Original Article

Early Postpartum Glucose Intolerance, Metabolic Syndrome and Gestational Diabetes Mellitus Determinants after Assisted Conception: A Prospective Cohort Study

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Abstract

Background: This study aimed to determine the prevalence of postpartum metabolic syndrome (MetS), glucose intolerance, and the determinants, 6-12 weeks postpartum in women with assisted reproduction technology conception gestational diabetes mellitus diagnosis (ART-GDM) compared to women with spontaneous conception and GDM diagnosis (SC-GDM).

Materials and Methods: In this prospective cohort study, two groups consisting of 62 ART-GDM and 64 SC-GDM singleton pregnant women were followed 6-12 weeks after delivery for postpartum MetS. Fasting glucose, 75-g 2-h OGTT, and lipid profile were assessed. Waist and hip circumference, and systolic and diastolic blood pressures (BP) were measured at postpartum. Clinical, paraclinical, and obstetric data were recorded from registry offices. The prevalence of MetS and glucose intolerance were determined. Predictors of MetS and glucose intolerance were evaluated by logistic regression.

Results: The prevalence of postpartum MetS was 20.8% in ART-GDM women and 10.9% in SC-GDM (P=0.123). Mean postpartum BMI and systolic BP were significantly higher in the ART-GDM group (P=0.016 and P=0.027 respectively). Adverse pregnancy outcomes were significantly higher in the ART-GDM group. Postpartum glucose intolerance prevalence did not vary significantly between the groups. Family history of diabetes was a predictive factor for postpartum MetS and glucose intolerance 6-12 weeks after delivery.

Conclusion: Early postpartum MetS and glucose intolerance prevalence after assisted conception did not vary significantly; however, postpartum body mass index (BMI) and systolic BP were significantly higher in the ART-GDM group. Lifestyle modification programs and long-term health care of ART women with GDM diagnosis can be recommended. Further studies with larger sample size and longer follow-up are necessary to verify our findings.

Keywords: Assisted Reproduction Technology, Gestational Diabetes Mellitus, Glucose Intolerance, Metabolic Syndrome, Postpartum Period

Introduction

Gestational diabetes mellitus (GDM) recognized as any degree of glucose intolerance with onset or first recognition during the second or third trimester of pregnancy, is one of the most prevalent metabolic disorders (1). The evident rise of GDM incidence could be due to advanced maternal age in pregnancy, application of the new diagnostic criteria with lower threshold and single abnormal value, or increasing trend of obesity and unhealthy diet in the general population (1, 2).

The metabolic perimeter of GDM in young women may persist in type 2 DM and the form of metabolic syn-

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drome (MetS) (3). There is some conflicting evidence on the relationship between GDM and the early increased occurrence of MetS the in some mothers and their children (3-5). MetS and GDM have common clinical features (6) and the prevalence of MetS shows 3- to 4- fold increase in women with a history of GDM (7). Previous data has shown that MetS features such as glucose intolerance, low high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia, hypertension, and central obesity, are commonly observed in women post GDM (8). These conditions could be associated with hypertension, dyslipidemia, and cardiovascular disease (9, 10). Considering the increased risk of the above-mentioned complications in GDM and MetS and their interconnected nature, it is worth identifying risk factors of early postpartum MetS in women with GDM diagnosis.

Moreover, recent evidence suggested that the risk of GDM and the need for insulin therapy during pregnancy increases in pregnancy induced by assisted reproductive technology (ART) (11, 12). Some mechanisms that might explain this increased risk in the infertile population include higher rates of advanced maternal age and obesity, infertility etiology as well as the treatment procedures, drugs, and epigenetic modifications (13, 14). As a first study, it would be interesting to investigate whether the risk of early postpartum MetS increases in this population.

Based on the importance of the topic, this study was designed to determine the relationship between GDM and early postpartum MetS. The main goal of the study was to compare the prevalence of MetS and glucose intolerance at 6-12 weeks postpartum, between spontaneous and ART pregnancies. The secondary aims were to determine the contributing risk factors in both populations.

Materials and Methods

Study design and settings

In this prospective cohort study, the ART and spontaneous pregnancies populations including all singleton pregnant women diagnosed with GDM at 24-28 weeks of pregnancy, were followed at Royan Institute (Endocrinology and Female Infertility Clinic) and Arash women's Hospital (maternity teaching hospital in Tehran) respectively, between 2015 and 2017. This research project was approved by the institutional review board and Ethics Committee of Iran University of Medical Sciences, and Royan Institute, Iran (IR.ACECR.ROYAN.REC.1395.2). All participants signed an informed consent after ensuring confidentiality and that the data will be reported anonymously. The inclusion criteria were having GDM in the second or third trimester confirmed by 75-g OGTT (one-step glucose tolerance test) and availability of clinical and medical records.

