 7.8 ≥ 8.0
ACOG	Yes	Selective—women with risk factors for undiagnosed type 2 diabetes or GDM[f]	75-g 2-h OGTT *or* 50-g GCT Confirmatory 100-g 3-hour OGTT	Fasting ≥ 7.0 *or* 2-hour ≥ 11.1 ≥7.2 to 7.8 Carpenter and Coustan NDDG Fasting ≥ 5.3 ≥ 5.8 1-hour ≥ 10.0 ≥ 10.6 2-hour ≥ 8.6 ≥ 9.2 3-hour ≥ 7.8 ≥ 8.0
NICE	Yes	Selective[j]	75-g 2-hour OGTT	Fasting ≥ 5.6 2-hour ≥ 7.8

Second Trimester Screening

Current international testing approach to gestational diabetes mellitus

Organization/ country	Selective vs universal testing	Method of screening	Screen positive threshold (mmol/L)	Diagnostic test	Diagnostic (plasma glucose) threshold for GDM (mmol/L)
IADPSG WHO ADIPS FIGO JDS EBCOG Endocrine Society China	Universal	One-step: 75-g 2-h OGTT		75-g 2-hour OGTT	Fasting ≥ 5.1 1-h ≥ 10.0 2-h ≥ 8.5 One abnormal value needed for diagnosis
ADA	Universal	One-step: 75-g 2-h OGTT Two-step: 50-g GCT	≥7.2 to 7.8[a]	75-g 2-hour OGTT 100-g 3-hour OGTT	Fasting ≥ 5.1 1-h ≥ 10.0 2-h ≥ 8.5 One abnormal value needed for diagnosis Carpenter and Coustan[b] (17) or NDDG (13) Fasting ≥ 5.3 Fasting ≥ 5.8 1-hour ≥ 10.0 1-hour ≥ 10.6 2-hour ≥ 8.6 2-hour ≥ 9.2 3-hour ≥ 7.8 3-hour ≥ 8.0 Two abnormal values needed for diagnosis
ACOG[c]	Universal	Two-step: 50-g GCT	≥7.2 to 7.8*	100-g OGTT	Carpenter and Coustan[b] (17) or NDDG (13) Fasting ≥ 5.3 Fasting ≥ 5.8 1-hour ≥ 10.0 1-hour ≥ 10.6 2-hour ≥ 8.6 2-hour ≥ 9.2 3-hour ≥ 7.8 3-hour ≥ 8.0 Two abnormal values needed for diagnosis[d]
CDA	Universal	Two-step: 50-g GCT (preferred) One-step: 75-g 2-h OGTT (alternative)	≥7.8	50-g GCT 75-g 2-hour OGTT	≥11.1 mmol/L[e] Fasting ≥ 5.3 1-hour ≥ 10.6 2-hour ≥ 9.0 One abnormal value needed for diagnosis
NICE	Selective	Risk factors[f]		75-g 2-hour OGTT	Fasting ≥ 7.0 2-hour ≥ 7.8 One abnormal value needed for diagnosis

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In individuals who are planning pregnancy, screen those with risk factors…

- Signs of insulin resistance or conditions associated with DM

- Consider testing all individuals of childbearing potential for undiagnosed diabetes. (Beginning 5 years after the diagnosis of cystic fibrosis–Immunosuppressive regimens, etc)

Table 2.3—Criteria for screening for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian American individuals) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥130/80 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Individuals with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. People with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. People who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other people, testing should begin at age 35 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. People with HIV

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- Early Screening

- If individuals are not screened prior to pregnancy, universal early screening at <15 weeks of gestation for undiagnosed diabetes may be considered over selective screening

    - Standard diagnostic criteria for identifying undiagnosed diabetes in early pregnancy are the same as those used in the nonpregnant population

- Early abnormal glucose metabolism, defined as fasting glucose threshold of 110 mg/dL (6.1 mmol/L) or an A1C of 5.9% (39 mmol/mol), may identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes (preeclampsia, macrosomia, shoulder dystocia, perinatal death), are more likely to need insulin treatment, and are at high risk of a later GDM diagnosis . An A1C threshold of 5.7% has not been shown to be associated with adverse perinatal outcomes

- The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) GDM diagnostic criteria for the 75-g OGTT, as well as the GDM screening and diagnostic criteria used in the two-step approach, were not derived from data in the first half of pregnancy and should not be used for early screening

ADA-2023

- The benefits of treatment for early abnormal glucose metabolism remain uncertain.

- Nutrition counseling and periodic testing of glucose levels weekly to identify individuals with high glucose levels are suggested.
- Testing frequency may proceed to daily, and treatment may be intensified, if the fasting glucose is predominantly >110 mg/dL prior to 18 weeks of gestation.

24-28 weeks of Gestation

- GDM diagnosis can be accomplished with either of two strategies:

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in individuals not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively), proceed to a 100-g OGTT.

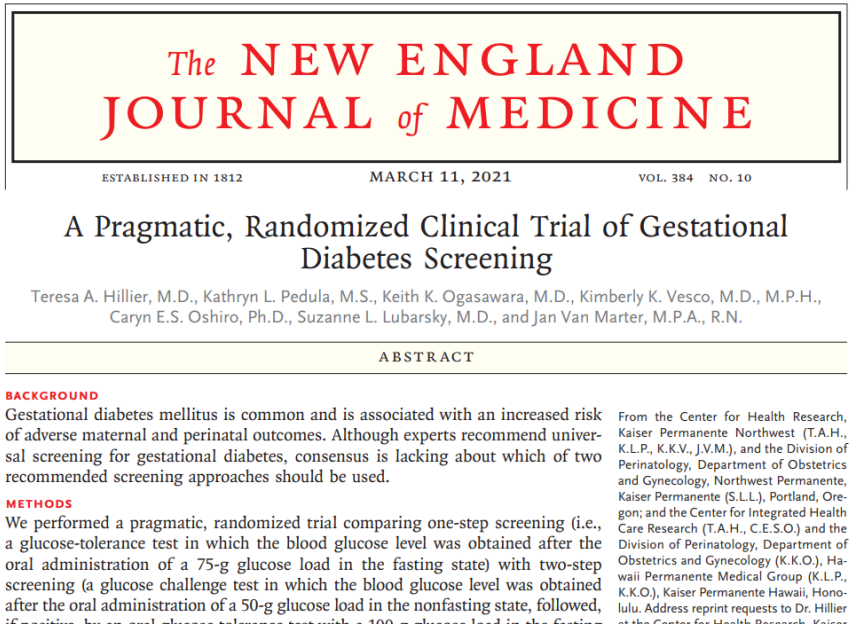
Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made when at least two* of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria [251]):

- Fasting: 95 mg/dL (5.3 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 155 mg/dL (8.6 mmol/L)
- 3 h: 140 mg/dL (7.8 mmol/L)

24-28 weeks of Gestation

- **One Step or Two-step?**
- Many regional studies have investigated the impact of adopting the IADPSG criteria on prevalence and have seen a roughly one- to threefold increase,



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A Pragmatic, Randomized Clinical Trial of Gestational Diabetes Screening

Teresa A. Hillier, M.D., Kathryn L. Pedula, M.S., Keith K. Ogasawara, M.D., Kimberly K. Vesco, M.D., M.P.H., Caryn E.S. Oshiro, Ph.D., Suzanne L. Lubarsky, M.D., and Jan Van Marter, M.P.A., R.N.

