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

Fahimeh Ramezani Tehrani,[1] Ali Sheidaei,[2] Maryam Rahmati,[1] Farshad Farzadfar,[3] Mahsa Noroozzadeh,[1] Farhad Hosseinpanah,[4] Mehrandokht Abedini,[5] Farzad Hadaegh,[6] Majid Valizadeh,[4] Farahnaz Torkestani,[7] Davood Khalili,[6] Faegheh Firouzi,[8] Masoud Solaymani-Dodaran,[9] Afshin Ostovar,[10] Fereidoun Azizi,[11] Samira Behboudi-Gandevani [12]

To cite: Ramezani Tehrani F, Sheidaei A, Rahmati M, *et al*. Various screening and diagnosis approaches for gestational diabetes mellitus and adverse pregnancy outcomes: a secondary analysis of a randomized non-inferiority field trial. *BMJ Open Diab Res Care* 2023;**11**:e003510. doi:10.1136/bmjdrc-2023-003510

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2023-003510).

Received 9 May 2023
Accepted 9 September 2023

For numbered affiliations see end of article.

Correspondence to
Dr Samira Behboudi-Gandevani; samira.behboudi-gandevani@nord.no

ABSTRACT

Introduction We evaluate which screening and diagnostic approach resulted in the greatest reduction in adverse pregnancy outcomes due to increased treatment.

Research design and methods This study presents a secondary analysis of a randomized community non-inferiority trial conducted among pregnant women participating in the GULF Study in Iran. A total of 35 430 pregnant women were randomly assigned to one of the five prespecified gestational diabetes mellitus (GDM) screening protocols. The screening methods included fasting plasma glucose (FPG) in the first trimester and either a one-step or a two-step screening method in the second trimester of pregnancy. According to the results, participants were classified into 6 groups (1) First-trimester FPG: 100–126 mg/dL, GDM diagnosed at first trimester; (2) First trimester FPG: 92–99.9 mg/dL, GDM diagnosed at first trimester; (3) First trimester FPG: 92–99.9 mg/dL, GDM diagnosed at second trimester; (4) First trimester FPG: 92–99.9 mg/dL, healthy at second trimester; (5) First trimester FPG<92 mg/dL, GDM diagnosed at second trimester; (6) First trimester FPG<92 mg/dL, healthy at second trimester. For our analysis, we initially used group 6, as the reference and repeated the analysis using group 2, as the reference group. The main outcome of the study was major adverse maternal and neonatal outcomes.

Results Macrosomia and primary caesarean section occurred in 9.8% and 21.0% in group 1, 7.8% and 19.8% in group 2, 5.4% and 18.6% in group 3, 6.6% and 21.5% in group 4, 8.3% and 24.0% in group 5, and 5.4% and 20.0% in group 6, respectively. Compared with group 6 as the reference, there was a significant increase in the adjusted risk of neonatal intensive care unit (NICU) admission in groups 1, 3, and 5 and an increased risk of macrosomia in groups 1, 2, and 5. Compared with group 2 as the reference, there was a significant decrease in the adjusted risk of macrosomia in group 3, a decreased risk of NICU admission in group 6, and an increased risk of hyperglycemia in group 3.

Conclusions 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

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is considerable worldwide controversy regarding optimal screening and diagnostic approaches for gestational diabetes mellitus (GDM).

WHAT THIS STUDY ADDS

⇒ This population-based study included 35 430 pregnant women and found that screening and diagnostic 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 neonatal intensive care unit admission that increased significantly in groups diagnosed with GDM compared with healthy pregnant women.

⇒ Further, individuals with slight increase in fasting plasma glucose (FPG) (92–100 mg/dL) at first trimester, who were diagnosed with 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 the second trimester.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study suggest a need for specific guidelines for the management of those with an early elevation of FPG, after achieving the glycemic goal.

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

Trial registration IRCT138707081281N1 (registered: February 15, 2017).

INTRODUCTION

Screening is a fundamental concept that links clinical practice in individuals, with public health practice in populations. The goal is to achieve early detection of asymptomatic individuals or subpopulations within a community to assess the likelihood of having a particular disease.[1]

Gestational diabetes mellitus (GDM) is the most prevalent chronic disorder during pregnancy, affecting approximately one in every six pregnancies worldwide.[2 3] It increases the substantial risk of short-term and long-term adverse maternal and neonatal outcomes such as macrosomia, caesarean section, preterm delivery, low Apgar Score, and also cardiovascular disease or type 2 diabetes later in life.[4–8]

It is well acknowledged that the screening and treatment of GDM could improve adverse pregnancy outcomes.[4] But due to the lack of high quality evidence, the optimal strategy, method, and criteria for identification of GDM has been a matter of debate for decades. Traditionally, the screening and diagnosis of GDM have been based on the second trimester oral glucose tolerance test (OGTT).[9] Recently, with limited trial data and by extrapolating the criteria of GDM from the second trimester to the first, it has been suggested that women with possible undiagnosed diabetes are screened, diagnosed, and treated in early pregnancy.[10] Today, although there are still large controversies,[10–14] there has been a move towards the worldwide adoption of the International Association of Diabetes in Pregnancy Study Groups (IADPSG) recommendations using fasting plasma glucose (FPG) values of 5.1–6.9 mmol/L before 24 weeks of gestation and one-step 2-hour 75 g OGTT in the second trimester of pregnancy.[10] Meanwhile, emerging data had challenged this recommendation since many of those women diagnosed in the first trimester no longer fulfilled GDM when screened later in the second trimester of pregnancy[14–17] and also there are conflicting results regarding the magnitude of the increased risks among those diagnosed with this criteria in the second trimester, compared with other criteria.[18–22] Moreover, the randomized controlled trials comparing the effect of various GDM screening approaches are insufficient and have shown differing results. Therefore, to address this knowledge gap, we conducted this secondary analysis of the randomized community trial (GULF Study) to determine which screening and diagnostic approach resulted in the greatest reduction in adverse pregnancy outcomes due to increased treatment.

RESEARCH DESIGN AND METHODS

This is a secondary analysis of a randomized community non-inferiority trial among pregnant women in the GULF Study. Detailed methods and results of the main trial have been reported previously.[23 24] Briefly, this study was conducted to determine non-inferiority of less strict GDM screening criteria compared with the stringent IADPSG criteria with respect to maternal and neonatal outcomes, in which 35 430 pregnant women in the first trimester of pregnancy, aged 18 years and over from five different geographic regions of Iran participated.

We employed one-to-one randomization at the city level to assign each city randomly to a protocol. For randomization, all of the provinces of Iran were initially divided into five categories based on their geographic location: north, east, west, south, and center of Iran. One province was randomly selected from each category. The cities within each province were then listed and divided into two clusters of the central city of the province and the other cities. In the next step, four cities were randomly chosen from the list of other cities in each province. For the allocation of protocols, five different protocols were randomly assigned to each provincial center, while the remaining cities in each province were allocated to the other protocols. The sample size for each city was determined based on the number of live births in the cities over the previous 5 years, using a probability proportional to size approach. (To obtain a statistical power of 85% with a one-sided type 1 error of 0.005 (considering multiple comparisons) approximately 4700 patients per group are needed to show the non-inferiority of more intensive compared with lower intensive strategies with a marginal difference of 0.03). Regarding the allocation of protocols, one of the five predetermined protocols was randomly assigned to each provincial center. The four selected cities in each province were then randomly assigned to the remaining protocols. We employed one-to-one randomization at the city level to assign each city randomly to a protocol. The initial sample size for each protocol was the same. However, due to various factors related to conducting the study, the final sample size of each protocol varied slightly (all cities began and ended the study simultaneously, ensuring that the number of participants in each city was not exactly equal to the estimated number). The exact number of sample sizes for protocols A to E were 7117 (20.09%), 6659 (18.79%), 7494 (21.15%), 6412 (18.10%), and 7748 (21.87%), respectively. The details of all study protocols have been published before,[23] In protocol A, GDM was characterized as an FPG level between 92 mg/dL and 125 mg/dL in the first trimester, and any abnormal result using the one-step screening approach in the second trimester involving a 2-hour 75 g OGTT with cut-off values of 92 mg/dL for fasting, 180 mg/dL for 1-hour, or 153 mg/dL for

2-hour measurements. Protocol B differed from protocol A in the definition of GDM in the first trimester, where it encompassed FPG values between 100 mg/dL and 125 mg/dL. In the second trimester, GDM was identified as occurring when two or more plasma glucose levels met or exceeded the specified criteria. Moving to protocol C, the first trimester definition for GDM was the same as protocol B, encompassing FPG levels between 100 mg/dL and 126 mg/dL. However, the second trimester definition aligned with protocol A, involving any abnormal value as determined by the one-step screening method using a 2-hour, 75 gram OGTT.

Protocol D was charachterized as GDM in the first trimester as FPG values ranging from 92 mg/dL to 125 mg/dL. Yet, for the second trimester, a two-step screening strategy was employed, applying the Carpenter-Coustan criteria as cut-off values. Lastly, protocol E displayed discrepancies from protocol D in relation to the first trimester definition of GDM and encompassed FPG levels between 100 mg/dL and 125 mg/dL. Lastly, protocol E displayed discrepancies from protocol D in relation to the first trimester definition of GDM. In this case, it encompassed FPG levels between 100 mg/dL and 125 mg/dL.[23 24]

Those with uncertainty regarding the date of the last menstrual period and without ultrasound estimation from 6 weeks to 14 weeks of gestational age and women with a diagnosis of type 2 diabetes or other chronic disorders were excluded from original study. Along with routine prenatal care,[25] all participants were scheduled to have two phases of GDM screening in the first and second trimesters of pregnancy, based on a prespecified protocol using FPG in the first trimester and either a one-step or a two-step screening method in the second trimester of pregnancy.

For the current analysis, a total of 35 430 pregnant women were involved. Based on the GDM status in the first and second trimesters of pregnancy, participants were classified based on the assigned protocol, FPG level in the first trimester and the trimester of GDM diagnosis as follows (table 1): (1) Those who had first trimester FPG levels 100–125 mg/dL, diagnosed as GDM, according to the all prespecified protocols; (2) Those who had first trimester FPG levels 92–99.9 mg/dL, diagnosed as GDM according to the protocols A and D; (3) Those who had first trimester FPG levels 92–99.9 mg/dL, and received routine prenatal care at the first trimester, according to the protocols B, C, and E, and re-screened for GDM based on either a one-step (protocols B and C) or a two-step screening method (protocol E), and diagnosed as GDM according to the prespecified protocols; (4) Those who had first trimester FPG levels 92–99.9 mg/dL, received routine prenatal care according to the protocols B, C, and E at the first trimester, and re-screened for GDM based on either a one-step (protocol B and C) or a two-step screening method (protocol E) and had negative results; (5) Those who had first trimester FPG levels <92 mg/dL, received routine prenatal care, according to the all prespecified protocols, at the first trimester, and re-screened for GDM based on either a one-step (protocol B and C) or a two-step screening method (protocol E) and had positive results for GDM; (6) Those who had first trimester FPG levels <92 mg/dL, received routine prenatal care, according to the all prespecified protocols, at the first trimester, re-screened for GDM based on either a one-step or a two-step screening method, and had negative results.

All study participants were followed until delivery, and all adverse maternal and neonatal outcomes were recorded in details. Guideline for the treatment of GDM was consistent with the American College of Obstetricians and Gynecologists 2013[26] and the American Diabetes Association (ADA) 2016[27] recommendations, including physical exercise, dietary intervention, and medication therapy (if necessary) as follows:

Treatment was initiated by implementing lifestyle modification, which included medical nutrition therapy and physical activity. Blood glucose monitoring was employed to achieve the specific targets, which included a fasting level of 95 mg/dL, a 1-hour postprandial level

Table 1 Definition of the study groups based on assigned protocol, FPG level in the first trimester, and the trimester of GDM diagnosis

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
*Assigned protocol	A–E	A & D	B & C & E	B & C & E	A–E	A–E
FPG level at first trimester (mg/dL)	100–125	92–99.9	92–99.9	92–99.9	< 92	< 92
GDM diagnosis in the first trimester	Positive	Positive	Negative	Negative	Negative	Negative
GDM diagnosis in the second trimester/first trimester	Positive	Positive	Positive	Negative	Positive	Negative

*In **Protocol A**, GDM was defined as an FPG between 92 mg/dL and 125 mg/dL in the first trimester, and any abnormal value using the one-step screening method in the second trimester with a 2-hour 75 g oral glucose tolerance test (OGTT) and cut-off values of fasting 92 mg/dL, 1 hour 180 mg/dL, or 2 hours 153 mg/dL. **Protocol B** differed from Protocol A in the definition of GDM in the first trimester, which was FPG between 100 mg/dL and 125 mg/dL, and in the second trimester, which was defined as two or more plasma glucose levels meeting or exceeding the criteria. **Protocol C** used the same definition for GDM in the first trimester as protocol B (FPG between 100 mg/dL and 126 mg/dL), and the same definition in the second trimester as protocol A (any abnormal value using the one-step screening method with a 2- hour, 75 g glucose tolerance test). **Protocol D** was defined GDM in the first trimester as FPG values between 92 mg/dL and 125 mg/dL. However, in the second trimester, a two-step screening method was used, using the cut-off values of Carpenter-Coustan criteria. **Protocol E** differed from protocol D in the definition of GDM in the first trimester, which was FPG between 100 mg/dL and 125 mg.
FPG, fasting plasma glucose; GDM, gestational diabetes mellitus.

of 140 mg/dL, or a 2-hour postprandial level of 120 mg/dL. The dietitian individually designed the medical nutrition therapy plan for participants with GDM. This plan ensured an adequate calorie intake to support the health of the fetus/neonate and the mother, achieve glycemic goals, and promote appropriate gestational weight gain. The plan was based on the Dietary Reference Intakes recommendation, which included a minimum carbohydrate intake of 175 g, a minimum protein intake of 71 g, and a fiber intake of 28 g. If participants were unable to achieve the desired glycemic goals within a 2-week period, specialized physicians such as obstetricians, internists, or endocrinologists at the second level of the healthcare system offered pharmacologic therapy. Insulin was the recommended first-line treatment for GDM. Furthermore, if participants declined insulin therapy, metformin was presented as an alternative or adjunct to insulin after thoroughly discussing the potential benefits and risks of metformin therapy. Self-monitoring of blood glucose (SMBG) was used for all individuals diagnosed with GDM to attain and maintain therapeutic goals in patients receiving insulin treatment. SMBG involved frequent capillary blood glucose tests scheduled four times a day: fasting, 2 hours after breakfast, lunch, and dinner, or if patients experienced symptoms of hypoglycemia for at least 2 weeks. Once the therapeutic target was achieved, SMBG was performed twice a day. The treatment guideline for GDM was consistent across all five protocols.

Terms definitions and endpoint outcomes

One-step screening was based on a 75 g 2-hour OGTT. Participants were diagnosed with GDM if at least one value exceeded the cut-off, including FPG≥92 mg/dL, but <126 mg/dL and/or 2-hour OGTT≥153 mg/dL. The two-step approach was as follows: first, a 50 g oral glucose challenge test was performed regardless of the fasting status. One-hour plasma glucose level <140 mg/dL was considered negative and needed no further test. Otherwise, women underwent 100 g 3-hour OGTT. GDM was diagnosed if two glucose values were above the threshold including: FPG>95 mg/dL; 1 hour glucose level>180 mg/dL; 2-hour glucose level>155 mg/dL; and 3-hour glucose level≥140 mg/dL.