Women with pre-gestational diabetes type 1 or 2, multiple pregnancies and chronic diseases such as hypertension, cardiovascular diseases, untreated thyroid disease, liver diseases, renal diseases, autoimmune diseases, and connective tissue disorders as well as those who were tak-

ing corticosteroids were excluded.

Two groups of GDM mothers (SC-GDM and ART-GDM) were followed during pregnancy, delivery and 6-12 weeks postpartum for assessment of adverse maternal, fetal and neonatal outcomes. In addition, the occurrence of MetS and glucose intolerance at postpartum was assessed.

Biochemical and clinical assessment during pregnancy

To distinguish pre-gestational diabetes, all pregnant women were evaluated during the first trimester by determination of fasting blood sugar (FBS) and the results were recorded in the hospital registry office. Gestational diabetes was approved by OGTT using 75 g oral glucose at 24-28 weeks of gestation, based on the American Diabetes Association/International Association of the Diabetes and Pregnancy Study Groups (ADA/IAPDSG) criteria (15).

After 8-12 hour fasting, blood samples were collected from all patients in the second and third trimesters of pregnancies. FBS (FBS 2nd trimester), insulin (insulin 2nd trimester), hemoglobin A1C (HbA1c 2nd trimester), and lipid profile were measured in the 2nd trimester of pregnancy. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated based on the formula. HOMA-IR was calculated using the following formula: Fasting insulin (U/mL)×fasting glucose (mg/dL)/405

FBS and HbA1c were rechecked in the 3rd trimester of pregnancy.

Data collection

A trained physician recorded socio-demographic characteristics, medical and obstetric history, potential risk factors of GDM and MetS, and details of GDM management and delivery, as well as maternal and neonatal outcomes. Postpartum questionnaires were also completed at 6-12 weeks postpartum. Clinical data were collected from hospital records.

Postpartum biochemical and clinical assessment

Postpartum FBS (PP FBS) determination, 75-g 2-h OGTT (PP GTT2 h), and lipid profile tests (in terms of PP cholesterol, PP triglycerides, PP LDL-cholesterol, PP HDL-cholesterol, and PP VLDL-cholesterol) were performed at 6-12 weeks after delivery. Postpartum prediabetes [impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)], and diabetes were defined according to the ADA criteria (16). Weight (PP weight), height (PP height), waist circumference (PP waist), and blood pressure (PP systolic and diastolic BP) were measured at 6-12 weeks postpartum. The waist circumference was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest using a stretch-resistant tape that provides a constant 100 g tension. BP was checked two times at a 30 minutes interval. The height and weight of each subject were measured while wearing light clothing and barefoot to calculate

body mass index (BMI). The MetS was defined by two criteria including National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) and International Diabetes Federation (IDF). According to the NCEP ATP III criteria, MetS was diagnosed if any three of five of the following disorders was observed: waist circumference ≥88 cm, triglycerides ≥150 mg/dl, HDL-cholesterol <50 mg/dl, FPG ≥100 mg/ dl, or BP ≥130/85 mmHg (17). The MetS was recognized based on the IDF definition: central obesity (waist circumference >88 cm) plus any two of the four above-noted factors (18).

Statistical analysis

The primary aim was comparing early postpartum MetS and glucose intolerance prevalence between the study groups and the secondary aim was the evaluation of potential risk factors of MetS and glucose intolerance in the study population. Data were analyzed by the Stata software (Version 13.0, STATA Corp, College Station, Texas). The P<0.05 was considered a statistically significant level. The normal quantity variables are presented as mean ± standard deviation (SD). Chi-square test was applied for making a comparison with respect to the categorical variables between the groups. Student's t test and Mann-Whitney test were applied when appropriate. The multivariable logistic regression analysis was used to adjust for women's age and

BMI for detection of predictive variables for early postpartum MetS and glucose intolerance in the whole study population (n=126). The covariate variables were FBS 2nd trimester, FBS 3rd trimester, HbA1c 3rd trimester, family history of DM, and prior GDM that were considered in the regression model.

The sample size estimation was made by using the NCSS software (Number Cruncher Statistical System software package 2007, Kaysville, UT, USA). According to the study by Vilmi-Kerälä et al. (19), the difference of 21.2% in the prevalence of MetS was considered between case and control subjects and a sample size of 64 subjects in each group would support us to evaluate early postpartum MetS prevalence in each group with a power of 80% and a type I error of 0.05.