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,

From the Center for Health Research, Kaiser Permanente Northwest (T.A.H., K.L.P., K.K.V., J.V.M.), and the Division of Perinatology, Department of Obstetrics and Gynecology, Northwest Permanente, Kaiser Permanente (S.L.L.), Portland, Oregon; and the Center for Integrated Health Care Research (T.A.H., C.E.S.O.) and the Division of Perinatology, Department of Obstetrics and Gynecology (K.K.O.), Hawaii Permanente Medical Group (K.L.P., K.K.O.), Kaiser Permanente Hawaii, Honolulu. Address reprint requests to Dr. Hillier

A recent randomized trial of testing for GDM at 24–28 weeks of gestation by the one-step method using IADPSG criteria versus the two-step method using a 1-h 50-g glucose loading test (GLT) and, if positive, a 3-h OGTT by Carpenter-Coustan criteria identified twice as many individuals with GDM using the one-step method compared with the two-step method. Despite treating more individuals for GDM using the one-step method, there was no difference in pregnancy and perinatal complications

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)

Hillier TA, Pedula KL, Ogasawara KK, Vesco KK, Oshiro CES, Lubarsky SL, Van Marter J. A Pragmatic, Randomized Clinical Trial of Gestational Diabetes Screening. N Engl J Med. 2021 Mar 11;384(10):895-904. doi: 10.1056/NEJMoa2026028. PMID: 33704936; PMCID: PMC9041326.

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)

Hillier TA, Pedula KL, Ogasawara KK, Vesco KK, Oshiro CES, Lubarsky SL, Van Marter J. A Pragmatic, Randomized Clinical Trial of Gestational Diabetes Screening. N Engl J Med. 2021 Mar 11;384(10):895-904. doi: 10.1056/NEJMoa2026028. PMID: 33704936; PMCID: PMC9041326.

National Evidence , Gult Study

National Evidence , Gult Study

A Cluster Randomized Noninferiority Field Trial of Gestational Diabetes Mellitus Screening in Iran

Objective: This study was conducted to demonstrate the noninferiority of less strict GDM screening criteria compared with the strict International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria with respect to maternal and neonatal outcomes.

Methods: A cluster randomized noninferiority field trial was conducted on 35 528 pregnant women; they were scheduled to have 2 phases of GDM screening based on 5 different prespecified protocols including fasting plasma glucose in the first trimester with threshold of 5.1 mmol/L (92 mg/dL) (protocols A, D) or 5.6 mmol/L (100 mg/dL) (protocols B, C, E) and either a 1-step (GDM is defined if one of the plasma glucose values is exceeded [protocol A and C] or 2 or more exceeded values are needed [protocol B]) or 2-step approach (protocols D, E) in the second trimester. Guidelines for treatment of GDM were consistent with all protocols. Primary outcomes of the study were the prevalence of macrosomia and primary cesarean section (CS). The null hypothesis that less strict protocols are inferior to protocol A (IADPSG) was tested with a noninferiority margin effect (odds ratio) of 1.7

Diabetol Metab Syndr. 2019 Dec 18:11:106. doi: 10.1186/s13098-019-0493-z. eCollection 2019.

Cost effectiveness of different screening strategies for gestational diabetes mellitus screening: study protocol of a randomized community non-inferiority trial

Fahimeh Ramezani Tehrani [1]; Gulf Study Cooperative Research Group

Collaborators, Affiliations + expand

PMID: 31890040 PMCID: PMC6921504 DOI: 10.1186/s13098-019-0493-z

Free PMC article

Methods:

This included FPG in the first trimester and either a 1- or a 2-step screening method in the second trimester of pregnancy. Based on the results of first trimester screening, pregnant women were classified into 3 groups of overt diabetes, GDM, and non-GDM. Those with overt diabetes who had an FPG level ≥ 7.0 mmol/L (126 mg/dL) were excluded from the study. The remaining non-GDM cases were again screened for GDM at 24 to 28 weeks of gestation. Based on the results of second trimester screening, the remaining pregnant women were classified into 2 groups of GDM and non-GDM. All study participants were followed until delivery, and all prenatal information as well as feto-maternal and neonatal outcomes were recorded in detail.

Definitions of various protocols for screening of gestational diabetes mellitus

		Protocol A	Protocol B	Protocol C	Protocol D	Protocol E
First trimester	Diagnostic criteria for GDM	GDM is defined as: 5.1 mmol/L (92 mg/dL) < FPG < 7 mmol/L (126 mg/dL)	GDM is defined as: 5.6 mmol/L (100 mg/dL) < FPG < 7 mmol/L (126 mg/dL)	GDM is defined as: 5.6 mmol/L (100 mg/dL) < FPG < 7 mmol/L (126 mg/dL)	GDM is defined as: 5.1 mmol/L (92 mg/dL) < FPG < 7 mmol/L (126 mg/dL)	GDM is defined as: 5.6 mmol/L (100 mg/dL) < FPG < 7 mmol/L (126 mg/dL)
Second trimester	Method for GDM screening	One step with 2-h 75-g OGTT	One step with 2-h 75-g OGTT	One step with 2-h 75-g OGTT	Two steps with 50-g GCT-1 h following 3-h 100-g OGTT	Two steps with 50-g GCT-1 h following 3-h 100-g OGTT
	Diagnostic threshold of test	Fasting ≥ 5.1 mmol/L (92 mg/dL) 1 h ≥ 10 mmol/L (180 mg/dL) 2 h ≥ 8.5 mmol/L (153 mg/dL)	Fasting ≥ 5.1 mmol/L (92 mg/dL) 1 h ≥ 10 mmol/L (180 mg/dL) 2 h ≥ 8.5 mmol/L (153 mg/dL)	Fasting ≥ 5.1 mmol/L (92 mg/dL) 1 h ≥ 10 mmol/L (180 mg/dL) 2 h ≥ 8.5 mmol/L (153 mg/dL)	50-g GCT: BS-1 h: ≥ 7.8 mmol/L (140 mg/dL) 100-g OGTT: Fasting ≥ 5.3 mmol/L 1 h ≥ 10 mmol/L (180 mg/dL) 2 h ≥ 8.6 mmol/L (155 mg/dL) 3 h ≥ 7.8 mmol/L (140 mg/dL)	50-g GCT: BS-1 h: ≥7.8 mmol/L (140 mg/dL) 100-g OGTT: Fasting ≥ 5.3 mmol/L 1 h ≥ 10 mmol/L (180 mg/dL) 2 h ≥ 8.6 mmol/L (155 mg/dL) 3 h ≥ 7.8 mmol/L (140 mg/dL)
	Diagnostic criteria for GDM	GDM defined as any of the given plasma glucose values are met or exceeded	GDM defined as 2 or more of the given plasma glucose values are met or exceeded	GDM defined as any of the given plasma glucose values are met or exceeded	GDM defined as 2 or more of the given plasma glucose are met or exceeded	GDM defined as 2 or more of the given plasma glucose values are met or exceeded

Abbreviations: BS, blood sugar; FPG, fasting plasma glucose; GCT, glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