Outcomes of the study were defined as follows:[23 24] Macrosomia was characterized as birth weight exceeding 4000 g and/or fetal weight more than the 90th percentile corresponding to a specific gestational age,[28] using ultrasound biometry for estimating the fetal weight and multinational WHO fetal growth chart for defining the percentile. Primary cesarean section was outlined as cesarean deliveries within the context of all births involving women without a prior history of cesarean delivery. Hypoglycemia was defined as plasma glucose concentration below 2.6 mmol/L during the first 48 hours following delivery; hyperbilirubinemia was identified by a value more than the 95th percentile for a given point after birth; pre-eclampsia was determined as an increase in blood pressure to 140 mm Hg systolic or 90 mm Hg diastolic on at least two occasions, with a time interval of at least 4 hours, after 20 weeks of gestation in women who had previously normal blood pressure and proteinuria equal to or exceeding 300 mg per 24 hours urine collection, or protein/creatinine ratio of 0.3 or higher, or a dipstick reading of 1+ (with further considerations in the absence of other quantitative methods). In cases without proteinuria, new-onset hypertension combined with the new onset of any of the thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and cerebral or visual symptoms were also considered;[29] preterm birth was determined as when birth occurs between 20 weeks and 37 weeks of gestation; birth trauma was defined as brachial plexus palsy or clavicular, humeral, or skull fracture. Low birth weight (LBW) was described as weight at birth less than 2500 g at birth, irrespective of the gestational age.

Statistical analysis

We used frequency (proportion) and mean (SD) for the categorical and continuous variables in the data description. The frequencies of categorical variables were compared using the χ^2 test across the groups. For this purpose, one-way analysis of variance was used in the case of continuous variables.

We divided the samples into six fully separated groups according to their FPG levels in the first trimester, assigned protocol, and GDM diagnosis status. As there is no overlap between these groups, we can compare the risk of developing adverse pregnancy outcomes. For the purpose of the current analysis first we considered group 6 (healthy pregnant women all throughout the pregnancy period) as the reference group, then we repeated our analysis considering the second group (participants with 92 mg/dL<FPG<100 mg/dL in the first trimester who were diagnosed with GDM according to the protocols A or D). The log probability model (generalized linear model with binary outcomes and a log link function) was used to estimate the risk ratio (RR) of developing adverse pregnancy outcomes in other groups to these reference groups. In addition to the crude model, we adjusted the models for age, gestational ages at enrollment and at delivery (except when preterm birth was the outcome), prepregnancy body mass index (BMI), type of delivery (except when the outcome was caesarean section), assigned protocol, type of medication (lifestyle modification, lifestyle modification+oral agent, lifestyle modification+insulin, lifestyle modification+oral agent+insulin).

All the statistical analysis and graph generation were conducted in R statistical software. We set the significant level at 95% for tests and presentation of CIs.

RESULTS

The participants' baseline characteristics, pregnancy history, and incidence of adverse pregnancy outcomes according to the specified groups are presented in table 2. The mean BMIs (SDs) of pregnant women were

Table 2 The participants' baseline characteristics, pregnancy history, and incidence of adverse pregnancy outcomes by the defined groups

Variable*	Group 1 n=**1388**	Group 2 n=**1198**	**Group 3 n=374**	Group 4 n=**1725**	Group 5 n=**2070**	Group 6 n=**28675**
Age, years, mean (SD)	32 (6)	31 (6)	31 (6)	31 (6)	32 (6)	30 (6)
BMI, kg/m^2, mean (SD)	27.8 (5.4)	26.9 (4.9)	27.7 (5)	26.5 (4.7)	27 (4.8)	25.5 (4.7)
Overweight/obese	680 (71)	594 (63)	255 (68)	1046 (61)	1295 (67)	13154 (49)
Gestational age at enrollment, mean (SD)	7.7 (3.5)	8.2 (3.3)	9.2 (3.3)	9.0 (3.3)	9.3 (3.6)	9.2 (3.8)
Gestational age at delivery, mean (SD)	36.9 (6.9)	37.3 (6.1)	37.0 (7.1)	36.6 (8.1)	37.6 (5.7)	37.3 (6.5)
Gravity, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
Parity, median (IQR)	1 (0–2)	1 (0–2)	1 (1-2)	1 (1-2)	1 (0–2)	1 (0–2)
Parity upper1	667 (73)	631 (72)	250 (77)	1082 (76)	1297 (73)	15289 (69)
Abortion, median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)
History GH or pre-eclampsia	31 (2.2)	21 (1.8)	9 (2.4)	21 (1.2)	40 (1.9)	380 (1.3)
History of macrosomia	16 (1.6)	17 (1.8)	15 (4.0)	31 (1.8)	35 (1.8)	291 (1.2)
History of preterm birth	19 (2.0)	24 (2.5)	13 (3.5)	31 (1.8)	56 (2.9)	461 (1.8)
History of LBW	25 (2.6)	25 (2.6)	11 (3.0)	49 (2.9)	60 (3.1)	716 (2.8)
History of GDM	54 (5.6)	33 (3.5)	22 (5.9)	44 (2.6)	91 (4.7)	289 (1.1)
Severe hemorrhage after delivery	3 (0.3)	3 (0.3)	0	3 (0.2)	9 (0.5)	56 (0.2)
Fetal anomalies	7 (0.7)	5 (0.5)	4 (1.1)	17 (1.0)	7 (0.4)	170 (0.7)
Twin pregnancy	3 (0.3)	9 (0.9)	5 (1.3)	12 (0.7)	13 (0.7)	158 (0.6)
History of stillbirth	9 (0.9)	9 (1.0)	8 (2.2)	19 (1.1)	23 (1.2)	207 (0.8)
Instrumental delivery	2 (0.2)	2 (0.2)	2 (0.5)	2 (0.1)	1 (<0.1)	29 (0.1)
Family history of DM	174 (18)	119 (12)	79 (21)	198 (12)	282 (14)	2637 (10)
Family history of hypertension	160 (16)	135 (14)	64 (1)	292 (17)	312 (16)	3554 (14)
Macrosomia	128 (9.8)	89 (7.8)	19 (5.4)	105 (6.6)	166 (8.3)	1480 (5.4)
Type of delivery						
Primary caesarean section	201 (15)	175 (15)	46 (13)	248 (16)	347 (17)	4246 (16)
Repeated caesarean section	349 (27)	257 (23)	107 (30)	443 (28)	549 (28)	5946 (22)
Vaginal delivery	757 (58)	710 (62)	201 (57)	905 (57)	1099 (55)	17013 (63)
Preterm birth	113 (8.7)	79 (6.9)	27 (7.6)	104 (6.5)	140 (7.0)	1666 (6.1)
Neonatal hypoglycemia	54 (4.1)	30 (2.6)	24 (6.8)	5 (0.3)	129 (6.5)	42 (0.2)
Neonatal hypocalcemia	44 (3.2)	19 (1.6)	17 (4.5)	5 (0.3)	63 (3.0)	44 (0.2)
Neonatal hyperbilirubinemia	92 (7.2)	96 (8.5)	29 (8.2)	101 (6.5)	167 (8.5)	1914 (7.1)
Pre-eclampsia	186 (13)	124 (10)	44 (12)	174 (10)	244 (12)	2817 (9.9)
NICU admission	106 (7.6)	82 (6.8)	29 (7.8)	83 (4.8)	155 (7.5)	1260 (4.4)
Birth trauma	10 (0.7)	9 (0.8)	5 (1.3)	9 (0.5)	11 (0.5)	153 (0.5)
LBW	116 (9.1)	94 (8.4)	34 (9.6)	128 (8.2)	163 (8.3)	2472 (9.2)
IUFD	7 (0.5)	17 (1.4)	2 (0.5)	14 (0.8)	13 (0.6)	189 (0.7)
Treatment						
Medication	346 (25)	155 (13)	207 (55)	0 (0)	698 (34%)	0 (0)
Diet	1022 (74)	1025 (86)	167 (45)	0 (0)	1372 (66%)	0 (0)
c-DAO	220 (15.9)	153 (12.8)	54 (14.4)	208 (12.06)	277 (13.4)	3767 (13.1)
c-MAO	296 (21.3)	200 (16.7)	69 (18.5)	262 (15.2)	388 (18.7)	4603 (16.1)
c-NAO	374 (26.9)	304 (25.4)	91 (24.3)	340 (19.7)	570 (27.5)	6037 (21.1)

c-DAO: composite delivery adverse outcome which was defined as primary cesarean section and/or shoulder dystocia and/or instrumental delivery and/or postpartum hemorrhage.
c-MAO: composite maternal adverse outcome which was defined as preterm birth and/or pre-eclampsia, and/or pregnancy induced hypertension, and/or infection.
c-FAO: composite fetal adverse outcome which was defined as macrosomia and/or hypoglycemia and/or and/or hypocalcemia and/or hyperbilirubinemia and/or NICU admission and/or birth trauma and/or low birth weight.
Bold values indicate significance level.
*Values are presented in number (percentage), otherwise unless stated.
BMI, body mass index; c-NAO, composite neonatal adverse outcome; DM, diabetes mellitus; GDM, gestational diabetes mellitus; GH, gestational hypertension; IUFD, Intrauterine fetal demise; LBW, low birth wight; NICU, neonatal intensive care unit.

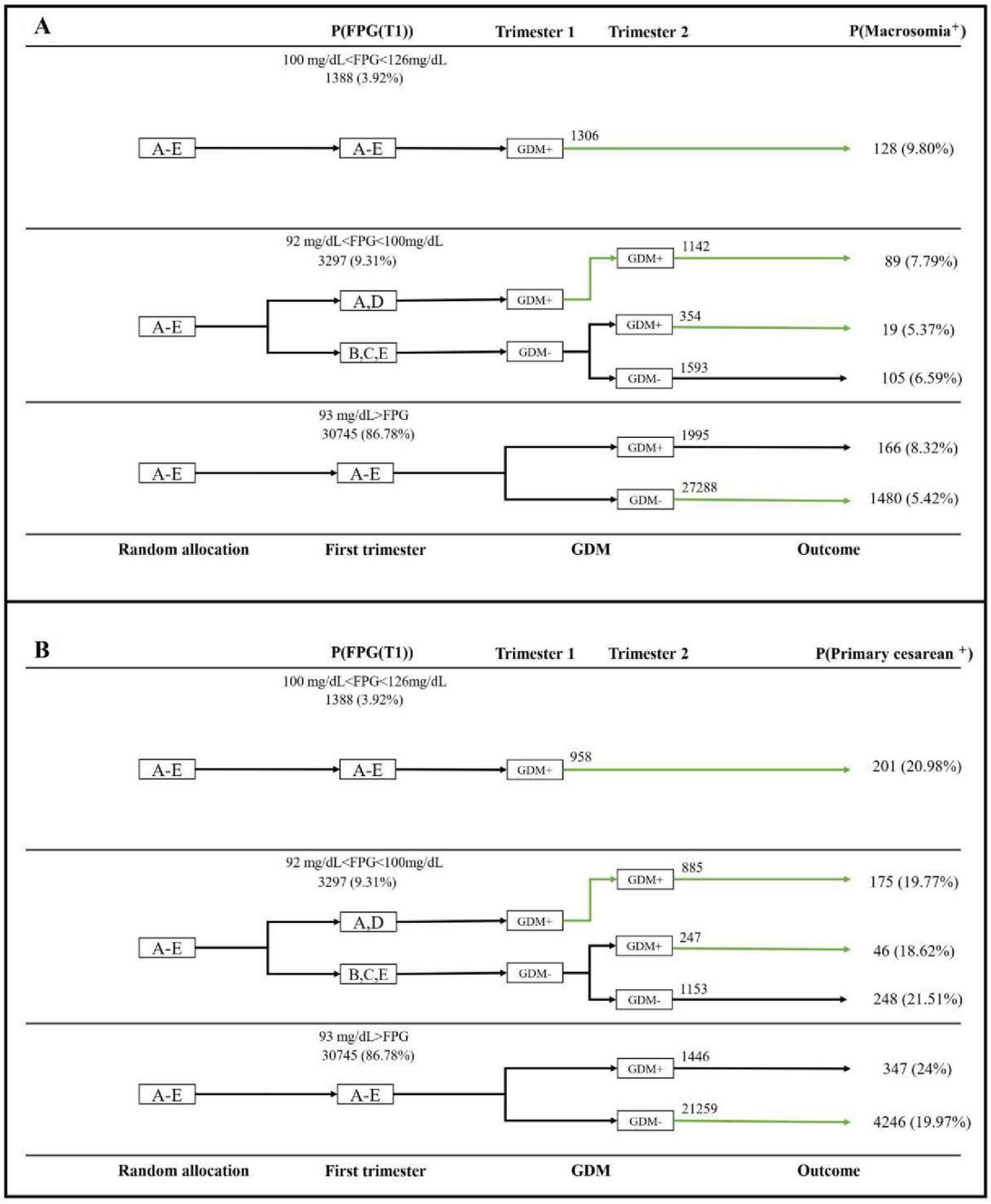

Figure 1 The participants' flow diagrams for macrosomia (A) and primary cesarean section (B) based on their assigned protocol, FPG level in the first trimester, and GDM diagnosis status. The green arrows indicate treatment received. FPG, fasting-plasma-glucose; GDM, gestational diabetes mellitus.

27.8 (5.4) kg/m^2, 26.9 (4.9) kg/m^2, 27.7 (5) kg/m^2, 26.5 (4.7) kg/m^2, 27 (4.8) kg/m^2, 25.5 (4.7) kg/m^2 in groups 1–6, respectively. Family history of diabetes mellitus (DM) in group 1 was 18% and it was 12%, 21%, 12%, 14%, and 10% for groups 2–6, respectively.

The participants' flow diagrams for two primary outcomes according to the original study protocol (macrosomia and primary cesarean section) based on the specified groups is presented in figure 1. It has been shown that 9.8% of women in group 1, 7.8% in group 2, 5.4% in group 3, 6.6% in group 4, 8.3% in group 5, and 5.4% in group 6 experienced macrosomia. Primary caesarean section was the route of delivery in 21.0%, 19.8%, 18.6%, 21.5%, 24.0%, and 20.0% of pregnant women in groups 1–6, respectively (figure 1).