Results

According to the determined sample size, 64 eligible patients in each study group were followed up prospectively in their pregnancy duration. Two patients in the ART-GDM group were lost to follow-up due to withdrawal the participation, this rate of losing subjects (1.5%) did not decrease the power of this study significantly. 126 women with GDM pregnancy including 62 ART (ART-GDM) and 64 spontaneous conceptions (SC-GDM) were followed for the incidences of postpartum glucose intolerance and MetS at 6-12 weeks after delivery (Fig.1).
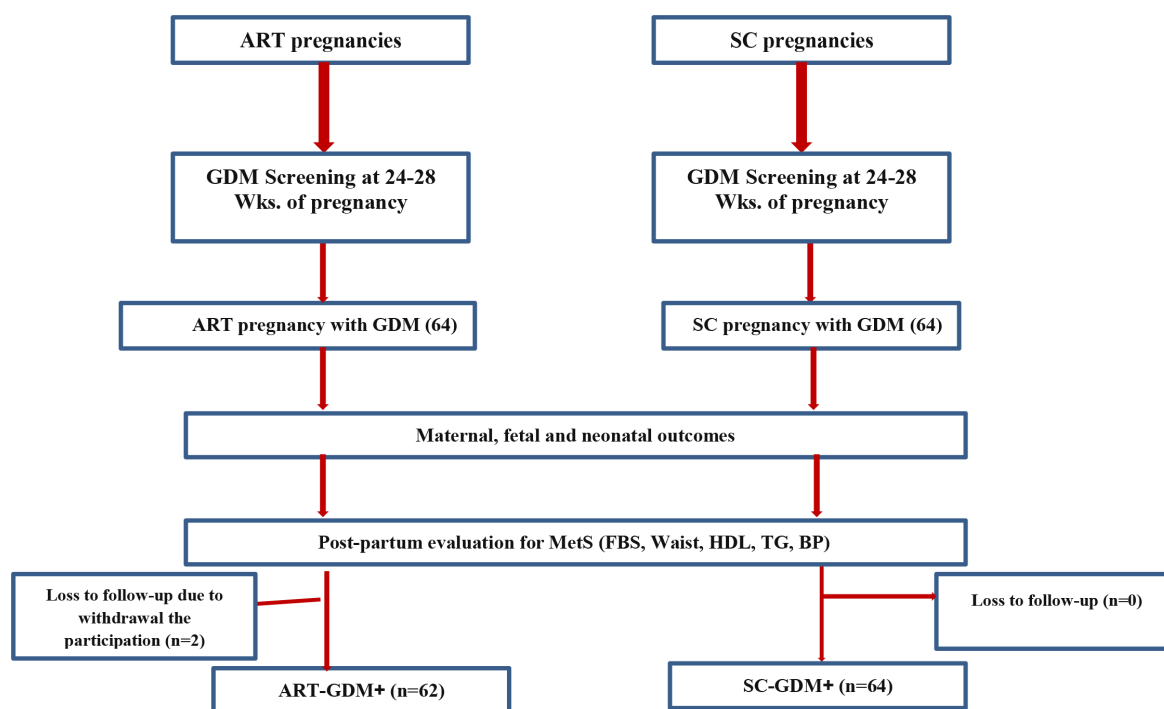
Fig.1: Flow diagram of the study, ending in follow up assessments at postpartum. ART; Assisted reproductive technology, GDM; Gestational diabetes mellitus, SC; Spontaneous conception, FBS; Fasting blood sugar, HDL; High-density lipoprotein, TG; Triglyceride, and BP; Blood pressure.

Table 1 summarizes the baseline characteristics of the women who participated in this study. There were no significant differences in the mean of maternal age, pre-pregnancy BMI, or systolic and diastolic BP between the two groups (P>0.05). In addition, the rates of first-degree family history of diabetes mellitus and hypertension, as well as most history of adverse outcomes in prior pregnancy, were not significantly different between the two groups. However, the rates of nulliparity and prior history of a macrocosmic infant were significantly different between the two groups (P=0.001 and P=0.025). Importantly, the results of biochemical assessments showed that the mean of second trimester insulin (P=0.041) and HOMA-IR (P=0.027), as well as third trimester FBS (P=0.008), were significantly higher in the ART-GDM group compared to the SC-GDM group.

The comparison of maternal, fetal, and neonatal outcomes between the SC-GDM and ART-GDM groups is presented in Table 2. The means of neonatal weight and gestational age at delivery were significantly lower in the ART-GDM group (P=0.003). Maternal outcomes showed that the rates of pregnancy-induced hypertension (PIH) and preeclampsia were significantly higher in the ART-GDM group (P=0.013 and P=0.031). In addition, the incidence of fetal and neonatal complications in terms of preterm birth, small for gestational age (SGA), neonatal intensive care unit (NICU) admission, and neonatal hypoglycemia, was significantly higher in the ART-GDM group (P=0.008, P=0.008, P=0.01, and P=0.04, respectively). Other adverse pregnancy outcomes did not show any significant difference between the two groups.