Randomization and allocation of study

All provinces in Iran

Stratification according to the geographical region

North of Iran (**Golestan province**)
West of Iran (**Kurdistan province**)
Center of Iran (**Yazd province**)
East of Iran (**South Khorasan province**)
South of Iran (**Bushehr province**)

Clustering based on socio-economic situation

First cluster: centers of provinces

Random allocation of protocol among center of provinces

Golestan province: Gorgan city (E)
Kurdistan province: Sanandaj city (B)
Yazd province: Yazd city (C)
South Khorasan province: Birjand city (D)
Bushehr province: Bushehr city (A)

Second cluster: Other cities in each province

Random selection of 4 cities in each provinces

Random allocation of protocol among 4 cities in each province

South Khorasan Province
City 1: Ghaen (E)
City 2: Ferdous (C)
City 3: Tabas (A)
City 4: Nehbandan (B)

Bushehr Province
City 1: Dashtestan (C)
City 2: Dashti (D)
City 3: Gonaveh (E)
City 4: Kangan (B)

Yazd Province
City 1: Ardakan (D)
City 2: Mehriz (B)
City 3: Meibod (E)
City 4: Bafgh (A)

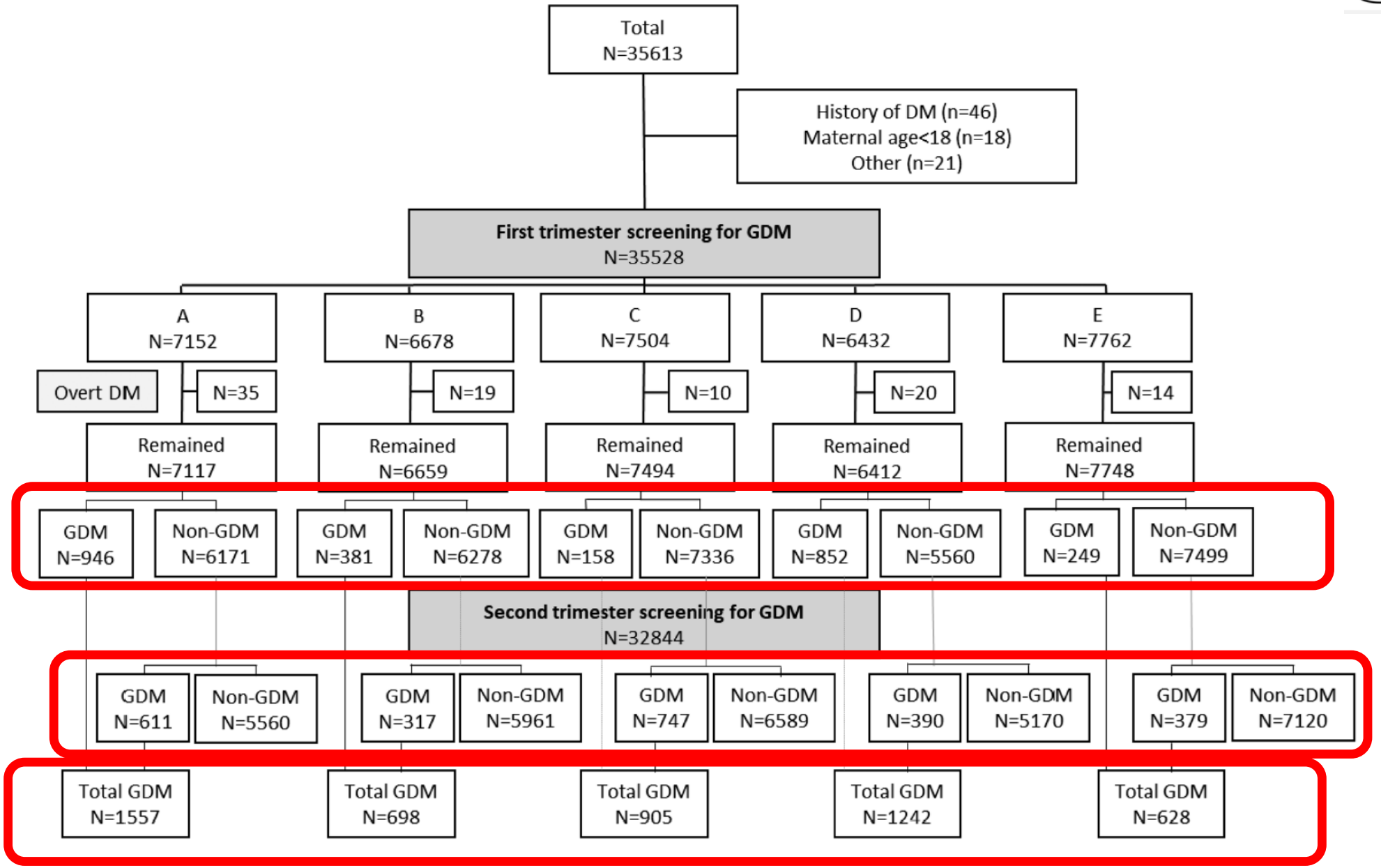
Kurdistan Province
City 1: Saghez (A)
City 2: Ghorveh (E)
City 3: Marivan (C)
City 4: Baneh (D)

Golestan Province
City 1: Gonbad (C)
City 2: Agh-ghela (D)
City 3: Torkaman (A)
City 4: Ali-abad (B)

Endpoint Outcomes

- Primary outcomes:
  macrosomia and primary cesarean section (CS).
- Secondary outcomes:
  preeclampsia, preterm birth, low birth weight (LBW), birth trauma including fracture of clavicle and brachial plexus injury, neonatal hypoglycemia, hypocalcemia and hyperbilirubinemia, admission to the neonatal intensive care unit (NICU), and still birth.

Study flow chart.



Randomized Controlled Trial > J Clin Endocrinol Metab. 2022 Jun 16;107(7):e2906-e2920.
doi: 10.1210/clinem/dgac181.

A Cluster Randomized Noninferiority Field Trial of Gestational Diabetes Mellitus Screening

Fahimeh Ramezani Tehrani [1], Samira Behboudi-Gandevani [2], Farshad Farzadfar [3] [4], Farhad Hosseinpanah [5], Farzad Hadaegh [6], Davood Khalili [6], Masoud Soleymani-Dodaran [7], Majid Valizadeh [5], Mehrandokht Abedini [8], Maryam Rahmati [1], Razieh Bidhendi Yarandi [9], Farahnaz Torkestani [10], Zahra Abdollahi [11], Marzieh Bakhshandeh [12], Mehdi Zokaee [13], Mina Amiri [1], Farzam Bidarpour [14], Mehdi Javanbakht [15], Iraj Nabipour [16], Ensieh Nasli Esfahani [17], Afshin Ostovar [18] [4], Fereidoun Azizi [19]