The adjusted RR of developing the adverse pregnancy outcomes in other groups to reference group 6 as well as their 95% CIs are presented in figure 2. Having considered group 6 as a reference, the result showed significant increase in the adjusted risk of neonatal intensive care unit (NICU) admission in groups 1 (RR=4.56; 95% CI 2.75 to 7.31; p<0.001), 2 (RR=3.51; 95% CI 2.04 to 5.85; p<0.001), 3 (RR=2.84; 95% CI 1.52 to 5.10; p<0.001) and 5 (RR=3.41; 95% CI 2.13 to 5.27; p<0.001). The adjusted

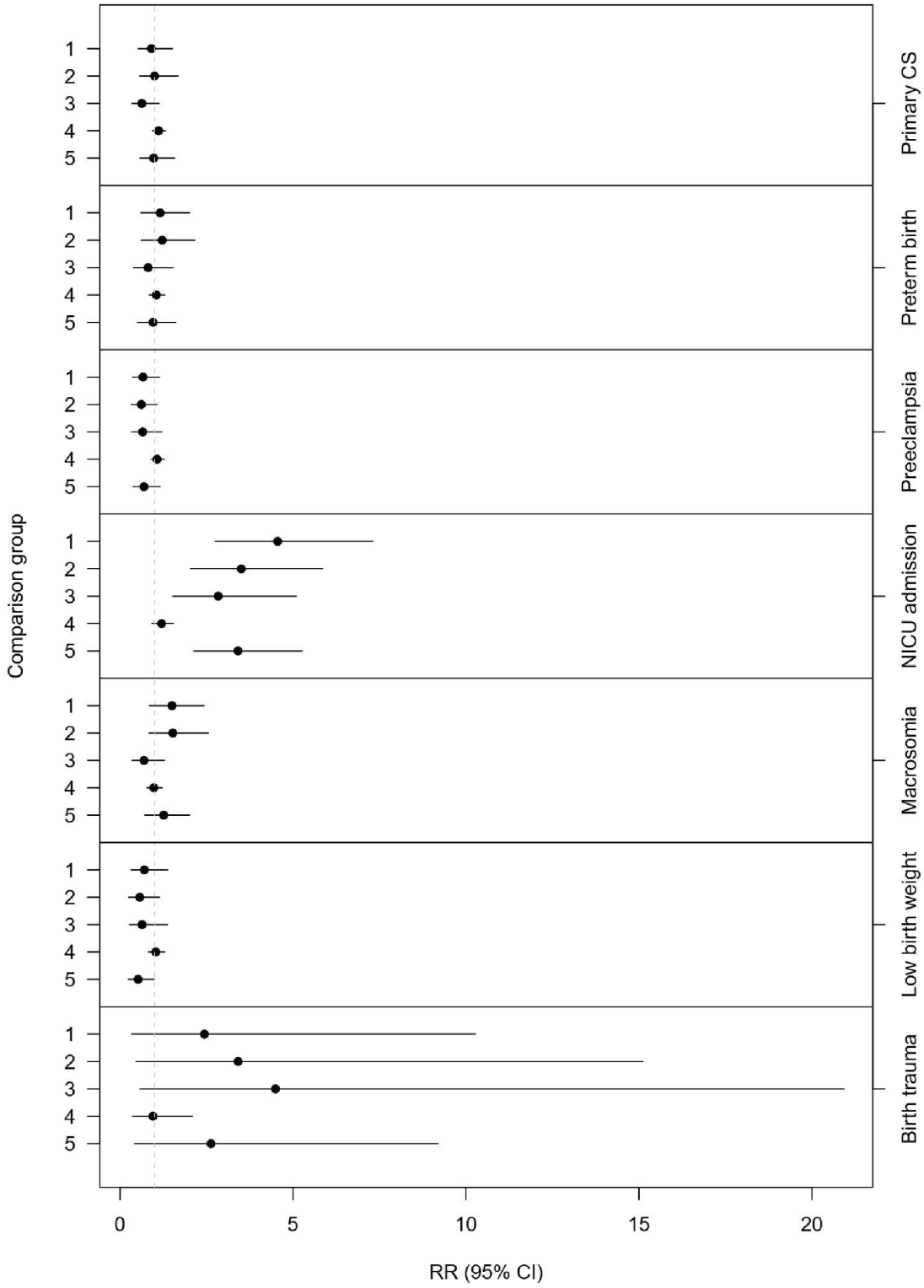

Figure 2 The adjusted risk ratio (RR) of groups in comparison with reference group 6, the participants with FPG<92 mg/dL in trimester 1, who were not diagnosed as GDM-positive. FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; NICU, neonatal intensive care unit.

RR of macrosomia in groups 1, 2, and 5 to reference group 6 and their 95% CIs were (RR=1.50; 95% CI 0.84 to 2.43; p=0.07), (RR=1.53; 95% CI 0.84 to 2.55; p=0.07), and (RR=1.26; 95% CI 0.72 to 2.01; p=0.19), respectively. Moreover, group 5 revealed a lower risk of LBW in group 5 compared with group 6 (RR=0.52; 95% CI 0.24 to 0.99; p=0.04).

The crude and adjusted RR of different groups in comparison to the reference group 2 are shown in table 3. After adjusting for age, gestational age at enrollment and

Table 3 The crude and adjusted RR of different groups in comparison to the reference group 2

	Unadjusted RR (95% CI)					Adjusted* RR (95% CI)				
Outcomes	Group1	Group3	Group4	Group5	Group6	Group1	Group3	Group4	Group5	Group6
Macrosomia	1.26 (0.97 to 1.63)	0.69 (0.41 to 1.09)	0.85 (0.64 to 1.11)	1.07 (0.84 to 1.37)	**0.7 (0.57 to 0.86)**	0.98 (0.72 to 1.35)	**0.45 (0.26 to 0.74)**	0.64 (0.36 to 1.21)	0.83 (0.62 to 1.11)	0.65 (0.39 to 1.19)
Primary cesarean section	1.06 (0.89 to 1.27)	0.94 (0.69 to 1.25)	1.09 (0.92 to 1.29)	**1.21 (1.03 to 1.43)**	1.01 (0.89 to 1.16)	0.91 (0.69 to 1.21)	**0.63 (0.42 to 0.94)**	1.12 (0.65 to 2)	0.98 (0.77 to 1.25)	1.01 (0.6 to 1.76)
Preterm birth	1.25 (0.95 to 1.65)	1.1 (0.71 to 1.65)	0.94 (0.71 to 1.26)	1.01 (0.78 to 1.33)	0.89 (0.72 to 1.11)	0.95 (0.68 to 1.33)	0.67 (0.41 to 1.05)	0.86 (0.47 to 1.76)	0.78 (0.58 to 1.07)	0.82 (0.46 to 1.63)
Hypoglycemia	**1.57 (1.02 to 2.47)**	**2.58 (1.52 to 4.35)**	**0.12 (0.04 to 0.28)**	**2.46 (1.69 to 3.71)**	**0.06 (0.04 to 0.09)**	1.32 (0.74 to 2.4)	0.98 (0.48 to 2.01)	**0.01 (0 to 0.04)**	**1.87 (1.13 to 3.22)**	**0.01 (0.01 to 0.02)**
Hypocalcemia	**2 (1.19 to 3.48)**	**2.87 (1.49 to 5.47)**	**0.18 (0.06 to 0.45)**	**1.92 (1.18 to 3.28)**	**0.1 (0.06 to 0.17)**	1.92 (0.91 to 4.27)	1.22 (0.49 to 3.12)	**0.02 (0 to 0.06)**	1.04 (0.51 to 2.25)	**0.01 (0 to 0.03)**
Hyperbilirubinemia	0.84 (0.64 to 1.11)	0.96 (0.63 to 1.41)	**0.76 (0.58 to 0.99)**	1 (0.79 to 1.27)	0.84 (0.69 to 1.03)	0.88 (0.6 to 1.3)	0.73 (0.44 to 1.19)	0.25 (0.15 to 0.42)	0.91 (0.66 to 1.27)	0.26 (0.16 to 0.42)
Pre-eclampsia	**1.29 (1.05 to 1.61)**	1.14 (0.81 to 1.56)	0.97 (0.78 to 1.21)	1.14 (0.93 to 1.4)	0.95 (0.81 to 1.14)	1.08 (0.8 to 1.45)	1.07 (0.71 to 1.59)	1.74 (0.96 to 3.36)	1.12 (0.86 to 1.47)	1.63 (0.93 to 3.07)
NICU admission	1.12 (0.85 to 1.48)	1.13 (0.74 to 1.68)	**0.7 (0.52 to 0.95)**	1.09 (0.85 to 1.42)	0.64 (0.52 to 0.8)	1.3 (0.89 to 1.91)	0.81 (0.47 to 1.36)	**0.34 (0.19 to 0.62)**	0.97 (0.69 to 1.39)	0.29 (0.17 to 0.49)
Birth trauma	0.96 (0.39 to 2.41)	1.78 (0.55 to 5.12)	0.69 (0.27 to 1.77)	0.71 (0.29 to 1.75)	0.71 (0.39 to 1.5)	0.71 (0.2 to 2.52)	1.32 (0.31 to 5.2)	0.28 (0.05 to 2.37)	0.77 (0.26 to 2.43)	0.29 (0.07 to 2.18)
Low birth weight	1.08 (0.83 to 1.41)	1.16 (0.78 to 1.67)	0.98 (0.76 to 1.28)	0.99 (0.77 to 1.27)	1.09 (0.9 to 1.35)	1.23 (0.84 to 1.79)	1.12 (0.65 to 1.87)	1.81 (0.87 to 4.16)	0.91 (0.65 to 1.29)	1.75 (0.87 to 3.92)
c-DAO	**1.24 (1.02 to 1.50)**	1.13 (0.85 to 1.51)	0.94 (0.78 to 1.15)	1.05 (0.87 to 1.26)	1.03 (0.88 to 1.20)	0.94 (0.74 to 1.19)	0.68 (0.49 to 0.94)	0.95 (0.75 to 1.20)	**0.81 (0.66 to 0.99)**	1.00 (0.84 to 1.20)
c-MAO	**1.28 (1.09 to 1.50)**	1.11 (0.86 to 1.42)	0.91 (0.77 to 1.08)	1.12 (0.96 to 1.31)	0.96 (0.84 to 1.09)	1.02 (0.84 to 1.23)	0.88 (0.68 to 1.15)	1.02 (0.85 to 1.24)	0.96 (0.81 to 1.13)	1.01 (0.87 to 1.17)
c-FAO	1.06 (0.93 to 1.21)	0.96 (0.78 to 1.18)	**0.78 (0.68 to 0.89)**	1.09 (0.96 to 1.22)	**0.83 (0.75 to 0.92)**	1.01 (0.87 to 1.17)	**0.74 (0.60 to 0.92)**	0.97 (0.82 to 1.13)	0.95 (0.83 to 1.08)	0.99 (0.89 to 1.12)

c-FAO: composite fetal adverse outcome which was defined as macrosomia and/or hypoglycemia and/or hypocalcemia and/or hyperbilirubinemia and/or NICU admission and/or birth trauma and/or low birth weight.
c-DAO: composite delivery adverse outcome which was defined as primary cesarean section and/or shoulder dystocia and/or instrumental delivery and/or postpartum hemorrhage.
c-MAO: composite maternal adverse outcome which was defined as preterm birth and/or pre-eclampsia, and/or pregnancy-induced hypertension, and/or infection.
*The group effects are adjusted for age, gestational ages at enrollment and at delivery, body mass index, type of delivery, family history of diabetes mellitus, type of treatment, and the assigned protocol. The model for cesarean section is not adjusted for the type of delivery. The model for preterm birth is not adjusted for gestational age at delivery. The reference is group 2: The patients in protocols A or D with 92 mg/dL<FPG<100 mg/dL in the first trimester received treatment according to their protocol.
FPG, fasting plasma glucose; NICU, neonatal intensive care unit; RR, relative risk.

at delivery, BMI, type of delivery, family history of DM, type of treatment, and the assigned protocol, we found that among mothers who had FPG between 92 mg/dL and 100 mg/dL in the first trimester, those mothers who were not diagnosed with GDM (group 3) were approximately half (RR: 0.45, CI 0.26 to 0.74) likely to develop macrosomia, compared with reference group 2 (mothers with a positive GDM diagnosis). After adjustment for the abovementioned potential confounders, risk of hypoglycemia increased by 87% in group 5 in comparison to group 2 (RR=1.87; 95% CI 1.13 to 3.22); furthermore, the risk of NICU admission decreased by 31% in group 6 compared with group 2 (RR=0.69; 95% CI 0.51 to 0.94).

DISCUSSION

In the current secondary analysis of the randomized community non-inferiority trial, we presented the results of various GDM screening approaches in terms of adverse pregnancy outcomes. We found that (1) Screening and diagnostic 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 (2) Individuals with slight increase in FPG (92–100 mg/dL) at first trimester, who were diagnosed with 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 the second trimester. These results were independent of potential confounders of age at enrollment, gestational age at delivery, BMI, type of delivery, family history of DM, the assigned protocols and type of medication.

Medical screening detects risk factors for disease or the presence of disease in asymptomatic or high-risk population subgroups in order to intervene early and reduce morbidity and mortality.[30] A criterion of an ideal screening test is to demonstrate reasonable accuracy. The development of ever-more-sensitive diagnostic tests that challenge existing disease definitions is a major contributor to the rising problem of overdiagnosis and the subsequent risk of overtreatment.[31]

Optimum screening for GDM has been a matter of debate for years. The primary goal of GDM screening is to provide comprehensive GDM care in order to reduce the magnitude of the risk of adverse pregnancy outcomes to levels to those of healthy pregnant women without GDM. This community-based field randomized trial with different comparison groups and a high sample size could help with the clarification of conflicting results reported by previous studies.

For the initial comparison, we compared the risk of adverse pregnancy outcomes across various groups with healthy non-GDM participants as controls. The results of the study revealed that detecting and managing GDM could reduce the risk of adverse pregnancy outcomes to the risk level observed in healthy pregnancies. Interestingly, in some GDM cases, the risk of adverse pregnancy outcomes was even lower than in healthy pregnant women. These findings could be attributed to the fact that a diagnosis of GDM medicalizes a pregnancy, leading to an increase in the healthcare delivery level from general practitioners or midwives into the hospital system with specialized care. It triggers interventions such as extra antenatal visits, frequent blood sugar measurements, SMBG, performing regular biophysical profiles, and planned childbirth with earlier labor induction or caesarean section.[32] We hypothesize that the intensive treatments of GDM including both tight glycemic control and several obstetrics monitoring/interventions in these patients may decrease the risk of adverse pregnancy outcomes in GDM cases to a similar or lower level than the risk observed in healthy pregnant women. However, while some babies can benefit, all babies treated, particularly pharmacologically, are exposed to some potential harm. In the current study, for example, the risk of NICU admission in treated groups was higher than in the healthy population. Consistent with this hypothesis, some studies showed that treatment of GDM could increase the risk of some neonatal outcomes including hypoglycemia, NICU admission, and SGA (Small for gestational age).[14 33 34] In the recent well-designed published study, in agreement with our findings, Simmons *et al* assessed whether treatment of gestational diabetes before 20 weeks' gestation improves maternal and infant health (TOBOGM Study). A total of 802 pregnant women before the 20 weeks of gestation who had a risk factor for hyperglycemia and a diagnosis of gestational diabetes were randomly assigned to receive immediate treatment for gestational diabetes or deferred or no treatment, depending on the results of a repeat OGTT at 24–28 weeks' gestation (control).[35] The TOBOGM (The Treatment of Booking Gestational Diabetes Mellitus) Study showed that treatment of early GDM in the higher band of glucose had more beneficial effects than diagnosing and treating GDM in the lower band of glycemia in the first trimester.

In another randomized controlled trial, Crowther *et al* sought to investigate the potential effects of using lower versus higher glycemic criteria at 24–32 weeks' gestation for treatment of GDM on the maternal and infant outcomes.[36] A total of 4061 women were randomly assigned to either the lower glycemic criterion group, as FPG levels of at least 92 mg/dL (≥5.1 mmol/L), a 1-hour level of at least 180 mg/dL (≥10.0 mmol/L), or a 2-hour level of at least 153 mg/dL (≥8.5 mmol/L), or the higher glycemic criterion group, which involved FPG levels of at least 99 mg/dL (≥5.5 mmol/L), or a 2-hour blood sugar level of 162 mg/dL (≥9.0 mmol/L). The results showed that using lower glycemic criteria for the diagnosis of GDM did not result in a lower risk of a large for gestational age infant than the use of higher glycemic criteria.