Table 1: Comparison of clinical and biochemical characteristics before and during pregnancy between SC-GDM and ART-GDM groups referred for postpartum examination

Variables	ART-GDM+ (n=62)	SC-GDM+ (n=64)	P value
Clinical			
Maternal age (Y)	31.2 ± 4.9	32.3 ± 4.9	0.234
Parity (=0)	54 (87.1)	25 (39.1)	0.001
Pre-pregnancy BMI (kg/m^2)	27.3 ± 3.8	26.0 ± 4.7	0.112
Family history of DM	31 (50)	24 (37.5)	0.157
Family history of HTN	29 (46.8)	28 (43.8)	0.733
Systolic blood pressure (mmHg)	107.9 ± 11.4	106.7 ± 10.5	0.544
Diastolic blood pressure (mmHg)	66.9 ± 7.8	68.4 ± 8.6	0.334
Prior history of GDM	3 (4.8)	9 (14.1)	0.078
Prior history of pre-eclampsia,	2 (3.2)	1 (1.6)	0.540
Prior history of LBW	1 (1.6)	6 (9.4)	0.057
Prior history of preterm birth	2 (3.2)	5 (7.8)	0.261
Prior history of macrosomic infant	0 (0)	5 (7.8)	0.025
Prior history of multiple pregnancies	3 (4.8)	4 (6.3)	0.730
Prior history of abortion	42 (67.7)	47 (74.6)	0.397
Prior history of neonatal death	2 (3.2)	1 (1.56)	0.540
Prior history of oligohydramnious	0 (0)	2 (3.1)	0.161
Biochemical			
FBS 2nd trimester (mg/dl)*	87.9 ± 8.4	84.2 ± 12.2	0.053
HbA1c 2nd trimester (mg/dl)	5.0 ± 0.6	4.9 ± 0.6	0.296
TG 2nd trimester (mg/dl)*	191.4 ± 60.9	202.6 ± 54.0	0.294
Cholesterol 2nd trimester (mg/dl)	204.6 ± 39.3	225.4 ± 40.0	0.005
HDL 2nd trimester (mg/dl)	63.6 ± 13.2	65.8 ± 12.8	0.367
LDL 2nd trimester (mg/dl)	103.1 ± 35.4	119.1 ± 32.8	0.012
VLDL 2nd trimester (mg/dl)	37.8 ± 10.8	40.5 ± 10.8	0.177
Insulin 2nd trimester (mg/dl)*	14.4 ± 9.1	11.3 ± 5.7	0.041
HOMA-IR 2nd trimester	3.2 ± 2.1	2.4 ± 1.4	0.027
FBS 3rd trimester (mg/dl)*	88.5 ± 9.5	83.1 ± 10.8	0.008
HbA1c 3rd trimester (mg/dl)	5.1 ± 0.6	5.0 ± 0.7	0.863

The quantitative and qualitative variables are presented as mean ± SD or n (%), respectively. The normal quantitative variables and the qualitative variables were compared respectively by Student's t and chi-square tests between groups. *; These quantitative variables had non-normal distribution and compared between groups by Mann-Whitney test, ART; Assisted reproductive technology, GDM; Gestational diabetes mellitus, SC; Spontaneous conception, HTN; Hypertension, HDL; High-density lipoprotein, TG; Triglyceride, LDL; Low-density lipoprotein, VLDL; Very-low-density lipoprotein, HOMA-IR; Homeostatic model assessment of insulin resistance, FBS; Fasting blood sugar, HbA1C; Hemoglobin A1c, and LBW; Low birth weight.

Table 2: Comparison of maternal, fetal and neonatal outcomes between SC-GDM and ART-GDM groups