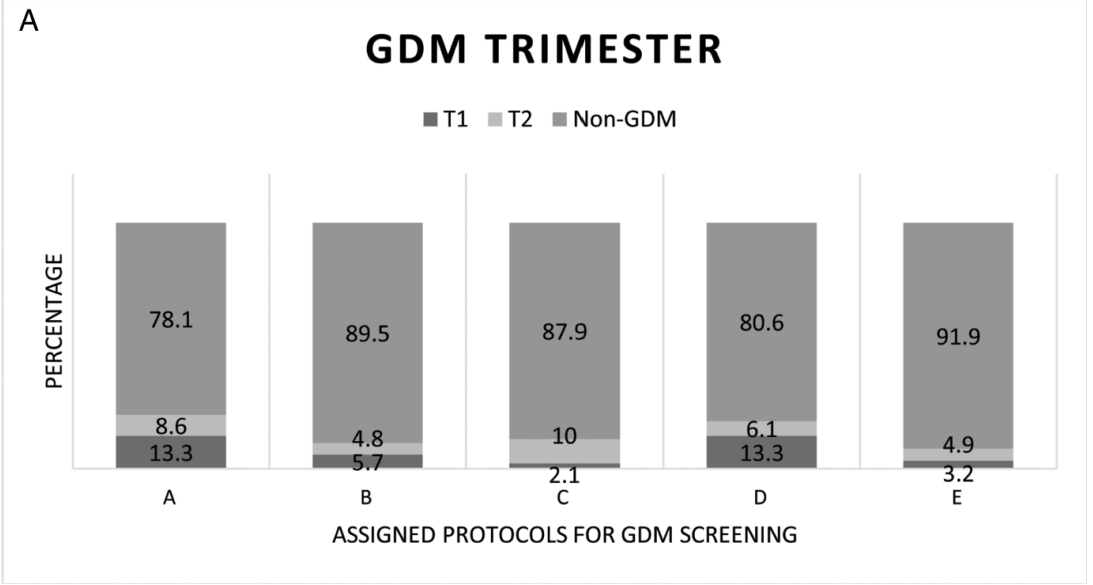
Affiliations + expand

PMID: 35325164 DOI: 10.1210/clinem/dgac181

	Protocol A	Protocol B	Protocol C	Protocol D	Protocol E	Total
	n = 7117	n = 6659	n = 7494	n = 6412	n = 7748	n = 35 430
Background characteristics						
Age, y	30 (5.9)	30.6 (5.8)	29.8 (5.7)	29.2 (5.9)	29.6 (6)	29.9 (5.9)
Gestational age at the time of entry, wk	8.9 (3.7)	8.6 (3.3)	9.5 (3.9)	9.3 (3.5)	9.2 (4.0)	9.1 (3.7)
Gestational age at birth, wk	38.7 (1.7)	38.9 (1.8)	38.8 (1.7)	38.7 (1.9)	38.7 (1.8)	38.7 (1.8)
BMI at first trimester, kg/m^2	26.2 (4.6)	26.5 (4.7)	25.6 (4.9)	25.2 (4.8)	25.4 (4.8)	25.7 (4.8)
Gestational weight gain, kg	10.6 (7.6-13.7)	10.7 (7.8-13.7)	11.3 (8.4-14.3)	11.1 (8.2-14)	11.1 (8.2-14.2)	11 (8-14)
Systolic blood pressure, mm Hg	102.5 (9.2)	102.4 (9.4)	100.0 (9.4)	100.5 (9.9)	100.3 (9.6)	101.1 (9.6)
Diastolic blood pressure, mm Hg	64.2 (7.1)	64.9 (6.8)	62.9 (7.5)	63.4 (7.8)	62.4 (7.6)	63.5 (7.4)
Parity	1 (0.9)	1.1 (0.9)	1 (0.9)	1.1 (0.9)	1.1 (0.9)	1.0 (0.9)
≥1	3733 (52.4)	3239 (48.6)	4038 (53.9)	3869 (60.3)	4337 (56.0)	19 216 (54.2)
Number of abortions	0.2 (0.6)	0.2 (0.6)	0.2 (0.6)	0.2 (0.5)	0.3 (0.6)	0.2 (0.6)
Gravidity	2.1 (1.1)	2.1 (1.1)	2.1 (1.1)	2.2 (1.2)	2.2 (1.2)	2.1 (1.2)
History of smoking	757 (10.6)	1039 (15.6)	682 (9.1)	333 (5.2)	715 (9.2)	3526 (9.9)
History of adverse pregnancy outcomes[a]						
Macrosomia	50 (0.7)	64 (1.0)	85 (1.1)	79 (1.2)	127 (1.6)	405 (1.1)
Preterm birth	99 (1.4)	122 (1.8)	146 (1.9)	119 (1.9)	118 (1.5)	604 (1.7)
LBW	149 (2.1)	153 (2.3)	222 (3.0)	181 (2.8)	181 (2.3)	886 (2.5)
Preeclampsia, gestational hypertension	89 (1.3)	84 (1.3)	113 (1.5)	102 (1.6)	114 (1.5)	502 (1.4)
GDM	96 (1.3)	101 (1.5)	124 (1.6)	89 (1.4)	123 (1.6)	533 (1.5)
Third trimester vaginal bleeding	24 (0.3)	12 (0.2)	17 (0.2)	19 (0.3)	26 (0.3)	98 (0.3)
Severe hemorrhage after delivery	11 (0.2)	10 (0.2)	28 (0.4)	13 (0.2)	12 (0.2)	74 (0.2)
Fetal anomalies	32 (0.5)	29 (0.5)	50 (0.7)	44 (0.7)	55 (0.7)	210 (0.6)
Twin pregnancy	28 (0.4)	44 (0.7)	39 (0.5)	41 (0.6)	48 (0.6)	200 (0.6)
Instrumental delivery	7 (0.1)	13 (0.2)	6 (0.1)	8 (0.1)	4 (0.05)	38 (0.1)
Stillbirth	35 (0.5)	59 (0.9)	59 (0.8)	65 (1.0)	57 (0.7)	275 (0.8)
Family medical history						
Type 2 diabetes	502 (7.0)	655 (9.8)	816 (10.9)	784 (12.2)	732 (9.5)	3489 (9.8)
Hypertension	640 (9.0)	977 (14.7)	989 (13.2)	969 (15.1)	942 (12.2)	4517 (12.7)
Protocol characteristic						
Protocol adherence	6622 (96.1)	6131 (98.1)	6936 (95.4)	5387 (85.4)	7124 (93.2)	32 200 (90.9

Prevalence of GDM in different protocols

Protocols	Prevalence of GDM	Early detection
A	21.9%	13.3%,
B	10.5%	5.7%
C	12.1%	2.1%
D	19.4%,	13.3%
E	8.1%	3.2%



Primary Outcomes: Macrosomia and primary Cesarean Section

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MAY 8, 2008 VOL. 358 NO. 19

Hyperglycemia and Adverse Pregnancy Outcomes

The HAPO Study Cooperative Research Group*

ITT analyses showed that the upper boundary of the 95% CI for both primary CS and macrosomia were lower than the noninferiority margin of 1.7, satisfying the noninferiority of less strict protocols B, C, D, and E compared with protocol A. However, noninferiority was not shown in comparing primary CS in protocol E vs A.