In addition, we found that women in group 2, who were diagnosed with GDM based on first trimester FPG levels 92–99.9 mg/dL, had higher risk of macrosomia

compared with others with first trimester FPG>100 mg/dL, or those who were diagnosed with GDM in second trimester or healthy non-GDM pregnant women. We hypothesize that this group may have not received the pharmacological treatment needed to reduce their risk of adverse pregnancy outcomes. It should be noted that all of the pregnant women with mild GDM (group 2) received the GDM care which was initiated with adjustment of their individual diet and lifestyle and were monitored for their fasting and postmeal glucose levels to meet their glycemic targets recommended by ADA guideline 2016 including fasting, 95 mg/dL, 1-hour postprandial, 140 mg/dL or 2-hour postprandial, 120 mg/dL.[23 27] If women did achieve glycemic goals within 2 weeks, it demonstrated that lifestyle modification per se could successfully treat GDM and pharmacologic therapy did not. If glycemic targets were achieved over a 2-week period, this would indicate that lifestyle modification alone can serve as a successful treatment approach for GDM, and potentially eliminate the need for pharmacological therapy. Remarkably, most of the GDM cases were treated with these lifestyle modifications.[24] In this respect, the importance of dietary modification in GDM is a premise unlikely to be contested and major scientific bodies recommended dietary and lifestyle modification as the mainstay and first step of GDM treatment.[12] However, in clinical practice, there are limited data regarding the optimal follow-up management and interval for monitoring of blood glucose levels for these women with mild first-trimester GDM diagnoses. In our study, most of these women achieved glycemic goals within 2 weeks with lifestyle modification and were monitored monthly to keep the fasting glycemic targets. The existing guidelines for managing GDM do not offer comprehensive recommendations regarding the specific details and frequency of monitoring for pregnant women diagnosed with GDM in the first trimester. Additionally, there is a lack of specific guidance for monitoring pregnant women who have successfully achieved glycemic control through dietary interventions within a two-week period.[11–13 25 26 37 38] As such, although they were monitored monthly, it might be possible that these patients suffer from delayed detection of blood glucose surge and missed the glycemic goals in some phases of pregnancy. On the other hand, due to the lack of re-screening for GDM between the 24th and 28th weeks of gestation, the elevated insulin resistance during the second trimester may not have been detected in a timely manner. As a result, these individuals did not receive appropriate treatment with insulin or oral antihyperglycemic agents, nor did they receive other necessary obstetric care such as timely biophysical profile testing. Notably, since the peak postprandial blood glucose levels occur later in pregnant women than in the non-pregnant state,[39] the 2-hour postprandial test which was used for monitoring blood glucose level, may not precisely detect the IR surge in the second trimester of pregnancy. However, in contrast, insulin/oral agent-treated patients had specific tight self and physician's monitoring for maintaining therapeutic goals of glucose. Hence, we hypothesized that in women diagnosed with mild GDM during the first trimester, the achievement of glycemic targets within 2 weeks through dietary modifications may create a false sense of confidence for both the patient and the healthcare providers. This false confidence can hinder the timely diagnosis and prevention of adverse pregnancy outcomes.

Another potential explanation that may contribute to higher risk of adverse outcomes in nutrition-treated women from the first trimester of pregnancy, is that lower carbohydrate intake in this group may have led to higher fat intake which exacerbated maternal insulin resistance by free fatty acids.[40–42] Taken together we hypothesized that both issues led to higher risk of adverse pregnancy outcomes in the group of women who received treatment from the first trimester of pregnancy. Consistent with these hypotheses, Yamamoto *et al*, in a systematic review and meta-analysis, highlighted the issue that although modified dietary interventions favorably influenced outcomes related to maternal glycemia and birth weight, the quality of the evidence about GDM and diet therapy in the scientific literature is low. As we suggest, they indicated that that there is room for improvement in specific dietary recommendation and guideline for management of women with GDM, after achieving the glycemic goal.[43]

Further, we found that among pregnant women diagnosed with GDM using different screening and diagnostic approaches, there were no statistically significant differences in the risk of adverse maternal and neonatal outcomes compared with healthy pregnant women, except for a significantly higher risk of NICU admission in groups diagnosed with GDM compared with healthy pregnant women. However, this may primarily be attributed to various factors, including a preference for planned delivery to reduce the risk of excessive fetal weight gain and associated perinatal complications, such as perinatal mortality, shoulder dystocia, birth trauma, and cesarean delivery. Additionally, there is a need for optimal control of newborns with diabetic mothers with tight glycemic control, which may potentially lead to side effects such as neonatal hypoglycemia.[5 44–46]

The strengths and limitations of this study have been reported before.[24] In summary, the generalizability of findings due to community-based design, large sample size, broad inclusion criteria, and adjusting for potential risk factors are the main strengths of this study. In contrast, since we used the primary healthcare setting as a platform of study, women with known chronic disorders were not included in our study. Moreover, a central reference laboratory was not used for all our measurements, though all laboratory procedures, equipment, and supplies were homogeneous in different geographic regions of the study, and monthly external quality controls were performed for each laboratory. Additionally, it is important to note that all individuals diagnosed with GDM during the first trimester were considered to have GDM throughout the entire pregnancy and were not

re-evaluated during the second trimester. Consequently, we were unable to compare the outcomes of pregnant women who had GDM both in the first trimester and confirmed through re-screening in the second trimester. Due to the small number of some adverse pregnancy outcomes among the study groups, the results attributed to these outcomes should be interpreted with caution. However, since this study was a field trial, we could not precisely collect the details of adherence to various types of medication including monitoring of carbohydrate intake. Besides, the details of other treatments for adverse delivery outcomes such as antibiotic therapy in case of urinary tract infections was not available. Our approach to randomization was designed to achieve geographic diversity and ensure a representative sample across the different regions of Iran. While age, parity, and BMI are indeed important variables, we focused our randomization strategy on factors that were considered central to our research objectives. However, to address this limitation, these variables were included in a regression model to control for the variation introduced by these factors that were not entirely accounted for by the randomization process. Additionally, we considered a statistical power of 85% (instead of the conventional threshold of 80%) to enhance confidence in detecting the specified effect size or differences between groups. As such, we conducted a comparison of six different diagnostic approaches for GDM across varying levels of FPG values and also used a one-step or two-step screening method. The inclusion of multiple study groups may introduce confusion about this study.

In conclusion, this secondary analysis improved our understanding of the impact of the various GDM screening approaches in the general population. The results of this study showed that the different screening and diagnostic approaches for GDM could reduce 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. Diagnosing pregnant women with slightly elevated FPG as GDM, may induce a false assurance for both the patient and the care provider; moreover lack of practical comprehensive guidelines for monitoring of these women throughout the pregnancy period may lead to neglect of hyperglycemia in the second trimester. We recommend that these women undergo a second-trimester OGTT for re-screening. The present study highlighted a need for more specific and improved guidelines for the management of pregnant women with the early elevation of FPG. A lower threshold for GDM diagnosis, coupled with a lack of clear guidelines for managing these patients could potentially lead to overdiagnosis of GDM that may harm pregnant women without improvement of pregnancy outcome.

Author affiliations
[1]Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]School of Public Health, Department of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran
[3]Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[4]Obesity Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]Infertility and Cell Therapy Office, Transplant & DiseaseTreatment Center, Ministry of Health and Medical Education, Tehran, Iran
[6]Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[7]Faculty of Medicine, Shahed University, Tehran, Iran
[8]Tehran Medical Branch, Islamic Azad University, Tehran, Iran
[9]Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran
[10]Osteoporosis Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[11]Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[12]Faculty of Nursing and Health Sciences, Nord University, Bodø, Norway

Acknowledgements The authors thank Farahnaz Torkestani (Shahed University of Medical Science, Tehran, Iran), Zahra Abdollahi (Department of Nutrition, Ministry of Health and Medical Education, Tehran, Iran), Marzieh Bakhshandeh (Family Health Department, Ministry of Health and Medical Education, Tehran, Iran), Mehdi Zokaee (Population, Family and School Health Department, Kurdistan University of Medical Sciences, Sanandaj, Iran), Farzam Bidarpour (Kurdistan University of Medical Sciences, Sanandaj, Iran), Mehdi Javanbakht (University of Southampton, Hampshire, England), Iraj Nabipour (The Persian Gulf Tropical Medicine Research Center, The Persian Gulf Biomedical Sciences Research Institute, Bushehr University of Medical Sciences, Bushehr, Iran), Razieh Bidhendi Yarandi (Department of Biostatistics, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran), Ensieh Nasli Esfahani (Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran) for the sincere collaboration in the study. The authors also thank Golestan, Bushehr, Birjand, Kurdistan and Yazd Universities of Medical Sciences for their cooperation for this study. The authors also thank the cooperative executive committee, including: Abbas Najari, MD (Centre for Collective Refection & Implementation of Ideas, Undersecretary for Research and Technology, Ministry of Health and Medical Education, Tehran, Iran); Abdolmohhamad Khajeian, MD (Deputy of Health, Bushehr University of Medical Sciences, Bushehr, Iran); Azita Anaraki, MD (Population, Family and School Health Department, Bushehr University of Medical Sciences, Bushehr, Iran); Fariba Ghazaghi, MSc (Population, Family and School Health Department, Birjand University of Medical Sciences, Birjand, Iran); Forouzan Lahouni, MS (Population, Family and School Health Group, Kurdistan University of Medical Sciences, Sanandaj, Iran); Forouzandeh Kalantari, MD (Population, Family and School Health Department, Yazd University of Medical Sciences, Yazd, Iran); Hossein Fallah, MSc (Nutrition Department, Ministry of Health and Medical Education, Tehran, Iran); Khadije Kordi, MD (Population, Family and School Health Department, Golestan University of Medical Sciences, Gorgan, Iran); Lotfollah Saed, MD (Department of Internal Medicine, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran); Shabahang Amirshekari, MSc (Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran); Mahsa Norooozzadeh, MSc (Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran); Maryam Farahmand, PhD (Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran); Marzieh Rostami Dovom, PhD (Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran); Mehdi Hedayati, PhD (Cellular and Molecular Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran); Mehdi Mehdizade, MD (Deputy of Health, Birjand university of Medical science, Birjand, Iran); Mohammad Hassan Lotf, MD (Deputy of Health, Kurdistan University of Medical Sciences, Sanandaj, Iran); Mohammad-Esmaeil Motlagh, MD (Department of Pediatrics, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran); Mozhgan Bashghareh, MSc (Population, Family and School Health Department, Golestan University of Medical Sciences, Gorgan, Iran); Nosrat Zamanipour, MSc (Population, Family and School Health Department, Birjand

University of Medical Sciences, Birjand, Iran); Parvin Mirmiran, PhD (Nutrition and Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran); Saeid Sadeghian Sharif, PhD (Faculty of Nutrition Science and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran Iran); Saeid Shahraz, PhD (Heller School of Social Policy and Management, Brandeis University, Waltham, Massachusetts, USA); Samareh Khari, MD (Population, Family and School Health Department, Golestan University of Medical Sciences, Gorgan, Iran); Sedigheh Alishahi, MSc (Population, Family and Fchool Health Department, Yazd University of Medical Sciences, Yazd, Iran); Shole Shahgheibi, MD (Department of Obstetrics and Gynecology, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran); Sima Nazarpour, PhD (Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran); Yadollah Mehrabi, PhD (Department of Epidemiology, School of Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran); Zahra Ghaedmohammadi, MSc (Population, Family and School Health Department, Bushehr University of Medical Sciences, Bushehr, Iran).

Contributors FRT, AS and MR had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: FRT, SB-G, FFa, MA, FHo, FHa, FT, FA. Acquisition, analysis, or interpretation of data: FRT, AS, MR, SB-G, FHo, MN, FT, DK, FFi, AO, MS-D. Drafting of the manuscript: FRT, MR, SB-G. Critical revision of the manuscript for important intellectual content: FF, MA, MF, FHa, FHo, MV, FA. Supervision: FRT, FA, SB-G. All authors approved the final manuscript. FRT is the guarantor who has full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding Research reported in this publication was supported by Elite Researcher Grant Committee under award number IR.NIMAD.REC.1394.013 from the National Institute for Medical Research Development (NIMAD), and this study is funded by Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Grant number: 4-43006578). Nord University, Bodø, Norway covered the processing charge to this article.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the national ethics committee of the National Institute for Medical Research Development (Approval number: IR.NIMAD.REC.1394.013). In addition, the Iranian Ministry of Health and Medical Education (MoHME) approved the study protocol and prespecified GDM modalities were made available to all those provinces as mandatory guidelines. As a result, this was considered a part of routine prenatal care, and specific individual informed consent was not obtained from pregnant women.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request under the agreement.

ORCID iD

Samira Behboudi-Gandevani http://orcid.org/0000-0003-3526-640X

REFERENCES

1 Speechley M, Kunnilathu A, Aluckal E, *et al*. Screening in public health and clinical care: similarities and differences in definitions, types, and aims - a systematic review. *J Clin Diagn Res* 2017;11:LE01–4.
2 Behboudi-Gandevani S, Amiri M, Bidhendi Yarandi R, *et al*. The impact of diagnostic criteria for gestational diabetes on its prevalence: a systematic review and meta-analysis. *Diabetol Metab Syndr* 2019;11.
3 Paulo MS, Abdo NM, Bettencourt-Silva R, *et al*. Gestational diabetes mellitus in Europe: a systematic review and meta-analysis of prevalence studies. *Front Endocrinol (Lausanne)* 2021;12.
4 Ye W, Luo C, Huang J, *et al*. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ* 2022;377:e067946.
5 Bidhendi Yarandi R, Vaismoradi M, Panahi MH, *et al*. Mild gestational diabetes and adverse pregnancy outcome: a systemic review and meta-analysis. *Front Med (Lausanne)* 2021;8.
6 Behboudi-Gandevani S, Bidhendi-Yarandi R, Panahi MH, *et al*. The effect of mild gestational diabetes mellitus treatment on adverse pregnancy outcomes: a systemic review and meta-analysis. *Front Endocrinol (Lausanne)* 2021;12.
7 Assaf-Balut C, Familiar C, García de la Torre N, *et al*. Gestational diabetes mellitus treatment reduces obesity-induced adverse pregnancy and neonatal outcomes: the St. Carlos gestational study. *BMJ Open Diabetes Res Care* 2016;4:e000314.
8 Vounzoulaki E, Khunti K, Abner SC, *et al*. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. *BMJ* 2020;369.
9 Davidson KW, Barry MJ, Mangione CM, *et al*. Screening for gestational diabetes: US preventive services task force recommendation statement. *JAMA* 2021;326:531–8.
10 Metzger BE, Gabbe SG, Persson B, *et al*. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010;33:676–82.
11 World Health Organization. *Diagnostic Criteria And Classification Of Hyperglycaemia First Detected In Pregnancy*. Geneva: World Health Organization, 2013.
12 American Diabetes Association Professional Practice Committee. Classification and diagnosis of diabetes: standards of medical care in Diabetes-2022. *Diabetes Care* 2022;45:S17–38.
13 National Institute for Health and Care Excellence. NICE guideline. *Diabetes in pregnancy: management from preconception to the postnatal period (NG3)*. London: NICE, Available: http://www.nice.org.uk/guida [accessed Jul 2017].
14 Simmons D, Nema J, Parton C, *et al*. The treatment of booking gestational diabetes mellitus (TOBOGM) pilot randomised controlled trial. *BMC Pregnancy Childbirth* 2018;18:151.
15 Zhu W-W, Yang H-X, Wei Y-M, *et al*. Evaluation of the value of fasting plasma glucose in the first prenatal visit to diagnose gestational diabetes mellitus in China. *Diabetes Care* 2013;36:586–90.
16 Corrado F, D'Anna R, Cannata ML, *et al*. Correspondence between first-trimester fasting Glycaemia, and oral glucose tolerance test in gestational diabetes diagnosis. *Diabetes Metab* 2012;38:458–61.
17 Benhalima K, Van Crombrugge P, Moyson C, *et al*. Women with mild fasting hyperglycemia in early pregnancy have more neonatal intensive care admissions. *J Clin Endocrinol Metab* 2021;106:e836–54.
18 Ramezani Tehrani F, Naz MSG, Yarandi RB, *et al*. The impact of diagnostic criteria for gestational diabetes mellitus on adverse maternal outcomes: a systematic review and meta-analysis. *J Clin Med* 2021;10:666.
19 Tehrani FR, Naz MSG, Bidhendi-Yarandi R, *et al*. Effect of different types of diagnostic criteria for gestational diabetes mellitus on adverse neonatal outcomes: a systematic review, meta-analysis, and meta-regression. *Diabetes Metab J* 2022;46:605–19.
20 Sevket O, Ates S, Uysal O, *et al*. To evaluate the prevalence and clinical outcomes using a one-step method versus a two-step method to screen gestational diabetes mellitus. *J Matern Fetal Neonatal Med* 2014;27:36–41.
21 Saccone G, Caissutti C, Khalifeh A, *et al*. One step versus two step approach for gestational diabetes screening: systematic review and meta-analysis of the randomized trials. *J Matern Fetal Neonatal Med* 2019;32:1547–55.
22 Hillier TA, Pedula KL, Ogasawara KK, *et al*. A pragmatic, randomized clinical trial of gestational diabetes screening. *N Engl J Med* 2021;384:895–904.
23 Ramezani Tehrani F, Behboudi-Gandevani S, Gulf Study Cooperative Research Group. Cost effectiveness of different screening strategies for gestational diabetes mellitus screening: study protocol of a randomized community non-inferiority trial. *Diabetol Metab Syndr* 2019;11:106.