Variables	ART-GDM+ (n=62)	SC-GDM+ (n=64)	P value
Neonatal sex, Male	25 (40.3)	36 (56.3)	0.074
Neonatal height (cm)	49.3 ± 3.0	50.1 ± 1.5	0.084
Neonatal weight (kg)	3096.9 ± 516.8	3339.4 ± 354.7	0.003
Neonatal head circumference (cm)	34.6 ± 1.7	35.0 ± 1.3	0.121
Neonatal chest (cm)	32.9 ± 2.0	33.5 ± 1.3	0.119
Gestational age at delivery (weeks)	37.8 ± 0.2	38.5 ± 0.1	0.003
Gestational weight gain	11.3 ± 4.9	11.5 ± 5.6	0.825
Delivery BMI (kg/m^2)	31.7 ± 4.1	30.5 ± 4.4	0.126
Maternal outcomes			
PIH	10 (16.1)	2 (3.1)	0.013
Preeclampsia	7 (11.3)	1 (1.6)	0.031
Antepartum hemorrhage	9 (14.5)	3 (4.7)	0.060
Emergency cesarean	25 (40.3)	16 (25.0)	0.066
PROM	6 (9.7)	1 (1.6)	0.060
Oligohydramnious	6 (9.7)	2 (3.1)	0.132
Polyhydramnious	3 (4.8)	3 (4.7)	0.968
Fetal death	1 (1.6)	0 (0)	0.308
Fetal and neonatal outcomes			
Preterm birth	9 (14.5)	1 (1.6)	0.008
IUGR	6 (9.7)	2 (3.1)	0.125
SGA	9 (14.5)	1 (1.6)	0.008
LGA	2 (3.2)	5 (7.8)	0.261
Macrosomia	1 (1.6)	4 (6.3)	0.189
LBW			
NICU admission	12 (19.7)	3 (4.7)	0.010
Respiratory distress	7 (11.5)	4 (6.3)	0.303
Neonatal hypoglycemia	8 (13.1)	2 (3.1)	0.040
Perinatal mortality	1 (1.6)	0 (0)	0.308
Apgar<7 at 5 minutes	2 (3.2)	1 (1.6)	0.559
Birth trauma	0 (0)	2 (3.1)	0.496

The quantitative and qualitative variables are presented as mean ± SD or n (%), respectively. All of the quantitative variables had normal distribution and compared between groups by student t test. The qualitative variables were compared between groups by chi-square test. ART; Assisted reproductive technology, BMI; Body mass index, GDM; Gestational diabetes mellitus, SC; Spontaneous conception, PIH; Pregnancy induced hypertension, PROM; Premature rupture of membranes, IUGR; Intrauterine growth restriction, SGA; Small for gestational age, LGA; Large for gestational age, LBW; Low birth weight, and NICU; Neonatal intensive care unit.

Table 3 compares the clinical and laboratory characteristics within 6-12 weeks after delivery between the SC-GDM and ART-GDM groups. The results of postpartum metabolic parameters revealed no significant differences between the two groups except for mean BMI and systolic BP which were higher in the ART-GDM group (P=0.016 and P=0.027). The parameters included in the diagnostic criteria of MetS, fasting plasma glucose, waist circumference, triglyceride, and HDL cholesterol were not significantly different between the ART-GDM and SC-GDM groups except for the systolic BP. Additionally, and the 2-hours glucose after 75-g GTT was not significantly different between the ART-GDM and SC-GDM women. The frequency of MetS using the NCEP ATP III criterion was 10.9 and 20.8% in the SC-GDM and ART-GDM groups, respectively. The univariate analysis presented that the odds ratio of postpartum MetS using NCEP ATP III Criteria did not vary significantly between ART and spontaneous GDM pregnancies after adjustment for age, and BMI [aOR; 1.88(0.68-5.22)]. These values for MetS obtained through the IDF criterion were 17.2 and 19.4, respectively. However, the rate of postpartum glucose abnormalities including pre-diabetes [IFG and IGT], and diabetes did not show any significant differences between the two groups.

Table 3: Comparison of postpartum parameters between SC-GDM and ART-GDM groups

Variables	ART-GDM+ (n=62)	SC-GDM+ (n=64)	P value
PP Weight (kg)	74.2 ± 13.1	69.6 ± 12.7	0.052
PP BMI (kg/m^2)	28.8 ± 4.4	26.7 ± 4.5	0.016
PP Waist (cm)	92.6 ± 9.8	92.2 ± 10.3	0.734
PP Hip (cm)	107.9 ± 1.3	105.5 ± 1.1	0.167
PP Systolic BP (mmHg)*	110.5 ± 10.2	104.9 ± 16.3	0.027
PP Diastolic BP (mmHg)	69.5 ± 8.1	68.9 ± 8.3	0.683
PP FBS (mg/dl)*	94.6 ± 10.7	92.2 ± 13.4	0.261
PP GTT2h (mg/dl)	104.4 ± 3.9	105.0 ± 3.2	0.902
PP TG (mg/dl)*	114.2 ± 91.9	116.6 ± 58.2	0.827
PP Cholesterol (mg/dl)	178.7 ± 31.4	186.7 ± 35.8	0.185
PP HDL (mg/dl)	55.1 ± 11.5	55.3 ± 10.8	0.946
PP LDL (mg/dl)	100.9 ± 27.8	107.5 ± 26.8	0.179
PP VLDL (mg/dl)	21.6 ± 11.9	22.6 ± 10.9	0.657
PP metabolic syndrome	13 (20.8)	7 (10.9)	0.123
PP GTT 75 g result Normal FBS Pre-diabetes (IGT or IFG) DM	 45 (73.8) 14 (23.0) 2 (3.3)	 51 (79.7) 11 (17.2) 2 (3.1)	0.718
PP GTT 75 g result Normal FBS Glucose intolerance (pre-diabetes+DM)	 45 (73.8) 16 (26.2)	 51 (79.7) 13 (20.3)	0.433
MetS using NCEP ATP III criteria	13 (20.8)	7 (10.9)	0.123
MetS using IDF Criteria	12 (19.4)	11 (17.2)	0.753

