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

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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.

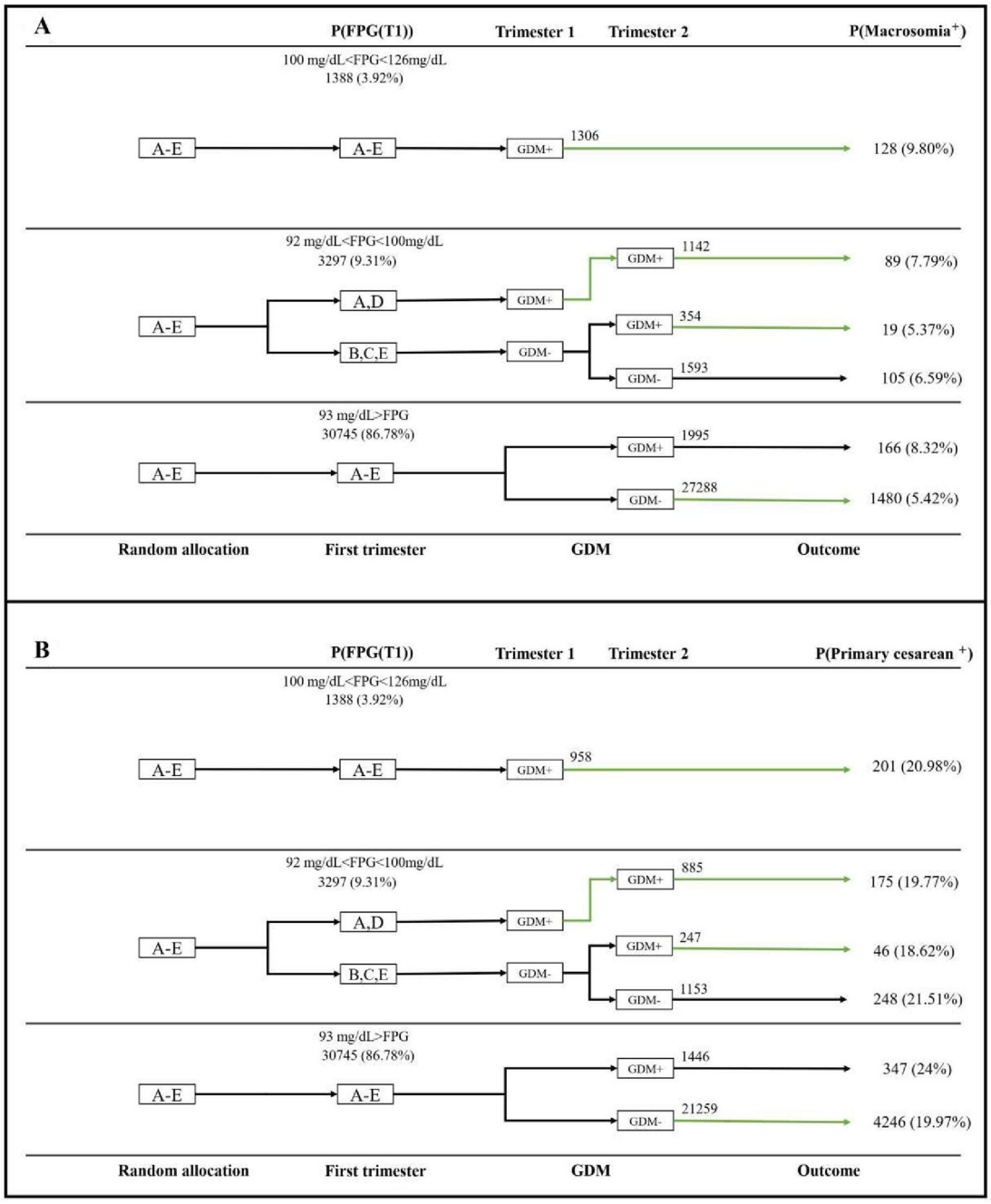

Figure 1 The participants' flow diagrams for macrosomia (A) and primary cesarean section (B) based on their assigned protocol, FPG level in the first trimester, and GDM diagnosis status. The green arrows indicate treatment received. FPG, fasting-plasma-glucose; GDM, gestational diabetes mellitus.