24 Ramezani Tehrani F, Behboudi-Gandevani S, Farzadfar F, *et al*. A cluster randomized noninferiority field trial of gestational diabetes mellitus screening. *J Clin Endocrinol Metab* 2022;107:e2906–20.
25 The American Colledge of Obstetricians and Gynecologist. *Guideline For Perinatal Care*. Available: https://www.buckeyehealthplan.com/content/dam/centene/Buckeye/medicaid/pdfs/ACOG-Guidelines-for-Perinatal-Care.pdf
26 Practice bulletin No.137. gestational diabetes mellitus. *Obstet Gynecol* 2013;122:406–16.
27 Standards of medical care in Diabetes-2016: summary of revisions. *Diabetes Care* 2016;39 Suppl 1:S4–5.
28 Practice bulletin No.173: fetal macrosomia. *Obstet Gynecol* 2016;128:e195–209.
29 Mustafa R, Ahmed S, Gupta A, *et al*. A comprehensive review of hypertension in pregnancy. *J Pregnancy* 2012;2012.
30 Maxim LD, Niebo R, Utell MJ. Screening tests: a review with examples. *Inhal Toxicol* 2014;26:811–28.
31 de Groot JAH, Naaktgeboren CA, Reitsma JB, *et al*. Methodologic approaches to evaluating new highly sensitive diagnostic tests: avoiding overdiagnosis. *CMAJ* 2017;189:E64–8.
32 Hegerty CK. The new gestational diabetes: treatment, evidence and consent. *Aust N Z J Obstet Gynaecol* 2020;60:482–5.
33 Martis R, Crowther CA, Shepherd E, *et al*. Treatments for women with gestational diabetes mellitus: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev* 2018;8:CD012327.
34 Brown J, Grzeskowiak L, Williamson K, *et al*. Insulin for the treatment of women with gestational diabetes. *Cochrane Database Syst Rev* 2017;11:CD012037.
35 Simmons D, Immanuel J, Hague WM, *et al*. Treatment of gestational diabetes mellitus diagnosed early in pregnancy. *N Engl J Med* 2023;388:2132–44.
36 Crowther CA, Tran T. Lower versus higher Glycemic criteria for diagnosis of gestational diabetes. *N Engl J Med* 2022;387:1720–1.
37 ACOG practice bulletin No.190: gestational diabetes mellitus. *Obstet Gynecol* 2018;131:e49–64.
38 Valizadeh M, Hosseinpanah F, Ramezani Tehrani F, *et al*. Iranian endocrine society guidelines for screening, diagnosis, and management of gestational diabetes mellitus. *Int J Endocrinol Metab* 2021;19:e107906.
39 Ben-Haroush A, Yogev Y, Chen R, *et al*. The postprandial glucose profile in the diabetic pregnancy. *Am J Obstet Gynecol* 2004;191:576–81.
40 Hernandez TL, Brand-Miller JC. Nutrition therapy in gestational diabetes mellitus: time to move forward. *Diabetes Care* 2018;41:1343–5.
41 Sivan E, Boden G. Free fatty acids, insulin resistance, and pregnancy. *Curr Diab Rep* 2003;3:319–22.
42 Hernandez TL, Van Pelt RE, Anderson MA, *et al*. A higher-complex carbohydrate diet in gestational diabetes mellitus achieves glucose targets and lowers postprandial lipids: a randomized crossover study. *Diabetes Care* 2014;37:1254–62.
43 Yamamoto JM, Kellett JE, Balsells M, *et al*. Gestational diabetes mellitus and diet: a systematic review and meta-analysis of randomized controlled trials examining the impact of modified dietary interventions on maternal glucose control and neonatal birth weight. *Diabetes Care* 2018;41:1346–61.
44 Hiersch L, Berger H, Okby R, *et al*. Gestational diabetes mellitus is associated with adverse outcomes in twin pregnancies. *Am J Obstet Gynecol* 2019;220:102.
45 Chung YS, Moon H, Kim EH. Risk of obstetric and neonatal morbidity in gestational diabetes in a single institution: a retrospective, observational study. *Medicine (Baltimore)* 2022;101:e30777.
46 Watson D, Rowan J, Neale L, *et al*. Admissions to neonatal intensive care unit following pregnancies complicated by gestational or type 2 diabetes. *Aust N Z J Obstet Gynaecol* 2003;43:429–32.

Ramezani Tehrani and Gulf Study Cooperative Research Group
Diabetol Metab Syndr (2019) 11:106
https://doi.org/10.1186/s13098-019-0493-z

Diabetology & Metabolic Syndrome

STUDY PROTOCOL Open Access

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

Fahimeh Ramezani Tehrani* and Gulf Study Cooperative Research Group

Abstract

Background: There is lack of ideal and comprehensive economic evaluations of various GDM strategies. The aim of this study is to the compare efficacy and cost-effectiveness of five different methods of screening for gestational diabetes mellitus (GDM).

Methods: This study is a randomized community non-inferiority trial among 30,000 pregnant women in five different geographic regions of Iran, who were randomly assigned to one of the five GDM screening methods. All first trimester pregnant women, seeking prenatal care in governmental health care systems, who met our eligibility criteria were enrolled. The criteria suggested by the International-Association-of-Diabetes-in-Pregnancy-Study-Group, the most intensive approach, were used as reference. We used the non-inferiority approach to compare less intensive strategies to the reference one. Along with routine prenatal standard care, all participants were scheduled to have two phases of GDM screening in first and second-trimester of pregnancy, based on five different pre-specified protocols. The screening protocol included fasting plasma glucose in the first trimester and either a one step or a two-step screening method in the second trimester of pregnancy. Pregnant women were classified in three groups based on the results: diagnosed with preexisting pre-gestational overt diabetes; gestational diabetes and non-GDM women. Each group received packages for standard-care and all participants were followed till delivery; pregnancy outcomes, quality of life and cost of health care were recorded in detail using specific standardized questionnaires. Primary outcomes were defined as % birth-weight > 90th percentile and primary cesarean section. In addition, we assessed the direct health care direct and indirect costs.

Results: This study will enable us to compare the cost effectiveness of different GDM screening protocols and intervention intensity (low versus high).

Conclusion: Results which if needed, will also enable policy makers to optimize the national GMD strategy as a resource for enhancing GDM guidelines.

Trial registration Name of the registry: Iranian Registry of Clinical Trials. Trial registration number: IRCT138707081281N1. Date of registration: 2017-02-15. URL of trial registry record: https://www.irct.ir/trial/518

Keywords: Cost-effectiveness, Gestational diabetes, Screening, Perinatal outcome

*Correspondence: ramezani@endocrine.ac.ir; framezan@post.harvard.edu
Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, No 24, Parvane Street, Yaman Street, Velenjak, P.O.Box: 19395-4763, Tehran, Iran

Background

Gestational diabetes (GDM) defined as hyperglycaemia at any time during pregnancy at levels below those that occurring in overt diabetes [1]. It is one of the most common glycemic disorders during pregnancy with occurrence of 1–28% of all pregnancies [2–5], along with the increased rate of obesity and advanced maternal age is rising in prevalence [6]. It is well documented that GDM is associated with both short as well as long term higher rates of adverse feto-maternal and neonatal outcomes [7–11]. From an obstetrical perspective, evidence shows that treatment of GDM is effective in reducing the risk of many of the important adverse pregnancy outcomes [12–14].

Despite the globally accepted importance of screening for and treating GDM [13], screening strategies, testing methods and even diagnostic optimum glycemic thresholds for GDM remained much controversy for decades and no international consensus has been yet established [15]. In addition, the former screenings were mainly performed to prevent adverse maternal outcomes compared to neonatal complications. Considering this, use of different tests and criteria will impact the prevalence of women diagnosed with GDM [5], and could also impact poor pregnancy outcomes [16, 17]. There is also much controversy about milder forms of GDM. For which, the associations of mild GDM with adverse pregnancy outcomes are not completely understood; there is ongoing debate about the benefits of treating mild GDM and the impact on health care costs [18–21].

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study demonstrated that hyperglycemia at levels below those previous recommended thresholds for GDM were associated with adverse maternal and neonatal outcomes; hence, the International Association of Diabetes in Pregnancy Study Group (IADPSG) introduced new cutoffs for the 2-hour (2 h) oral glucose tolerance test (OGTT) in GDM screening and diagnosis [22]. Besides, at present, a 3-h 100 g diagnostic test is used predominantly in the United States and some other areas, whereas much of the world uses the 75 g, 2-h OGTT [5]. At present, there is little information regarding the sensitivity and specificity of these test, and hence the relative clinical effectiveness of the two-steps of the 1-h 50-g glucose challenge test (GCT) following 3-h 100 g oral glucose tolerance (OGTT) diagnostic test and the one-step OGTT approaches in the same population. However using the IADPSG criteria, two to threefold more women qualified for a diagnosis of GDM, potentially adding to the costs of care of the already large number of pregnant women [23–25].

With both increased prevalence and adopting lowering of the thresholds for diagnosis, the healthcare cost of GDM can be expected to rise proportionately. It follows that the debate as to whether or not a benefit exists in the treatment of GDM assumes even greater importance now than in the past. However, since in most countries, resources are inevitably scarce, healthcare interventions should be evaluated for their impact the on cost as well as effectivity on clinical outcomes [26]. Moreover, while not recognizing that GDM is associated with adverse pregnancy outcomes, over-diagnosis may lead to psychological stress, unnecessary treatments and impaired quality of life [27–29].

There is lack of ideal and comprehensive economic evaluations of various GDM strategies; the majority of existing cost-effective analyses are based on decision analysis modelling not real data, limited obtained from randomized clinical trials that documented controversial results [20, 30–38]. In addition most studies have been conducted in well-developed high-income countries which obviously have more developed healthcare systems than low and middle-income countries, where gestational diabetes has the highest prevalence. According to a WHO report, global and local decision-making regarding GDM strategies are challenging due to the lack of optimum economic evaluations of various GDM screening protocols, making it difficult to validated implement any national recommendations from a health economic perspective [31]. Since resources are unavoidably scarce, national health care interventions should be assessed for their impact on costs as well as on clinical outcomes; the most highly recommended practice is that economic evaluation should be an integral part of randomized clinical trials [39]; each population needs to adopt its community specific guidelines [40].

In this ongoing randomized community-field non-inferiority trial, we aimed to compare the cost-effectiveness of five different pre-defined GDM screening protocols, both one and two step, using different fasting plasma glucose thresholds to ascertain the optimum GDM screening protocol.

Materials and methods

Research questions and objectives

This study is being performed to provide real data collected from an unbiased population trial for assessment of the following hypothesis: (i) the prevalence of GDM when using the less intensive GDM screening strategies is not more than obtained using the IADPSG criteria. (ii) The pre-specified primary outcomes in less intensive GDM screening strategies are not worse than those obtained using IADPSG criteria. (iv) The cost of health care using less intensive GDM screening strategies is not higher than incurred using IADPSG criteria. (v) The

numbers needed to treat (NNT) to prevent one primary outcome in less intensive strategies are the same as those obtained using IADPSG criteria.

The cost of prevention for one primary outcome in less intensive strategies is the same as that for IADPSG criteria.

According to our research hypothesis, primary outcomes hence are: percentage of birth weight > 90th percentile and primary cesarean section. Secondary outcomes are prevalence of neonatal hypoglycemia, birth weight < 10th percentile, neonatal admission to the intensive care unit, shoulder dystocia and birth trauma including fracture of clavicle and brachial plexus injury, intrauterine fetal death, preeclampsia and preterm labor, neonatal hyperbilirubinemia and hypocalcemia. In addition, the study will assess the direct health care costs including prenatal clinic visits, obstetrician visits, endocrinologist visits, dietician visits, blood glucose monitoring equipment, laboratory test cost, pharmacotherapy, additional fetal well-being assessments and hospitalization as well as indirect cost of productivity loss and charges to the family including traveling, food substitution, mother time off paid work, and partner time off work.

Overall study design

This is a randomized community-field trial including five GDM screening strategies in a parallel group design. Recruitment of the participants took place between September 2016 and January 2019 in 1015 health centers in 25 selected cities of five provinces of Iran.

All pregnant women < 14 weeks of gestation, who received prenatal care from governmental health care systems were eligible for enrollment, except where the following specific exclusion criteria prevented this: Maternal age < 18 years, preexisting diabetes, date of last menstrual period not certain, no ultrasound estimation from 6 to 14 weeks of gestational age available, chronic hypertension, asthma or currently receiving treatment with oral glucocorticoids, β-blockers, oral β-mimetics, Dilantin, or antiretroviral agents and past history of bariatric surgery.

All participants received standard prenatal care recommended by the American College of Obstetricians and Gynecologists (ACOG) [41]. Moreover, participants were scheduled to have two phases of GDM screening in the first and second trimesters of pregnancy, based on the pre-specified protocol for GDM screening, selected for each city.

At each prenatal visit, standardized questionnaires were administered to document prenatal as well as other data needed for research by trained midwives.

Sample size calculation

Based on previous studies, we assumed that the primary event rate of macrosomia to be equal to 10% for all groups with no difference. To obtain a statistical power of 85% with a 1-sided type one error of 0.005 (considering multiple comparisons) approximately 4700 patients per group are needed to show the non-inferiority of more intensive compared to lower intensive strategies with a marginal difference of 0.03. With a design effect of 0.001 (for cluster sampling) and loss to follow-up of 11%, sample size reached to 5200 in each group [42].

In addition, superiority analyses will be designed to show that one screening strategy is superior to another after non-inferiority has been demonstrated.

Randomization and allocation

Initially all provinces of Iran were categorized to five stratum based on their geographic location (North, East, West, South, and Center of Iran) and one province in each stratum were randomly selected; then, the list of the cities located in each province were provided. Since the socioeconomic status in the center of provinces may differ from other cities, in the second phase, all cities in each province were classified in two clusters of center of the province and other cities. At the end, four cities were randomly selected from the list of other cities in each province.

For allocation of protocols, in the cluster of the provincial centers, five different protocols were randomly allocated to each provincial center. Also, in the cluster of other cities, four other cities in each province were randomly allocated to the rest of the protocols (Fig. 1). Sample size for each city was estimated through probability proportional to size (PPS), defined by number of live births of the cities.

Intervention

Following the approval of this study, the study procedure was released as a guideline to all the selected cities. In this respect, workshops were conducted in each city to introduce the study protocol and train the caregivers and study staff accordingly. Dieticians, obstetricians, internal medics, laboratory technicians and endocrinologists in each province were invited to a scientific workshop to harmonize and coordinate the follow ups and treatment of GDM patients. Scientific teams with specialists and executive members conducted visits every 2 months. A telegram channel was developed for daily online communication of scientific members and executive members at both provincial and city levels to answer questions and solve any problems encountered.