The quantitative and qualitative variables are presented as mean ± SD or n (%), respectively. *; These quantitative variables had non-normal distribution and compared between groups by Mann-Whitney test. The normal quantitative variables and the qualitative variables were compared respectively by Student's t and chi-square tests between groups. ART; Assisted reproductive technology, BMI; Body mass index, BP; Blood pressure, FBS; Fasting blood sugar, GDM; Gestational diabetes mellitus, GTT; Glucose tolerance test, HDL; High-density lipoprotein, TG; Triglyceride, LDL; Low-density lipoprotein, VLDL; Very-low-density lipoprotein, DM; Diabetes mellitus, NCEP ATP III; The National Cholesterol Education Program Adult Treatment Panel III, and IDF; International diabetes federation.

Table 4 summarizes the results of the univariate analysis of the association between clinical and biochemical parameters with postpartum glucose intolerance and MetS in total population after adjusting for group. The results demonstrated a significant association between second trimester FBS (OR=1.06, 95% CI: 1.01-1.10, P=0.009), third trimester FBS (OR=1.10, 95% CI: 1.04-1.16, P=0.001), third trimester HbA1c (OR=3.04; 95% CI: 1.02-7.65, P=0.019), family history of diabetes in first relatives (OR=2.54; 95% CI: 1.07-6.01, P=0.034) and prior GDM (OR=4.60, 95% CI: 1.29-16.3, P=0.018) with postpartum glucose intolerance in GDM population. Also, there was a significant association between postpartum MetS with increased pre-pregnancy BMI (OR=1.20, 95% CI: 1.10-1.32, P=0.004), 2nd trimester FBS (OR=1.06; 95% CI: 1.01-1.11, P=0.011), insulin (OR=1.07; 95% CI: 1.01-1.14, P=0.040), and HOMA-IR (OR=1.40; 95% CI: 1.02-1.78, P=0.034), but decreased HDL cholesterol (OR=0.96; 95% CI: 0.92-0.99, P=0.040).

Table 4: Association of clinical and biochemical parameters and postpartum glucose intolerance and metabolic syndrome in GDM population

Variables	PP glucose intolerance (pre-diabetes/diabetes)		PP metabolic syndrome	
	OR* (CI 95%)	P value	OR* (CI 95%)	P value
Age (Y)	1.03 (0.95-1.12)	0.462	1.0 (0.9-1.1)	0.871
Pre-pregnancy BMI (kg/m^2)	1.04 (0.94-1.14)	0.448	1.20 (1.1-1.32)	0.004
2nd trimester systolic BP (mmHg)	1.00 (0.97-1.04)	0.839	1.0 (0.9-1.1)	0.174
2nd trimester diastolic BP (mmHg)	1.03 (0.98-1.09)	0.187	1.0 (0.9-1.1)	0.696
2nd trimester FBS (mg/dl)	1.06 (1.01-1.10)	0.009	1.06 (1.01-1.11)	0.011
2nd trimester HbA1c (mg/dl)	1.34 (0.69-2.57)	0.387	1.30 (0.6-2.8)	0.535
2nd trimester TG (mg/dl)	1.00 (0.99-1.01)	0.781	1.01 (1.001-1.02)	0.016
2nd trimester cholesterol (mg/dl)	0.99 (0.98-1.01)	0.097	1.0 (0.9-1.0)	0.167
2nd trimester HDL, (mg/dl)	0.98 (0.94-1.01)	0.213	0.96 (0.92-0.99)	0.040
2nd trimester LDL (mg/dl)	0.99 (0.97-1.00)	0.117	0.9 (0.8-1.1)	0.122
2nd VLDL (mg/dl)	1.00 (0.97-1.05)	0.662	1.04 (1.0-1.1)	0.074
2nd Insulin (mg/dl)	1.06 (0.99-1.15)	0.083	1.07 (1.01-1.14)	0.040
2nd trimester HOMA-IR	1.25 (0.96-1.62)	0.091	1.40 (1.02-1.78)	0.034
3rd trimester FBS (mg/dl)	1.10 (1.04-1.16)	0.001	1.04 (0.99-1.10)	0.105
3rd trimester HbA1c (mg/dl)	3.04 (1.02-7.65)	0.019	2.21 (0.81-5.94)	0.118
Family history of DM	2.54 (1.07-6.01)	0.034	2.19 (0.83-5.83)	0.113
Gravid	1.17 (0.48-2.80)	0.733	0.80 (0.33-2.41)	0.817
Parity	1.68 (0.61-4.61)	0.313	0.89 (0.20-2.22)	0.517
Prior GDM	4.60 (1.29-16.33)	0.018	0.40 (0.09-1.75)	0.223