Protocol B vs A

- macrosomia, 6% vs 5.9%, OR = 1.01, 95% CI, 0.95- 1.08
- primary CS, 14.1% vs 15.4%, OR = 0.85, 95% CI, 0.56-1.28,

protocol C vs A

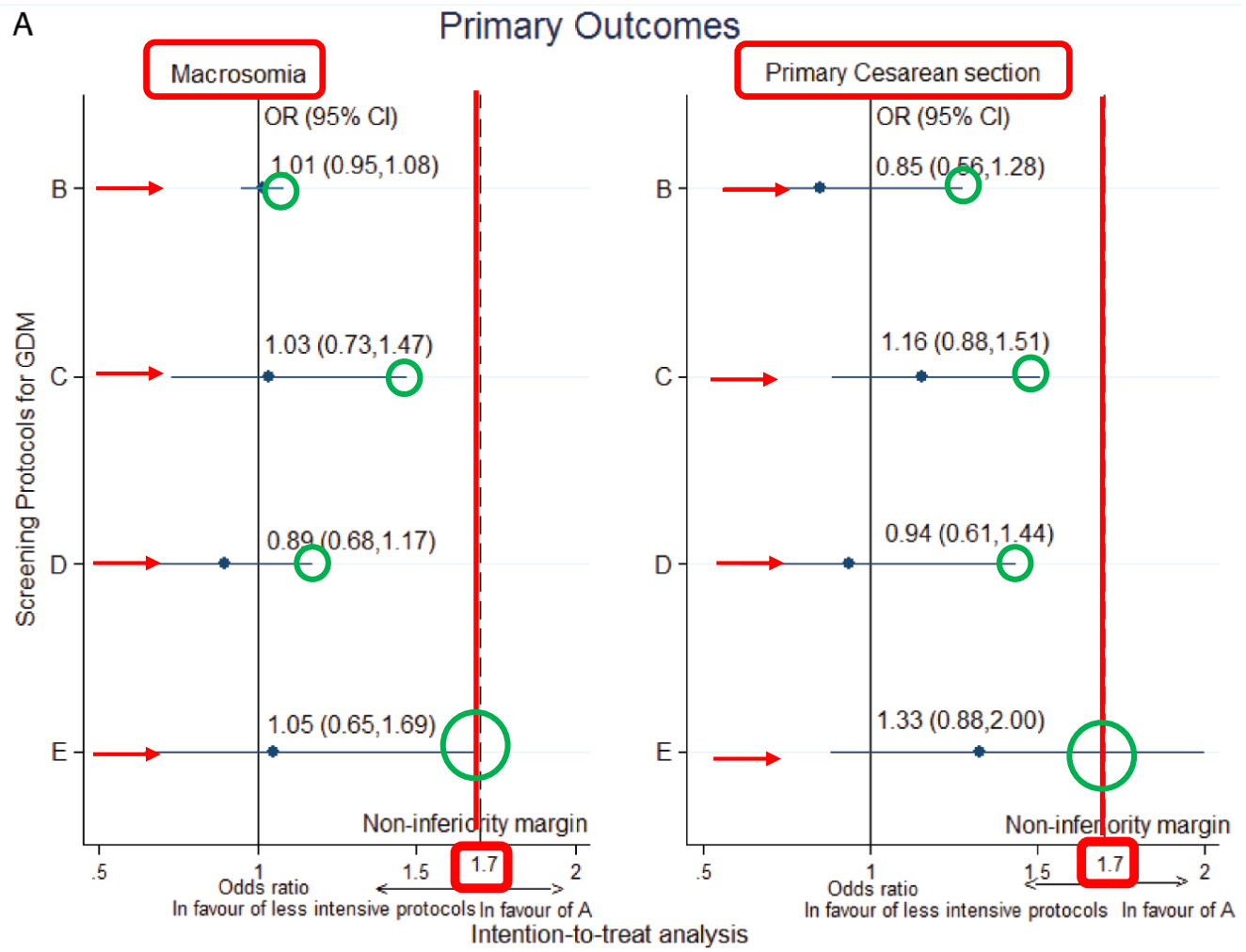
- macrosomia, 6.1% vs 5.9%, OR = 1.03, 95% CI, 0.73-1.47
- primary CS, 16.8% vs 15.4%, OR = 1.16, 95% CI, 0.88-1.51,

protocol D vs A

- (macrosomia, 5.3% vs 5.9%, OR = 0.89, 95% CI, 0.68-1.17
- primary CS, 14.5% vs 15.4%, OR = 0.94, 95% CI,0.61-1.44,