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

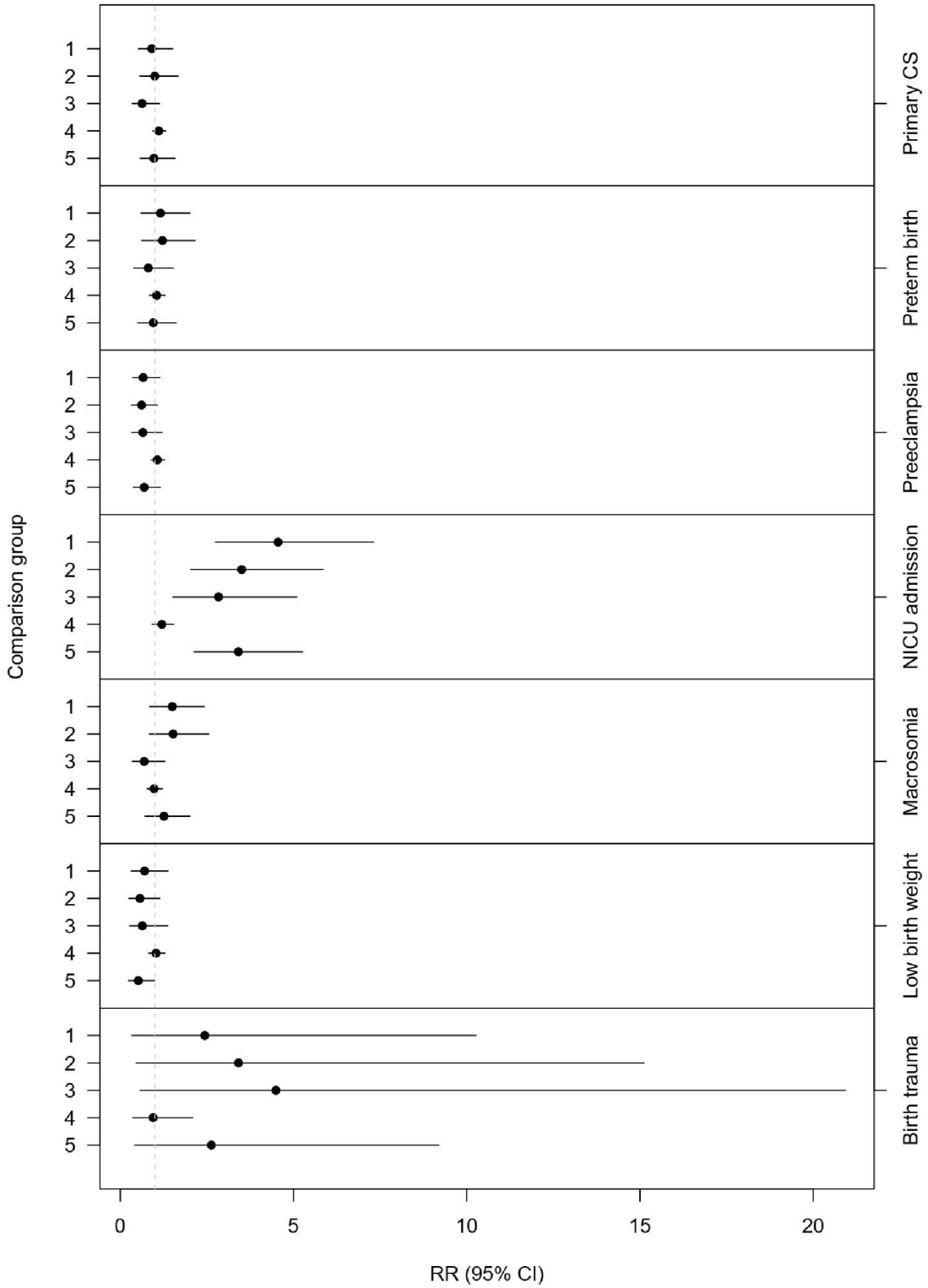

Figure 2 The adjusted risk ratio (RR) of groups in comparison with reference group 6, the participants with FPG<92 mg/dL in trimester 1, who were not diagnosed as GDM-positive. FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; NICU, neonatal intensive care unit.

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.

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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.

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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.