*; These ORs were obtained by univariate, BMI; Body mass index, BP; Blood pressure, FBS; Fasting blood sugar, DM; Diabetes mellitus, HDL; High-density lipoprotein, TG; Triglyceride, LDL; Low-density lipoprotein, VLDL; Very-low-density lipoprotein, HbA1C; Hemoglobin A1c, PP; Postpartum, GDM; Gestational diabetes mellitus, OR; Odds ratio, and CI; Confidence interval.

Multivariable logistic regression presented potential risk factors for MetS and glucose intolerance, 6-12 weeks postpartum (Table 5). The results showed family history of diabetes (OR=3.37, 95% CI: 1.10-10.30, P=0.033) as a predictive factor for early postpartum MetS. In addition, family history of diabetes (OR=2.69, 95% CI: 1.17-6.15, P=0.019) and second trimester FBS (OR=1.06, 95% CI: 1.02-1.11, P=0.004) were independent predictors of glucose intolerance, 6-12 weeks after delivery.

Table 5: Multivariable logistic regression for detection of risk factors of early postpartum metabolic syndrome and glucose intolerance in the study population

Variables	Model 1 for PP Metabolic syndrome OR (95% CI)	P value	Model 2 for PP Glucose intoleranse OR* (95% CI)	P value
Family history of DM	3.37 (1.10-10.30)	0.033	2.69 (1.17-6.15)	0.019
Prior GDM	2.01 (0.40-9.98)	0.393	1.78 (0.52-6.15)	0.363
2nd trimester FBS	1.03 (0.97-1.09)	0.354	1.06 (1.02-1.11)	0.004

*; In this model the women age and BMI were adjusted, GDM; Gestational diabetes mellitus, PP; Postpartum, OR; Odds ratio, CI; Confidence interval, FBS; Fasting blood sugar, and DM; Diabetes mellitus.

Discussion

Metabolic syndrome (MetS) is comprised of a cluster of glucose intolerance, hypertension, and dyslipidemia with abdominal adiposity. It is a well-known predisposing factor for insulin resistance, diabetes mellitus, and cardiovascular diseases and is rising rapidly worldwide particularly in Western and Asian countries (8). A recent meta-analysis reported an increased (approximately 4-fold) risk of MetS after GDM, especially in Caucasian and obese mothers (20).

The present study compared the delivery and postpartum outcomes of GDM between ART and spontaneous pregnancies, with regard to the early MetS and glucose intolerance and their components. Our results showed a higher prevalence of MetS according to the NCEP criteria in the ART-GDM (20.8%) compared to the SC-GDM (10.9%) group. The prevalence of MetS was 19.4% in the GDM-ART and 17.2% in the SC-GDM based on the IDF criteria. Moreover, there was an 88% increase in the risk of developing MetS following ART pregnancy; nevertheless, in our study, the overall differences between the two groups were not statistically significant. Numerous studies have demonstrated higher rates of postpartum MetS in GDM women compared to the control group within 1-11 years postpartum, with large variations according to the length of follow-up (7.5-60% in GDM and 4.6-26% in non-GDM women) (1). However, few investigations have reported MetS at 6-12 weeks after gestational diabetes and there is no evidence in GDM following assisted conception. Recently, Nouhjah et al. (2) observed that the frequency of early postpartum MetS was 18.2% in women with GDM and 11.6% in controls by the NCEP criteria, and 21% in women with gestational diabetes and 15.1% in controls by the IDF criteria.