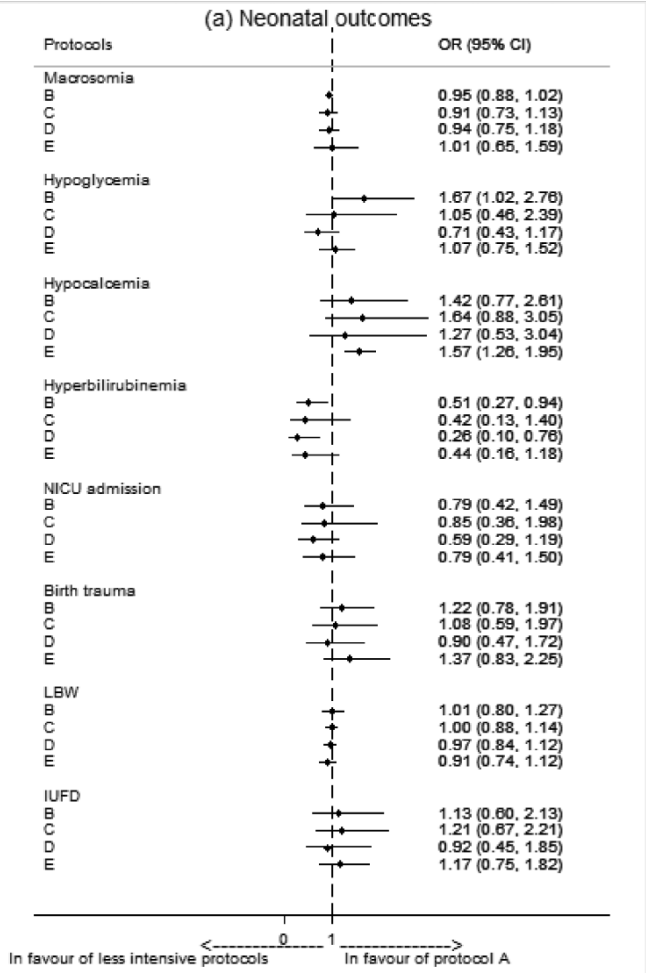
protocol E vs A

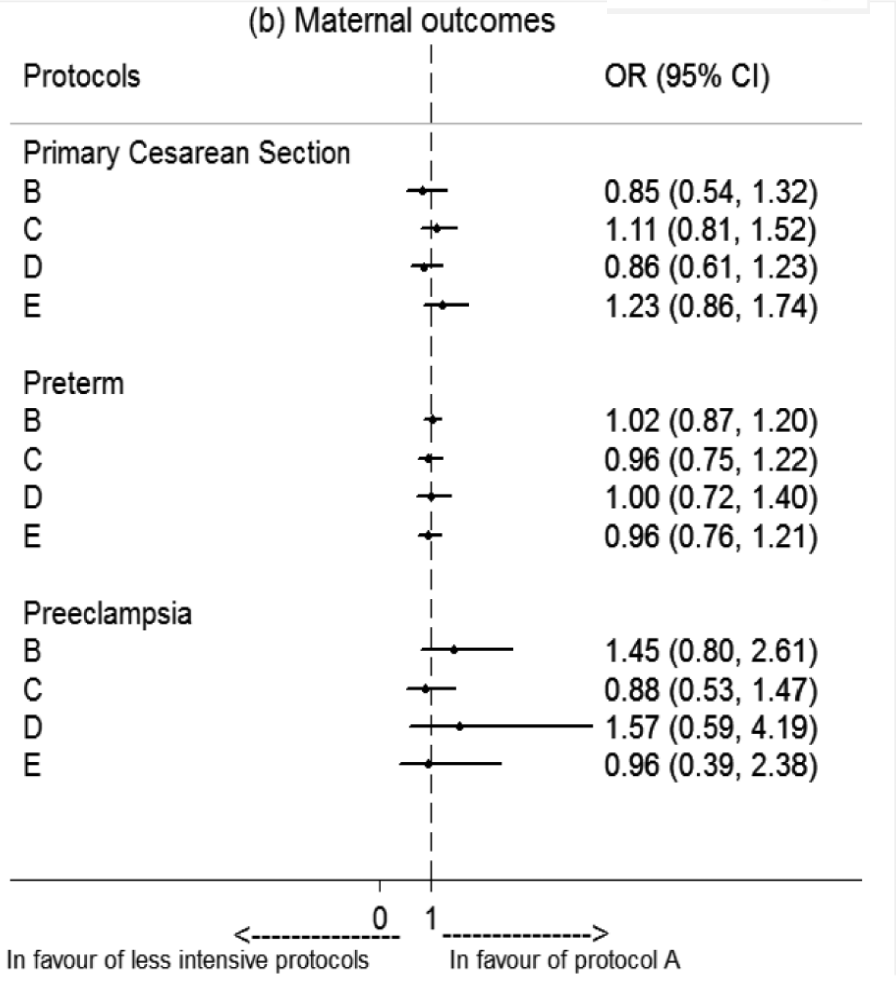
- macrosomia 6.2% vs 5.9%, OR = 1.05, 95% CI, 0.65-1.69),
- primary CS, 17.1% vs 15.4%, OR = 1.33, 95% CI, 0.88- 2.00.



Secondary outcomes

The results of logistic regression analyses showed that the adjusted OR of adverse pregnancy outcomes of preeclampsia, preterm birth, LBW, birth trauma, neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia, NICU admission, and still birth in the less strict criteria of B, C, D, and E were not statistically significant different compared with protocol A, considering multiplicity adjustment





Adjusted OR and 95% CI for maternal outcomes comparing each protocol (B,C,D,E) with protocol A (intention-to-treat analysis).
ORs are adjusted for gestational age, treatment modality, type of delivery, maternal body mass index, and gestational weight gain for all outcomes

Conclusions

- The IADPSG GDM definition significantly increased the prevalence of GDM diagnosis. However, the less strict approaches were not inferior to other criteria in terms of adverse maternal and neonatal outcomes.

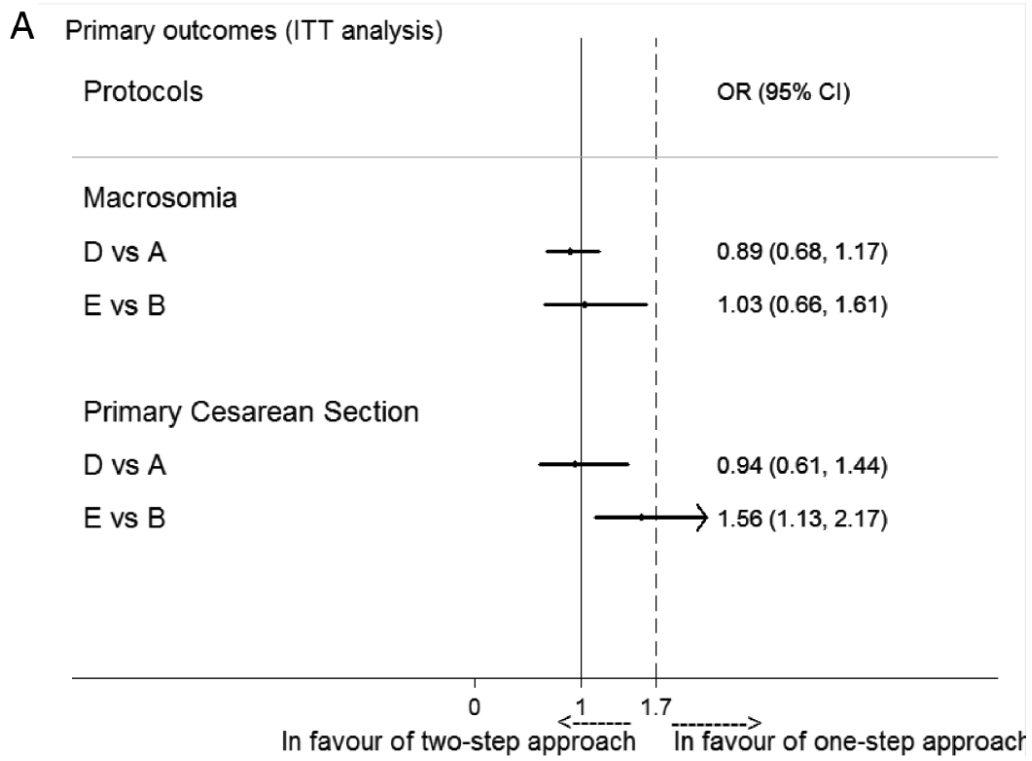
2-step test vs 1-step test method of screening

Primary Outcomes

Intention to treat analysis showed that the upper boundary of the 95% CI for the OR of both macrosomia and primary CS were below the margin 1.7, satisfying the noninferiority of the 2-step compared to the 1-step screening approach. However, primary CS comparing protocol E vs B noninferiority is not shown.

The respective results were as follows:

- macrosomia
  - D vs A: OR= 0.89, 95% CI, 0.68-1.17
  - E vs B: OR= 1.03, 95% CI, 0.66-1.61
- primary CS
  - D vs AOR = 0.94, 95% CI, 0.61-1.44 OR = 1.56,
  - E vs B: 95% CI, 1.13-2.17