Along with routine standard prenatal care, all pregnant women was screened for GDM based on the pre-specified protocol assigned to each city. In this respect, early screening of GDM was conducted in the first trimester of pregnancy, using fasting plasma glucose (FPG) from

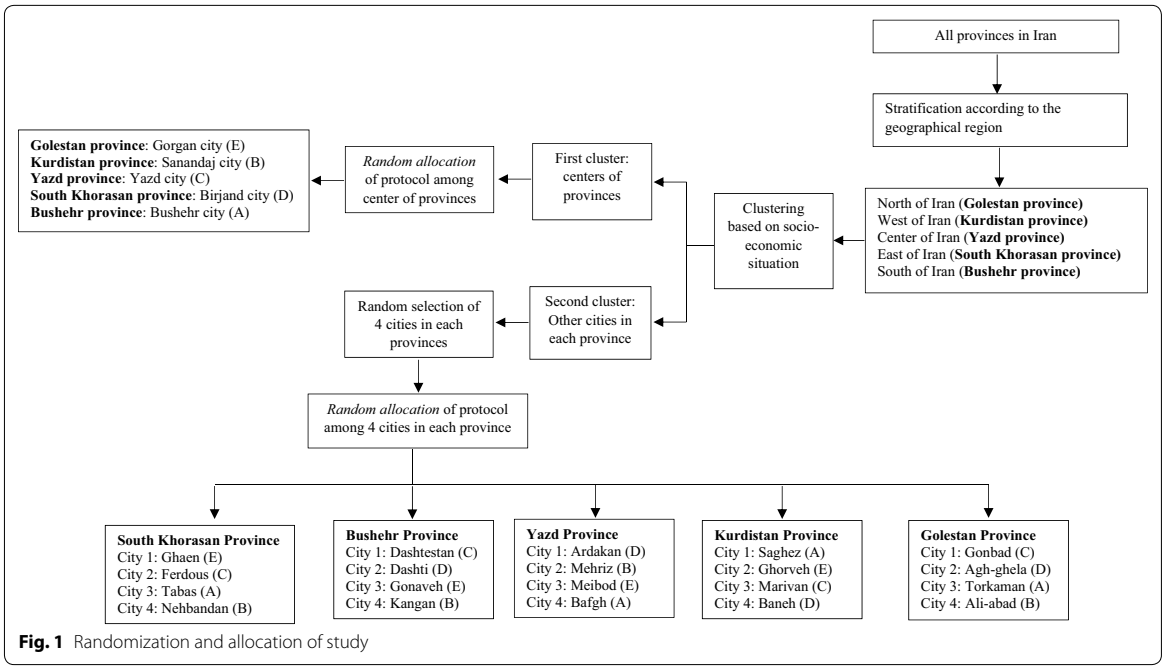

Fig. 1 Randomization and allocation of study

venous sample with the specific threshold based on each screening protocol; based on the results of those screening tests, pregnant women were classified in to three groups: (i) diagnosed with preexisting pre-gestational overt diabetes; (ii) gestational diabetes and (iii) non-GDM women. In addition, at 24–28 weeks of gestation, those not previously known to have diabetes (overt or gestational), were screened again for GDM based on pre-specified protocol criteria assigned to that city. All study participants were followed till delivery and pregnancy and neonatal outcomes and health cost were recorded in detail. Definitions of various protocols for screening are presented in Table 1.

Each group received packages of standard care based on their health status. In this respect, non-GDM pregnant women received routine standard care recommended by the American College of Obstetricians and Gynecologists (ACOG) 2013 [41]. Moreover, pregnant diabetic patients received specific prenatal and diabetic care, recommended by the American College of Obstetricians and Gynecologists (ACOG) 2013 [43] and the American Diabetes Association (ADA) 2016 [44].

Summary of management of Gestational Diabetes in Pregnancy

After diagnosis of GDM, treatment was initiated with medical nutrition therapy, physical activity, and weight management and blood glucose monitoring to achieve the targets recommended by ADA guideline 2016 [44] including fasting, 95 mg/dL, 1-h postprandial, 140 mg/dL or 2-h postprandial, 120 mg/dL. Medical nutrition therapy for GDM will be individually planed for participants by the dietitian. The food plan provides enough calorie intake to promote fetal/neonatal and maternal health, achieve glycemic goals, and promote appropriate gestational weight gain, based on the Dietary Reference Intakes (DRI) recommendation including a minimum of 175 g carbohydrate, a minimum of 71 g protein, and 28 g fiber [44].

If women did not achieve glycemic goals within 2 weeks, pharmacologic therapy will be offered by specialized physicians including obstetricians, internists or endocrinologists at the second level of the healthcare delivery system. Insulin is the first-line agent recommended for treatment of GDM. Self-monitoring of blood glucose (SMBG) was used for achieving and maintaining therapeutic goals in insulin-treated patients. The frequent use of capillary blood glucose tests of SMBG was scheduled four times a day, fasting, 2-h after breakfast, lunch and dinner or if the patients had hypoglycemic symptoms for at least 2 weeks. After achieving the therapeutic target, SMBG was performed two times a day. In addition, if women decline insulin therapy, metformin will be offered as an alternative or

Table 1 Definitions of various protocols for screening of gestational diabetes mellitus

Protocol	First trimester	Second trimester		
	Diagnostic criteria for GDM	Method for GDM screening	Diagnostic threshold of test	Diagnostic criteria
A	92 mg/dL < FPG > 126 mg/dL	One step with 2-h 75 g OGTT	Fasting ≥ 92 mg/dL 1 h ≥ 180 mg/dL 2 h ≥ 153 mg/dL	GDM is defined as any of the given plasma glucose values are met or exceeded
B	100 mg/dL < FPG > 126 mg/dL	One step with 2-h 75 g OGTT	Fasting ≥ 92 mg/dL 1 h ≥ 180 mg/dL 2 h ≥ 153 mg/dL	GDM is defined as two or more of the given plasma glucose values are met or exceeded
C	100 mg/dL < FPG > 126 mg/dL	One step with 2-h 75 g OGTT	Fasting ≥ 92 mg/dL 1 h ≥ 180 mg/dL 2 h ≥ 153 mg/dL	GDM is defined as any of the given plasma glucose values are met or exceeded
D	92 mg/dL < FPG > 126 mg/dL	Two steps with 50 g GCT—1 h following 3-h 100 g OGTT	50 g GCT: BS-1 h: ≥ 140 mg 100 g OGTT: Fasting ≥ 95 mg/dL 1 h ≥ 180 mg/dL 2 h ≥ 155 mg/dL 3 h ≥ 140 mg/dL	GDM is defined as if two or more of the given plasma glucose values in 100 g OGTT are met or exceeded
E	100 mg/dL < FPG > 126 mg/dL	Two steps with 50 g GCT—1 h following 3-h 100 g OGTT	50 g GCT: BS-1 h: ≥ 140 mg 100 g OGTT: Fasting ≥ 95 mg/dL 1 h ≥ 180 mg/dL 2 h ≥ 155 mg/dL 3 h ≥ 140 mg/dL	GDM is defined as if two or more of the given plasma glucose values in 100 g OGTT are met or exceeded

In the first trimester overt diabetes is defined as FPG ≥ 126 mg/dL

FPG fasting plasma glucose, *GCT* glucose challenge test, *OGTT* oral glucose tolerance test

adjunct to insulin after clarifying the harms and benefits of metformin therapy for patients [44] (Fig. 2).

Data collection

Data were collected from participants at scheduled time points (Table 2) using pre-specified questionnaires and clinical and para clinical exams by trained midwives. Moreover, data on neonatal mortalities that occurred after hospital discharge were collected at 4 weeks postpartum by telephone and subsequent reviews of medical records.

Questionnaires

1. *Prenatal questionnaire* This comprehensive questionnaire includes two sections: 1—contains the past medical, reproductive, obstetrics, and gynecological history, completed only at first prenatal visit 2—focuses on current pregnancy information and this part was completed at each prenatal visit during pregnancy (Additional file 1: PART 1: Prenatal Care Form).
2. *Delivery, postpartum and neonatal questionnaire* This questionnaire contains the details of delivery and its methods and any adverse maternal–fetal/neonatal outcomes (Additional file 1: PART 2. Childbirth and New-born Report Form).
3. *Quality of life questionnaire* The Iranian version of 36-item short form health survey questionnaire (SF-36) [45–48] was used to measure the physical and mental components of health-related quality of life. The SF-36 included 36 items with 8 subscales; physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and perceived mental health. This questionnaire was completed monthly for all GDM patients since the time of diagnosis. Also, it were done for 5% of non-GDM pregnant women visited from the first visit for prenatal care (Additional file 1: PART 3. 36-Item Short Form Survey Instrument).
4. *Cost-effectiveness questionnaire* This questionnaire included 50 items with three subscales: (i) self-purchased health care, (ii) travel costs for making return visit(s) to health care and (iii) time costs of travel-

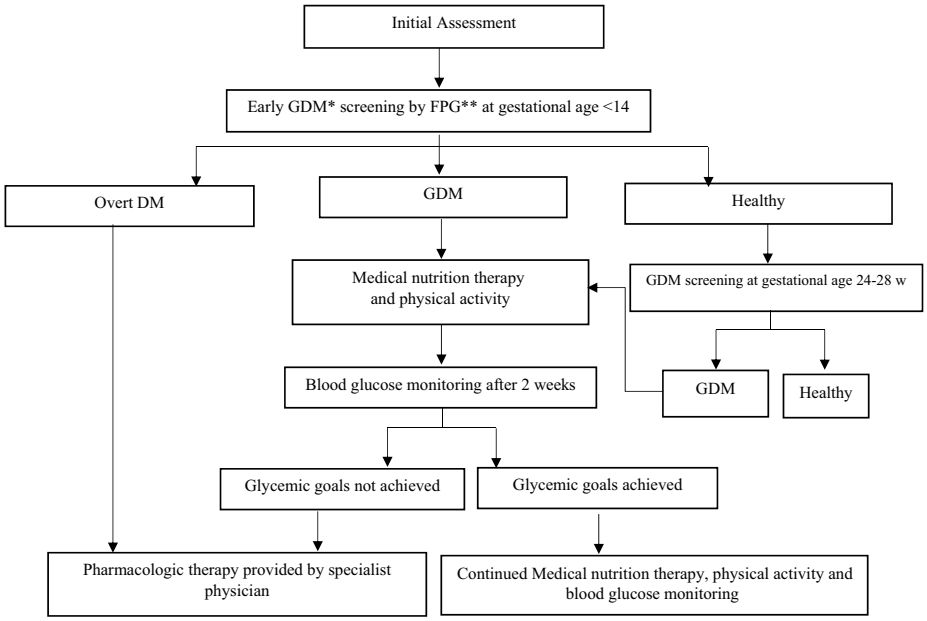

Fig. 2 Flow chart of screening and management of Gestational Diabetes in Pregnancy. *GDM: gestational diabetes mellitus; **FPG: fasting plasma glucose

ling and attending health care center. Effectiveness was measured in terms of quality adjusted life years (QALYs), using the EQ-5D 3L questionnaire completed by participants at the follow up time points. It includes five questions, each assessing one of five dimensions of the health related quality of life (Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression). Each of these dimensions has to be answered on a 3-level scale (no problems, some or moderate problems, and extreme problems). The scales are scored from 1 (no problem) to 3 (extreme problem) in each question; and finally the score digits are placed together to yield a 5-digit code for the health status of each patient (Additional file 1: PART 4. Cost effectiveness Form).

Maternal anthropometric, clinical, and laboratory assessments

Weight was measured to the nearest 100 g using digital scales while the participants were minimally clothed, without shoes. Height was measured to the nearest 0.5 cm, in a standing position without shoes, using a tape measure, while shoulders were in normal alignment. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). After a 15-min rest in the sitting position, two measurements of systolic and diastolic blood pressure (SBP and DBP) were taken on the right arm, using a standardized mercury sphygmomanometer (calibrated by the Iranian Institute of Standards and Industrial Researches); the mean of the two measurements was considered as the participant's blood pressure.

Plasma glucose were measured on the day of blood collection. A blood sample was drawn between 7:00 and 9:00 AM from all study participants, after 8 to 10 h overnight fasting. For the 75-g OGTT-82.5 g of glucose monohydrate solution (equivalent to 75 g anhydrous glucose), for the 50 g glucose challenge test (GCT)-55 g of glucose monohydrate solution (equivalent to 50 g anhydrous glucose) and for the 100-g OGTT-100 g of glucose monohydrate solution (equivalent to 110 g anhydrous glucose) were administered orally to subjects and plasma glucose was measured, using an enzymatic colorimetric method with glucose oxidase; inter- and intra-assay coefficients of variation were less than 2.3%. Analyses were performed using Pars Azmon kits (Pars Azmon Inc., Tehran, Iran) using the Selectra 2 auto-analyzer (Vital Scientific, Spankeren, Netherlands).

Neonatal anthropometric, clinical, and laboratory assessments

Neonatal anthropometric and clinical measurement were measured by trained staff. Birth weight was measured without diapers using a calibrated digital baby scale

Table 2 Outlines of periodic assessments of study participants

	Method or sample used	> 14 week	14–19 week	20–23 week	24–30 week	31–34 week	35–37 week	38 week	39 week	40 week	Birth	28 days after birth
Maternal[a,b]												
Past medical, reproductive and obstetrics history												
Weight	Calibrated scale	a	a	a	a	a	a	a	a	a		
Height	Stadiometer	a										
Blood pressure (systolic, diastolic)	Calibrated mercury sphygmomanometer	a	a	a	a	a	a	a	a	a		
Fundal height	Measuring tape		a	a	a	a	a	a	a	a		
Fetal heart rate			a	a	a	a	a	a	a	a		
Fetal ultrasound		a			a		a					
FPG	Venous sample	a										
OGTT-75 g or GCT following OGTT-100 g	Venous sample				a							
Quality of life	Questionnaire		a	a	a	a		a				
Drug adherence	Questionnaire		a	a	a	a		a				
GDM treatment satisfaction	Questionnaire		a	a	a	a		a				
Cost-effectiveness	Questionnaire		a	a	a	a		a			a	
Feto-maternal outcomes[c]											a	
Neonatal[a,b]												
C-peptide	Cord sample										a	
Weight	Calibrated baby scale										a	
Recumbent length	Infantometer										a	
Head circumference	Measuring tape										a	
Blood glucose[e]	Heel-stick sample										a	
Neonatal outcomes[d]											a	a

[a] Data collected from routine and expert scans that occur during the time points

[b] If GDM or other complication were diagnosed, subsequent additional visits, measurements and standard treatment were performed

[c] Feto-maternal outcomes continuously recoded include abortion, gestational hypertension, pre-eclampsia/eclampsia, preterm birth, instrumental delivery, primary cesarean section, polyhydramnios, oligohydramnios, premature rupture of membrane, placenta Previa, placenta abruption, postpartum hemorrhage, wound and incision infection

[d] Neonatal outcomes include shoulder dystocia, intrauterine growth restriction, macrosomia, Apgar score, neonatal hypoglycemia, neonatal hypocalcemia, neonatal hyperbilirubinemia, polycythemia, neonatal intensive care unit admission, neonatal care unit admission, Respiratory distress syndrome, congenital anomaly, neonatal asphyxia, intrauterine fetal death, perinatal death, Erb–Duchenne palsy, birth trauma, neonatal sepsis

[e] Measured for high risk groups

(SECA model 334; SECA Corp., Hamburg, Germany) to the nearest 1 gr, within an hour after delivery. Recumbent length was measured to nearest 0.1 cm from the top of the head to the sole of the feet using an infantometer (Easy-Glide Bearing Infantometer, Perspective Enterprises). Head circumference (HC) was measured at the largest occipito-frontal diameter and the measurement was rounded to the nearest 0.25 cm. The largest of three consecutive measurements was recorded.

In this respect, two measurements were obtained, and if results differed by >10 g for weight and 0.5 cm for length or head circumference, a third measurement were taken. The average of the two or three measurements was used for final analysis.

According to the national Iranian guidelines, all newborns were exclusively breastfed early after delivery. Infants were either screened for hypoglycemia 1–2 h after birth before a feeding based on the presence of defined risk factors including maternal GDM/overt DM, birth weight > 90th percentile, maternal BMI > 30, birth weight < 10th percentile, early preterm birth less than 34 weeks of gestation, perinatal acidosis, 5-min Apgar score of 0–3, failure of breastfeed and sepsis.