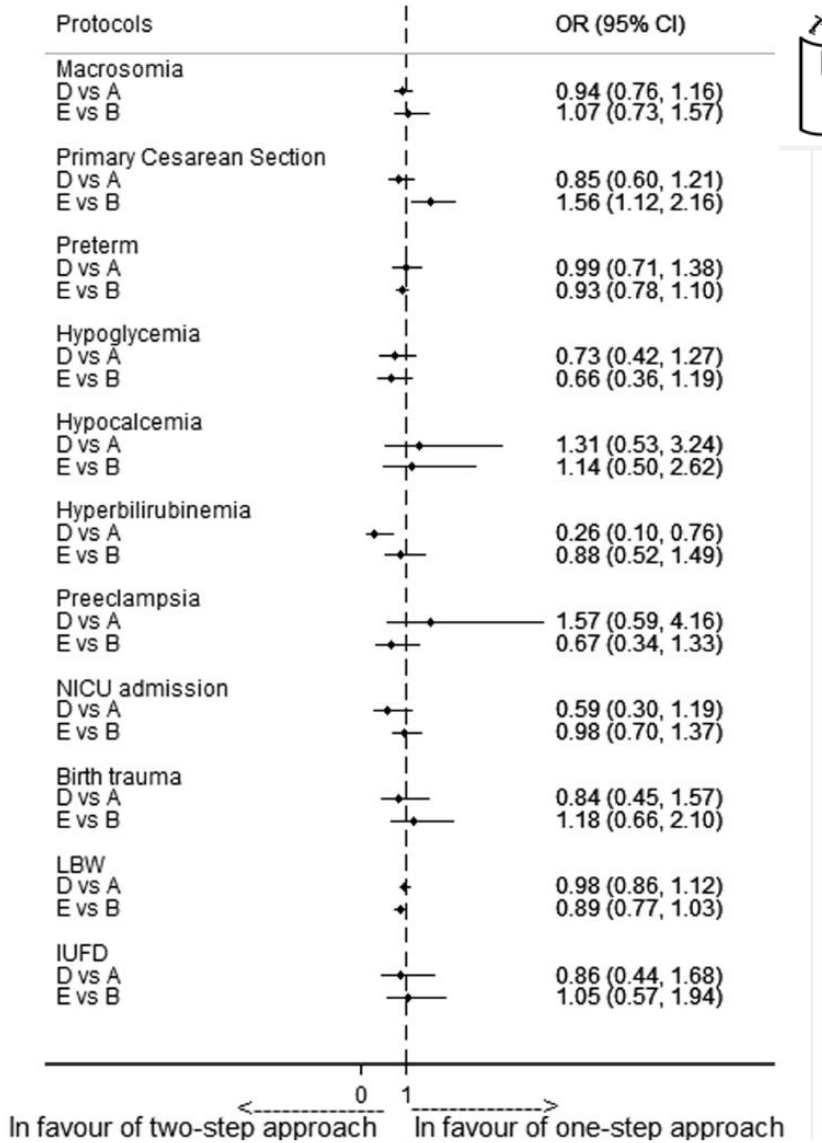


OR and 95% CI for primary and secondary outcomes comparing 2-step test vs 1-step test (D vs A and E vs B).

2-step test vs 1-step test method of screening

Secondary Outcomes

There were no statistically significant differences in the adjusted odds of adverse pregnancy outcomes in the 2-step compared with the 1-step screening approaches, considering multiplicity adjustment.



Adjusted OR and 95% CI for primary and secondary outcomes comparing 2-step test vs 1-step test (D vs A and E vs B). ORs are adjusted for gestational age, treatment modality, type of delivery, maternal body mass index, and gestational weight gain for all outcomes. There were no statistically significant differences considering multiplicity adjustment.

Does fasting plasma glucose values 5.1-5.6 mmol/l (92–100 mg) in the first trimester of gestation a matter?

Randomized Controlled Trial > Front Endocrinol (Lausanne). 2023 Jun 2:14:1155007.

doi: 10.3389/fendo.2023.1155007. eCollection 2023.

Does fasting plasma glucose values 5.1–5.6 mmol/l in the first trimester of gestation a matter?

Fahimeh Ramezani Tehrani [1], Farshad Farzadfar [2], Farhad Hosseinpanah [3], Maryam Rahmati [1], Faegheh Firouzi [1], Mehrandokht Abedini [4], Farzad Hadaegh [5], Majid Valizadeh [3], Farahnaz Torkestani [6], Davood Khalili [5], Masoud Solaymani-Dodaran [7], Razieh Bidhendi-Yarandi [8], Marzieh Bakhshandeh [9], Afshin Ostovar [10], Marzieh Rostami Dovom [1], Mina Amiri [1], Fereidoun Azizi [11], Samira Behboudi-Gandevani [12]