In this respect, blood glucose levels were measured using heel-stick sampling at 1, 3, 6, 12, and 24 h after birth before a feeding. Additional blood glucose measurements were performed in case of hypoglycemia or clinical symptoms including sweating, weak or high-pitched cry, feeding difficulties, poor sucking, tremors, hypothermia, irritability, lethargy/stupor, hypotonia, seizures, apnea, grunting or tachypnea or cyanosis. Using point-of-care testing, glucose was measured with the glucose oxidase method (Pars Azmon Inc., Tehran, Iran).

Cord serum C-peptide sample, as the index of fetal β-cell function, was collected at the time of delivery in a subsample of 1000 participants with different screening protocol. Samples collected were centrifuged for 10 min at 3000 rpm, stored at − 80 °C and transferred to central laboratory. C-peptide were determined with ELISA method (Mercodia AB, Uppsala, Sweden); the inter- and intra-assay coefficient of variation were < 2.3% and 1.5%, respectively.

The need for other assessments, such as serum bilirubin or imaging tests were determined based on clinical indications.

Definition of study outcomes

Outcomes of study were defined as follows: Macrosomia/large for gestational age (LGA) was defined as birth-weight > 4000 g and/or fetal-weight > 90th percentile for a given gestational age [49] using ultrasound biometry for estimating the fetal-weight and multinational World Health Organization (WHO) fetal growth chart for defining the percentile. Primary cesarean section was defined as the cesarean deliveries out of all births to women who had not had a previous cesarean delivery [50]; abortion refers to a termination of a pregnancy either natural or induced before the completion of 20 weeks of gestation. Polyhydramnios is defined as excess accumulation of amniotic fluid with 4-quadrant amniotic fluid index (AFI) more than 24 cm or a single maximum vertical pocket more than 8 cm [51]. Oligohydramnios refers to decreased amniotic fluid volume relative to gestational age with AFI less than 24 cm or a single maximum vertical pocket less than 8 cm [52]. Intrauterine growth restriction (IUGR)/fetal growth restriction was defined as fetal-weight less than the 10th percentile for gestational age [53] using ultrasound biometry for estimating the fetal-weight and multinational World Health Organization (WHO) fetal growth chart for defining the percentile. Small size for gestational age (SGA) refers to birth-weight less than the 10th percentile for gestational age [53, 54] using gender specific WHO weight-for-age chart for defining the percentile. Hypoglycemia was defined as plasma glucose concentration < 47 mg/dL in the first 48 h after delivery [55, 56]; hyperbilirubinemia was determined by value greater than the 95th percentile for any given point after birth [57]; Gestational hypertension was defined as a systolic pressure of ≥ 140 mmHg or a diastolic pressure of ≥ 90 mmHg taken on two occasions, at least 4 h apart [58, 59]; Preeclampsia was defined as an elevation in blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic on two occasions at least 4 h apart after 20 weeks of gestation in a women with a previously normal blood pressure and proteinuria ≥ 300 mg per 24 h urine collection or protein/creatinine ratio greater than or equal to 0.3 or dipstick reading of 1+ and more if other quantitative methods were not available. In the absence of proteinuria, new-onset hypertension with the new onset of any of the thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema and cerebral or visual symptoms [59]; preterm birth was defined as when birth occurs between 20 and 37 weeks of pregnancy [60]; shoulder dystocia was defined clinically, where providers are required to provide additional obstetric maneuvers when gentle downward traction has failed to affect the delivery of the shoulders [61] and birth trauma was defined as brachial plexus palsy or clavicular, humeral, or skull fracture. Mild GDM is defined as: a fasting glucose level of > 92 and < 100 mg per decilitre in 1st trimester of pregnancy and only one glucose measurement exceeding from established thresholds for 2-h 75gOGTT as follows: FPG > 92 mg/dL, 1-h plasma glucose > 180 mg/dL, 2-h plasma glucose > 53 mg/dL at the 24–28 weeks of gestation.

Data cleaning and missing data

The following minimal data must be available for women to be included in the analysis of pregnancy outcomes: Completed enrollment forms and questionnaire, completed results of GDM screening, type of delivery, birth weights and clear status of exclusionary criteria.

Missing values will be managed using appropriate imputation methods. Outliers will be identified using graphical tools including boxplot and/or Model-based methods like Chauvenet's criterion and Dixon's Q test [62, 63].

Data analysis

To illustrate distribution of the data, appropriate descriptive statistics such as measures of central tendency, index of dispersion and percentiles will be reported along with normality assumption testing through Kolmogorov-Smirnoff test. Maternal, neonatal and obstetric outcomes of the 4 less intensive screening strategies with IADPSG criteria will be compared using parametric or non-parametric statistical tests, where applicable.

In addition, based on the type of outcome variables, Generalized Linear Models (GLMs) with different link function such as linear, count or binary will be applied. Stepwise method with P-value < 0.2 will be used to identify significant confounding variables and estimate adjusted measures of interests. Moreover, longitudinal modeling through Generalized Estimating Equation (GEE) analysis approach will be conducted and to calculate Number Needed to Treat (NNT), the Linear GLM model will be applied as well. Since this is a cluster randomized trial, cluster effect in analysis will be considered.

Cost-effectiveness analysis (CEA)

A cost-effectiveness analysis, comparing 4 less intensive screening strategies with IADPSG criteria will be conducted on an intention-to-treat basis by estimating various parameters including Quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER), and incremental net benefit (INB). To estimate mean cost in each treatment group, regression models will be used. General linear models (GLM) with appropriate variance functions e.g. gamma, Poisson, etc. and link will be used to identify the relationship between treatment allocation and costs after adjusting for minimization and the appropriate prognostic covariates at baseline (e.g. Baseline EQ-5D score). To estimate the incremental effect of the treatment indicator variable, recycled predictions will be used [64].

A sensitivity analysis will be conducted to assess how sensitive the cost-effectiveness results are to variation in key parameters including cost.

Bayesian and Markov Modeling

Bayesian Cost Effectiveness Modeling (BCEM) will be used to overcome the complexity of the relationships linking a suitable measure of clinical benefit (e.g. quality-adjusted life years) and the associated costs. Simplifying assumptions, such as normality of the underlying distributions, are usually not granted, particularly for the cost variable, which is significantly skewed distributions. In addition, individual-level data sets are often characterized by the presence of structural zeros in the cost variable [65–67]. Bayesian models will be used to account for the presence of excess zeros in a distribution and have been applied in the context of cost data (Fig. 3).

Markov model will be used to extrapolate the results of the trial beyond the follow up, which will eventually provide longer-term cost-effectiveness. Markov decision processes (MDPs) are a powerful and appropriate technique for modelling medical decision. MDPs are most useful in classes of problems involving complex, stochastic and dynamic decisions like medical treatment decisions, for which they can find optimal solutions [68]. Physicians will always need to make subjective judgments about treatment strategies, but mathematical decision models can provide insight into the nature of optimal choices and guide treatment decisions [69]. Markov models can be used to describe various health states in a population of interest, and to detect the effects of various policies or therapeutic choices. In addition, we will apply decision tree analysis and then apply probabilistic approach.

All data analysis will be conducted using R (Version 2.2.2) and TreeAge (Version 13) softwares.

Approval and ethical considerations

This trial has been approved and funded by the National Institute for Medical Research Development under Grant Agreement No IR.NIMAD.REC.1394.013. Funding source had no involvement in the study. The protocol was approved by the national ethics committee of the National Institute for Medical Research Development (Approval number: IR.NIMAD.REC.1394.013). In addition, the Iranian Ministry of Health and Medical Education (MoHME) approved the study protocol and pre specified GDM modalities were made available to all those provinces as mandatory guidelines. This field trial has been registered in Iranian Registry of Clinical Trials (Trial Registration: IRCT138707081281N1).

Discussion

At present, there is a lack of international consensus about the diagnosis of gestational diabetes. Screening strategies, testing methods and even diagnostic optimum glycemic thresholds for GDM remain the subject

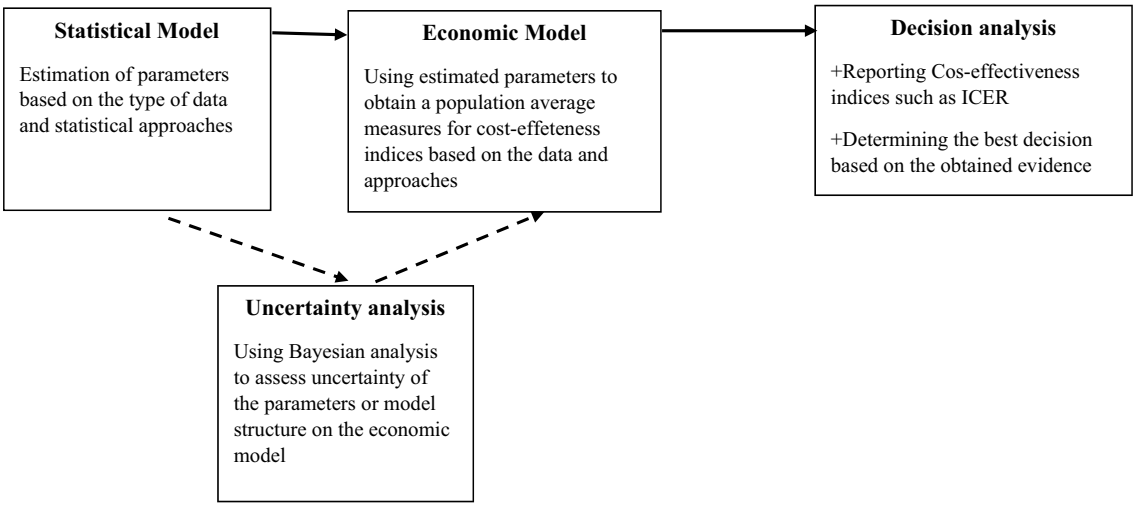

Fig. 3 A schematic illustration of the process of health economic evaluation

of considerable debate. Although gestational diabetes mellitus is a recognized marker for an increased risk of subsequent diabetes, its clinical significance with respect to its various definitions and various adverse pregnancy outcomes has not been clearly elucidated. Women with severe gestational diabetes and highly elevated fasting plasma glucose levels apparently are at an increased risk for adverse pregnancy outcomes if treatment is not provided, yet the association of milder forms of gestational diabetes with such outcomes remains unclear. Despite the HAPO study having provided valuable evidence of the association of maternal blood glucose with adverse pregnancy outcomes, it is worth noting that HAPO study was a purely observational study that conducted in western countries.

Considering the fact that majority of births annually occur in low- and low–middle income countries with high prevalence of GDM and limited resources [5], the cost-effectivity of this definition needs to be re-evaluated in other communities; the present study will hopefully provide such information from an eastern Mediterranean region. Moreover there is little information comparing the clinical efficacy, utility and feasibility of the two step GDM screening test and a 3-h oral glucose tolerance test (GTT) and the one step oral glucose tolerance test (OGTT) approaches, our study will provide comprehensive data on this comparison in the same population.

According to a WHO report, global and local decision making regarding GDM strategies are challenging due to the lack of optimum economic evaluations of various GDM screening protocols; as a result our study will provide the data needed for each community to adopt its specific GDM screening guidelines according to the reasonable cost for prevention of the adverse short and long term effects of GDM.

The limitations of our study of course should be addressed. Since specific questionnaires for evaluation of QOL and drug adherence in patients with GDM were not available, general questionnaires was used. In addition, we did not use the central reference laboratory for all of our measurement except C-peptide. Since homogeneity of laboratory procedures are essential to the success the study, we used standardized procedures in all provinces including local training of field center laboratory personnel, using a common protocol for measurement of glucose; using of standard equipment and supplies; monthly external quality controls for each laboratory. Moreover, glycosylated hemoglobin A1c (HbA1c) measurements were not available in our study.

Conclusions

Results which if needed, will also enable policy makers to optimize the national GMD strategy as a resource for enhancing GDM guidelines.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13098-019-0493-z.

Additional file 1: PART 1: Prenatal Care Form; PART 2. Childbirth and New-born Report Form; PART 3. 36-Item Short Form Survey Instrument; PART 4. Cost effectiveness Form.

Abbreviations
GDM: gestational diabetes mellitus; IADPSG: the International Association of Diabetes in Pregnancy Study Group; OGTT: oral glucose tolerance test; WHO: World Health Organization; ACOG: American College of Obstetricians and Gynecologists; FPG: fasting plasma glucose; ADA: American Diabetes Association; DRI: Dietary Reference Intakes; QALYs: quality adjusted life years; AFI: amniotic fluid index; SGA: small size for gestational age; IUGR: intrauterine growth restriction; GLMs: Generalized Linear Models; GEE: Generalized Estimating Equation; INB: incremental net benefit; ICER: incremental cost-effectiveness ratio; BCEM: Bayesian Cost Effectiveness Modeling.

Acknowledgements
We thank from Golestan, Bushehr, Birjand, Kurdistan and Yazd Universities of medical Sciences for their cooperation for this study.

Gulf Study Cooperative Research Group
Samira Behboudi-Gandevani, PhD (Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Mehrandokht Abedini, MD (Maternal health Department, Ministry of Health and Medical Education, Tehran, Iran);
Masoud Soleymani-Dodaran, MD, PhD, MPH, FFPH, CCT (Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran);
Davood Khalili, MD, MPH, PhD (Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Farshad Farzadfar, MD (Non-Communicable Diseases Research Center, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran);
Farhad Hoseinpanah, MD (Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Farzad Hadaegh, MD (Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Majid Valizadeh, MD (Obesity Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Farahnaz Torkestani, MD (Department of Obstetrics and Gynecology, Faculty of Medicine, Shahed University of Medical Sciences, Tehran, Iran);
Zahra Abdollahi, PhD (Nutrition Department, Undersecretary of Public Health, Ministry of Health & Medical Education, Tehran, Iran);
Marzieh Bakhshandeh, MSc (Maternal health Department, Ministry of Health and Medical Education, Tehran, Iran);
Razieh Bidhendi Yarandi, PhD (Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran);
Mehdi Zokaee, MD (Population, family and school health Department, Kurdistan University of Medical Sciences, Sanandaj, Iran);
Farzam Bidarpour, MD (Deputy of Health, Kurdistan University of Medical Sciences, Sanandaj, Iran);
Mehdi Javanbakht, PhD (Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen, UK);
Iraj Nabipour, MD (The Persian Gulf Biomedical Sciences Research Institute, Bushehr University of Medical Sciences);
Mohammad Ali Mansournia, MD (Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran);
Ensieh Nasli Esfahani, MD (Diabetes Research Center, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran);
Afshin Ostovar, MD (The Persian Gulf Biomedical Sciences Research Institute, Bushehr University of Medical Sciences, Bushehr, Iran);
Fereidoun Azizi, MD (Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran) and Executive committee.