Affiliations + expand

PMID: 37334302 PMCID: PMC10273274 DOI: 10.3389/fendo.2023.1155007

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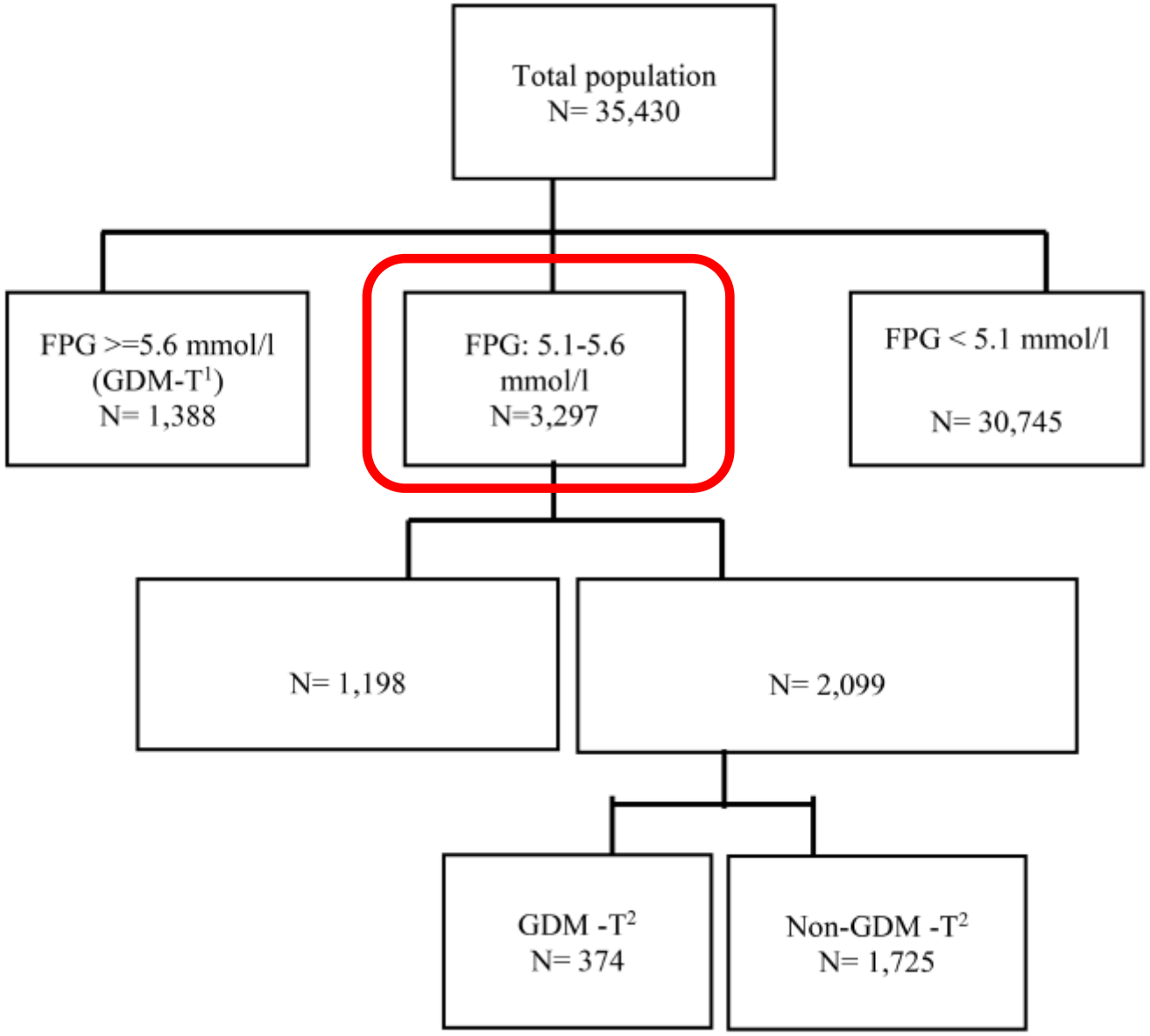
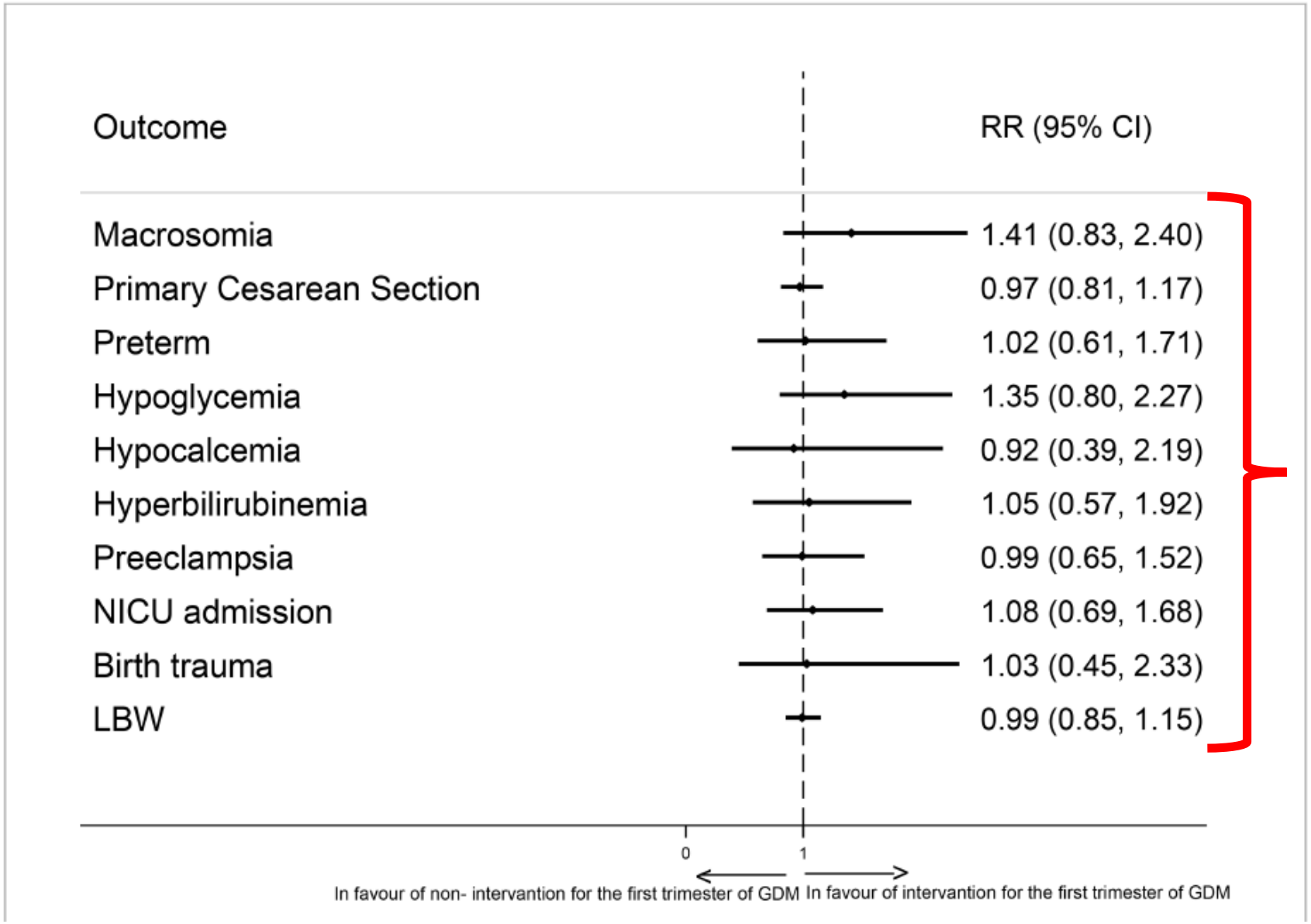
Does fasting plasma glucose values 5.1-5.6 mmol/l in the first trimester of gestation a matter?

- The aim of this secondary study was to investigate the effect of treatment on pregnancy outcomes among women who had fasting plasma glucose (FPG) 5.1- 5.6 mmol/l in the first trimester of pregnancy.

- Methods: We performed a secondary-analysis of a randomized community noninferiority trial of gestational diabetes mellitus (GDM) screening. All pregnant women with FPG values range 5.1-5.6 mmol/l in the first trimester of gestation were included in the present study (n=3297) and classified to either the

  - (i) intervention group who received treatment for GDM along with usual prenatal care (n=1,198),
  - (ii) control group who received usual-prenatal-care (n=2,099).


Total population
N= 35,430
FPG >=5.6 mmol/l
(GDM-T1)
N= 1,388
FPG: 5.1-5.6
mmol/l
N=3,297
FPG < 5.1 mmol/l
N= 30,745
N= 1,198
N= 2,099
GDM -T2
N= 374
Non-GDM -T2
N= 1,725



Adjusted risk ratio plot for pregnancy outcomes comparing intervention group and controls.

Conclusion

It is found that treating women with first-trimester FPG values of 5.1-5.6 mmol/l could not improve adverse pregnancy outcomes including:

macrosomia,
Primary C-S,
Preterm birth,
hypoglycemia,
hypocalcemia,
preeclampsia,
NICU admission,
Birth trauma and
LBW.

Therefore, extrapolating the FPG cut-off point of the second trimester to the first –which has been proposed by the IADPSG, might therefore not be appropriate.

NORD universitet

BMJ Open Diabetes Research & Care

Various screening and diagnosis approaches for gestational diabetes mellitus and adverse pregnancy outcomes: a secondary analysis of a randomized non-inferiority field trial

- **Aim of study:** We evaluate which screening and diagnostic approach resulted in the greatest reduction in adverse pregnancy outcomes due to increased treatment

- **Conclusion:** We conclude that screening approaches for GDM reduced the risk of adverse pregnancy outcomes to the same or near the same risk level of healthy pregnant women, except for the risk of NICU admission that increased significantly in groups diagnosed with GDM compared with healthy pregnant women. Individuals with slight increase in FPG (92–100 mg/dL) at first trimester, who were diagnosed as GDM, had an even increased risk of macrosomia in comparison to those group of women with FPG 92–100 mg/ dL in the first trimester, who were not diagnosed with GDM, and developed GDM in second trimester

Take homee message and Future Considerations

- Gestational diabetes and controversies are old friends!
- The conflicting recommendations from expert groups underscore the fact that there are data to support each strategy.
- The IADPSG criteria (“one-step strategy”) have been adopted internationally as the preferred approach. Data comparing population-wide outcomes with onestep versus two-step approaches have been inconsistent to date
- In addition, pregnancies complicated by GDM per the IADPSG criteria, but not recognized as such, have outcomes comparable to pregnancies with diagnosed GDM by the more stringent two-step criteria
- There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policymakers. Longer-term outcome studies are currently underway.

Thank you for your attention

Samira.behboudi@nord.no