Gulf Study Cooperative Executive committee
Abbas Najari, MD (Centre for Collective Reflection & Implementation of Ideas, Undersecretary for Research and Technology, Ministry of Health and Medical Education, Tehran, Iran);
Abdolmohhamad Khajeian, MD (Deputy of Health, Bushehr University of Medical Sciences, Bushehr, Iran);
Azita Anaraki, MD (Population, family and school health Department, Bushehr University of Medical Sciences, Bushehr, Iran);
Fariba Ghazaghi, MSc (Population, family and school health Department, Birjand University of Medical Sciences, Birjand, Iran);
Forouzan Lahouni, MS (Population, family and school health Group, Kurdistan University of Medical Sciences, Sanandaj, Iran);
Forouzandeh Kalantari, MD (Population, family and school health Department, Yazd University of Medical Sciences, Yazd, Iran);
Hossein Fallah, MSc (Nutrition Department, Ministry of Health and Medical Education, Tehran, Iran);
Khadije Kordi, MD (Population, family and school health Department, Golestan University of Medical Sciences, Gorgan, Iran);
Lotfollah Saed, MD (Department of Internal Medicine, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran);
Mahsa Norooozzadeh, MSc (Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Maryam Farahmand, PhD (Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Marzieh Rostami Dovom, PhD (Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Mehdi Hedayati, PhD (Cellular and Molecular Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Mehdi Mehdizade, MD (Deputy of Health, Birjand university of Medical science, Birjand, Iran);
Mina Amiri, PhD (Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Mohammad Hassan Lotfi, MD (Deputy of health, Kurdistan University of Medical Sciences, Sanandaj, Iran);
Mohammad-Esmaeil Motlagh, MD (Department of Pediatrics, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran);
Mozhgan Bashghareh, MSc (Population, family and school health Department, Golestan University of Medical Sciences, Gorgan, Iran);
Nosrat Zamanipour, MSc (Population, family and school health Department, Birjand University of Medical Sciences, Birjand, Iran);
Parvin Mirmiran, PhD (Nutrition and Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Saeid Sadeghian Sharif, PhD (Faculty of nutrition Science and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran Iran);
Saeid Shahraz, PhD (Heller School of Social Policy and Management, Brandeis University, Waltham, Massachusetts, USA);
Samareh Khari, MD (Population, family and school health Department, Golestan University of Medical Sciences, Gorgan, Iran);
Sedigheh Alishahi, MSc (Population, family and school health Department, Yazd University of Medical Sciences, Yazd, Iran);
Shole Shahgheibi, MD (Department of Obstetrics and Gynecology, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran);
Sima Nazarpour, PhD (Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Yadollah Mehrabi, PhD (Department of Epidemiology, School of Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran);
Zahra Ghaedmohammadi, MSc (Population, family and school health Department, Bushehr University of Medical Sciences, Bushehr, Iran).

Authors' contributions
FRT, SBG, MA, MSD, DKH, FF, FH, FH, MV, FT, ZA, MB, RBY, MZ, FB, IN, SSH, MAM, ENE, AO, FA contributed to conception of the article and study design. All authors contribute for study design in provinces manuscript drafting and critical discussion. All authors read and approved the final manuscript.

Funding
This trial has been approved and funded by the National Institute for Medical Research Development under Grant Agreement No IR.NIMAD.REC.1394.013. Funding source had no involvement in the study.

Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The protocol was approved by the national ethics committee of the National Institute for Medical Research Development (Approval number: IR.NIMAD.REC.1394.013). In addition, the Iranian Ministry of Health and Medical Education (MoHME) approved the study protocol and pre specified GDM modalities were made available to all those provinces as mandatory guidelines. This field trial has been registered in Iranian Registry of Clinical Trials (Trial Registration: IRCT138707081281N1).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 19 August 2019 Accepted: 9 November 2019
Published online: 18 December 2019

References

1. Wang C, Yang HX. Diagnosis, prevention and management of gestational diabetes mellitus. Chronic Dis Transl Med. 2016;2:199–203.
2. Eades CE, Cameron DM, Evans JM. Prevalence of gestational diabetes mellitus in Europe: a meta-analysis. Diabetes Res Clin Pract. 2017;129:173–81.
3. Lee KW, Ching SM, Ramachandran V, Yee A, Hoo FK, Chia YC, et al. Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2018;18:494.
4. Jiwani A, Marseille E, Lohse N, Damm P, Hod M, Kahn JG. Gestational diabetes mellitus: results from a survey of country prevalence and practices. J Matern Fetal Neonatal Med. 2012;25:600–10.
5. Behboudi-Gandevani S, Amiri M, Yarandi RB, Tehrani FR. The impact of diagnostic criteria for gestational diabetes on its prevalence: a systematic review and meta-analysis. Diabetol Metab Syndr. 2019;11:11.
6. Smith KB, Smith MS. Obesity statistics. Prim Care. 2016;43:121–35.
7. Prutsky GJ, Domecq JP, Sundaresh V, Elraiyah T, Nabhan M, Prokop LJ, et al. Screening for gestational diabetes: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2013;98:4311–8.
8. Minooee S, Tehrani FR, Rahmati M, Mansournia MA, Azizi F. Dyslipidemia incidence and the trend of lipid parameters changes in women with history of gestational diabetes: a 15-year follow-up study. Endocrine. 2017;58:228–35.
9. Lauenborg J, Mathiesen E, Hansen T, Glumer C, Jørgensen T, Borch-Johnsen K, et al. The prevalence of the metabolic syndrome in a Danish population of women with previous gestational diabetes mellitus is three-fold higher than in the general population. J Clin Endocrinol Metab. 2005;90:4004–10.
10. Garcia-Vargas L, Addison SS, Nistala R, Kurukulasuriya D, Sowers JR. Gestational diabetes and the offspring: implications in the development of the cardiorenal metabolic syndrome in offspring. Cardiorenal Med. 2012;2:134–42.
11. Farrar D, Simmonds M, Bryant M, Sheldon TA, Tuffnell D, Golder S, et al. Hyperglycaemia and risk of adverse perinatal outcomes: systematic review and meta-analysis. BMJ. 2016;354:i4694.
12. Farrar D, Simmonds M, Bryant M, Sheldon TA, Tuffnell D, Golder S, et al. Treatments for gestational diabetes: a systematic review and meta-analysis. BMJ Open. 2017;7:e015557.
13. Poolsup N, Suksomboon N, Amin M. Effect of treatment of gestational diabetes mellitus: a systematic review and meta-analysis. PLoS ONE. 2014;9:e92485.
14. 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.
15. Farrar D, Duley L, Dowswell T, Lawlor DA. Different strategies for diagnosing gestational diabetes to improve maternal and infant health. Cochrane Database Syst Rev. 2017;8:CD007122.
16. Carreiro M, Nogueira A, Ribeiro-Oliveira A. Controversies and advances in gestational diabetes—an update in the era of continuous glucose monitoring. J Clin Med. 2018. https://doi.org/10.3390/jcm7020011.
17. Hosseini E, Janghorbani M, Aminorroaya A. Incidence, risk factors, and pregnancy outcomes of gestational diabetes mellitus using one-step versus two-step diagnostic approaches: a population-based cohort study in Isfahan, Iran. Diabetes Res Clin Pract. 2018;140:288–94.
18. Landon MB, Rice MM, Varner MW, Casey BM, Reddy UM, Wapner RJ, et al. Mild gestational diabetes mellitus and long-term child health. Diabetes Care. 2015;38:445–52.
19. Landon MB. Is there a benefit to the treatment of mild gestational diabetes mellitus? Am J Obstet Gynecol. 2010;202:649–53.
20. Ohno MS, Sparks TN, Cheng YW, Caughey AB. Treating mild gestational diabetes mellitus: a cost-effectiveness analysis. Am J Obstet Gynecol. 2011;205(282):e1–7.
21. Rice MM, Landon MB, Units HDMFM, Health EKSNIoC. What we have learned about treating mild gestational diabetes mellitus. Semin Perinatol. 2016;40:298–302.
22. Diabetes IAo, Panel PSGC. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33:676–82.
23. Olagbuji BN, Atiba AS, Olofinbiyi BA, Akintayo AA, Awoleke JO, Ade-Ojo IP, et al. Prevalence of and risk factors for gestational diabetes using 1999, 2013 WHO and IADPSG criteria upon implementation of a universal one-step screening and diagnostic strategy in a sub-Saharan African population. Eur J Obstet Gynecol Reprod Biol. 2015;189:27–32.
24. Kanguru L, Bezawada N, Hussein J, Bell J. The burden of diabetes mellitus during pregnancy in low-and middle-income countries: a systematic review. Glob Health Action. 2014;7:23987.
25. Mayo K, Melamed N, Vandenberghe H, Berger H. The impact of adoption of the international association of diabetes in pregnancy study group criteria for the screening and diagnosis of gestational diabetes. Am J Obstet Gynecol. 2015;212(224):e1–9.
26. Fitria N, van Asselt AD, Postma MJ. Cost-effectiveness of controlling gestational diabetes mellitus: a systematic review. Eur J Health Econ. 2019;20:407–17.
27. Marchetti D, Carrozzino D, Fraticelli F, Fulcheri M, Vitacolonna E. Quality of life in women with gestational diabetes mellitus: a systematic review. J Diabetes Res. 2017;2017:7058082.
28. Kalra B, Gupta Y, Baruah MP. Renaming gestational diabetes mellitus: a psychosocial argument. Indian J Endocrinol Metab. 2013;17:S593–5.
29. Kalra S, Baruah MP, Gupta Y, Kalra B. Gestational diabetes: an onomastic opportunity. Lancet Diabetes Endocrinol. 2013;1:91.
30. Poncet B, Touzet S, Rocher L, Berland M, Orgiazzi J, Colin C. Cost-effectiveness analysis of gestational diabetes mellitus screening in France. Eur J Obstet Gynecol Reprod Biol. 2002;103:122–9.
31. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. World Health Organization report 2013. http://apps.who.int/iris/bitstream/handle/10665/85975/WHO_NMH_MND_13.2_eng.pdf;jsessionid=F503D782279A637B1B1D7AC70CC88404?sequence=1.
32. Lohse N, Marseille E, Kahn JG. Development of a model to assess the cost-effectiveness of gestational diabetes mellitus screening and lifestyle change for the prevention of type 2 diabetes mellitus. Int J Gynaecol Obstet. 2011;115:S20–5.
33. Round J, Jacklin P, Fraser R, Hughes R, Mugglestone M, Holt R. Screening for gestational diabetes mellitus: cost-utility of different screening strategies based on a woman's individual risk of disease. Diabetologia. 2011;54:256–63.
34. Oostdam N, Bosmans J, Wouters MG, Eekhoff EM, van Mechelen W, van Poppel MN. Cost-effectiveness of an exercise program during pregnancy to prevent gestational diabetes: results of an economic evaluation alongside a randomised controlled trial. BMC Pregnancy Childbirth. 2012;12:64.
35. Farrar D, Simmonds M, Griffin S, Duarte A, Lawlor DA, Sculpher M, et al. The identification and treatment of women with hyperglycaemia in pregnancy: an analysis of individual participant data, systematic reviews,

meta-analyses and an economic evaluation. Health Technol Assess. 2016;20:1–348.
36. Kolu P, Raitanen J, Puhkala J, Tuominen P, Husu P, Luoto R. Effectiveness and cost-effectiveness of a cluster-randomized prenatal lifestyle counseling trial: a seven-year follow-up. PLoS ONE. 2016;11:e0167759.
37. Moss JR, Crowther CA, Hiller JE, Willson KJ, Robinson JS. Costs and consequences of treatment for mild gestational diabetes mellitus—evaluation from the ACHOIS randomised trial. BMC Pregnancy Childbirth. 2007;7:27.
38. O'Dea A, Infanti JJ, Gillespie P, Tummon O, Fanous S, Glynn LG, et al. 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. Trials. 2014;15:27.
39. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2005.
40. Weile LK, Kahn JG, Marseille E, Jensen DM, Damm P, Lohse N. Global cost-effectiveness of GDM screening and management: current knowledge and future needs. Best Pract Res Clin Obstet Gynaecol. 2015;29:206–24.
41. https://www.buckeyehealthplan.com/content/dam/centene/Buckeye/medicaid/pdfs/ACOG-Guidelines-for-Perinatal-Care.pdf.
42. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG, CONSORT Group ft. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA. 2010;2012(308):2594–604.
43. Gestational Diabetes. Clinical, management guildline. http://aegleclinic.com/wp-content/uploads/2015/05/Gestational-Diabetes-ACOG-2013.pdf.
44. Standards of Medical Care in Diabetes—2016. Diabetes Care. 2016;39:S4–5.
45. Montazeri A, Goshtasebi A, Vahdaninia M, Gandek B. The Short Form Health Survey (SF-36): translation and validation study of the Iranian version. Qual Life Res. 2005;14:875–82.
46. Montazeri A, Vahdaninia M, Mousavi SJ, Omidvari S. The Iranian version of 12-item Short Form Health Survey (SF-12): factor structure, internal consistency and construct validity. BMC Public Health. 2009;9:341.
47. Darvishpoor Kakhki A, Abed Saeedi Z. Health-related quality of life of diabetic patients in Tehran. Int J Endocrinol Metab. 2013;11:e7945.
48. Kiadaliri AA, Najafi B, Mirmalek-Sani M. Quality of life in people with diabetes: a systematic review of studies in Iran. J Diabetes Metab Disord. 2013;12:54.
49. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 173: Fetal Macrosomia. Obstet Gynecol. 2016;128:e195–209.
50. Boyle A, Reddy U, Landy H, Huang C, Driggers R, Laughon S. Primary cesarean delivery in the United States. Obstet Gynecol. 2013;122:33–40.
51. Aviram A, Salzer L, Hiersch L, Ashwal E, Golan G, Pardo J, et al. Association of isolated polyhydramnios at or beyond 34 weeks of gestation and pregnancy outcome. Obstet Gynecol. 2015;125:825–32.
52. Kim BJ, Romero R, Lee SM, Park C-W, Park JS, Jun JK, et al. Clinical significance of oligohydramnios in patients with preterm labor and intact membranes. J Perinat Med. 2011;39:131–6.
53. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 24: Fetal Growth Restriction. Obstet Gynecol. 2013;133:e97–108.
54. Gardosi J, Clausson B, Francis A. The value of customised centiles in assessing perinatal mortality risk associated with parity and maternal size. BJOG. 2009;116:1356–63.
55. Sweet CB, Grayson S, Polak M. Management strategies for neonatal hypoglycemia. J Pediatr Pharmacol Ther. 2013;18:199–208.
56. Cornblath M, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. Pediatrics. 2000;105:1141–5.
57. Maisels MJ, Bhutani VK, Bogen D, Newman TB, Stark AR, Watchko JF. Hyperbilirubinemia in the newborn infant ≥ 35 weeks' gestation: an update with clarifications. Pediatrics. 2009;124:1193–8.
58. Mustafa R, Ahmed S, Gupta A, Venuto RC. A comprehensive review of hypertension in pregnancy. J Pregnancy. 2012;2012:105918.
59. https://www.acog.org/~/media/Task%20Force%20and%20Work%20Group%20Reports/public/HypertensioninPregnancy.pdf.
60. Committee on Practice Bulletins—Obstetrics T. Practice bulletin no. 130: prediction and prevention of preterm birth. Obstet Gynecol. 2012;120:964–73.
61. Chauhan SP, Gherman R, Hendrix NW, Bingham JM, Hayes E. Shoulder dystocia: comparison of the ACOG practice bulletin with another national guideline. Am J Perinatol. 2010;27:129–36.
62. Dean RB, Dixon W. Simplified statistics for small numbers of observations. Anal Chem. 1951;23:636–8.
63. Lin L, Sherman PD. Cleaning data the Chauvenet way. In: The Proceedings of the SouthEast SAS Users Group, SESUG Proceedings, Paper SA11. 2007.
64. Basu A, Rathouz PJ. Estimating marginal and incremental effects on health outcomes using flexible link and variance function models. Biostatistics. 2005;6:93–109.
65. Briggs AH. A Bayesian approach to stochastic cost-effectiveness analysis. Health Econ. 1999;8(3):257–61.
66. Briggs A, Bousquet J, Wallace M, Busse WW, Clark T, Pedersen S, et al. Cost-effectiveness of asthma control: an economic appraisal of the GOAL study. Allergy. 2006;61:531–6.
67. Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ. 1998;7:723–40.
68. Schaefer AJ, Bailey MD, Shechter SM, Roberts MS. Modeling medical treatment using Markov decision processes. In: Brandeau ML, Sainfort F, Pierskalla WP, editors. Operations research and health care. Springer: Boston; 2005. p. 593–612.
69. Komorowski M, Raffa J. Markov models and cost effectiveness analysis: applications in medical research. In: Secondary analysis of electronic health records. Cham: Springer; 2016. p. 351–67.

Publisher's Note