Current findings showed that the incidence of postpartum glucose abnormalities including pre-diabetes (23 vs. 17.2%) and diabetes (3.3 vs. 3.1%) was not significantly different between GDM after ART and spontaneous conception. In a recent meta-analysis, the prevalence of pre-diabetes and diabetes was respectively 3.9-50.9% and 2.8-58% in Asian women with gestational diabetes within 4 weeks to 15 years postpartum based on the length of follow-up (21). Considerable evidence proposed that beta-cell dysfunction likely contributes to an increase in the risk of glucose intolerance in the first year postpartum in GDM women (22-24).

Based on our data from the univariate analyses, FBS, HbA1c, a family history of diabetes in first relatives, and prior GDM were risk factors for postpartum glucose intolerance in the GDM population. Furthermore, pre-pregnancy BMI, and second trimester levels of FBS, insulin, HDL, and insulin resistance, were risk factors for postpartum MetS in the GDM population. Multivariate analyses confirmed family history of diabetes as an independent predictor of both glucose intolerance and MetS 6 to 12 weeks postpartum, in the GDM population. Additionally, second trimester FBS was another predictive factor of glucose intolerance 6-12 weeks after delivery. Numerous studies have indicated several putative factors for postpartum glucose intolerance including a family history of diabetes, elevated glucose level 120 minutes after a 75-g OGTT, elevated HbA1c levels during GDM diagnosis, perinatal complications, history of GDM, obesity, systolic or diastolic BP, maternal age, parity, and insulin or metformin therapy (25-29). Additionally, a history of GDM, pre-pregnancy overweight or obesity, pregnancy systolic BP, or requiring insulin or metformin were reported as predisposing factors that predict postpartum MetS in the GDM population (1, 19).

Though there were no significant differences in baseline characteristics such as mean maternal age, pre-pregnancy BMI, systolic and diastolic BP between the two groups, interestingly, our findings demonstrated that mean postpartum BMI and systolic BP were significantly higher in the ART-GDM group. In addition, higher incidence of nulliparity, 2nd trimester insulin levels, insulin resistance and 3rd trimester FBS levels were observed in the ART-GDM group. These findings may be related to ART characteristics and drugs especially progesterone using assisted conception. Previous investigations have indicated the association between progesterone administrations, history of the polycystic ovarian syndrome (PCOS), previous ovarian hyper-stimulation syndrome (OHSS) risk with the risk of GDM following ART cycles (11, 13).

Several investigations have reported increased BP, dyslipidemia, and higher fasting glucose levels in ART-conceived children (30-32). The current study showed the impact of mode of conception on delivery and postpartum outcomes of GDM pregnancies, especially in mothers. The pathophysiological mechanisms underlying the MetS are under the debate, but insulin resistance and visceral obesity are considered major causes. The presence of at

least three of five criteria of MetS is linked to an increased risk of heart disease, stroke, and diabetes.

However, it is not clear whether early postpartum raised BMI and BP on future MetS in ART mothers. Moreover, ART mothers were suffering from anxiety and stress, hormonal and environmental alternations, ex vivo manipulations, inflammatory changes, endothelial dysfunction, metabolic disturbance, and medical procedures during their pregnancies (33, 34). These conditions may influence long-term women's health and predispose occurrence of MetS and its components.

According to the present data, the ART-GDM group had a higher risk of maternal complications including PIH and preeclampsia, and adverse fetal and neonatal outcomes such as preterm birth, SGA, NICU admission, and neonatal hypoglycemia, compared to the SC-GDM group. Also, a shorter duration of gestation and a lower mean neonatal weight were observed in the ART-GDM group. It seems that GDM following ART conception increased the risk of undesirable and adverse obstetric and perinatal outcomes compared with SC-GDM. Data from a systematic review and meta-analysis showed that ART singleton pregnancies are associated with higher risks of pregnancy-related complications and adverse obstetric outcomes (35). Previous investigations indicated higher risks of adverse maternal and neonatal outcomes in the ART-GDM group compared to the SC-GDM group (11, 14, 36).

By the way, our study had several limitations that need to be addressed. First, this study lacks information regarding subfertility and infertility treatments during pregnancy. Second, we did not evaluate postpartum MetS and glucose intolerance in the general population. Further prospective studies with a larger sample size, particularly with inclusion a new group (natural pregnancy without GDM) and long-term follow-up are required to verify our results.

Conclusion

The present study indicated a higher rate of MetS in ART women with GDM at 6-12 weeks postpartum compared to SC women with GDM; however, the difference was not statistically significant. Postpartum BMI and systolic BP were significantly higher in the ART-GDM group. Further investigations with larger sample-size and longer follow-up are necessary to verify our findings. Lifestyle modification and long-term health care of ART women with GDM can be recommended.

Acknowledgments

Authors' Contributions

A.K., A.M.; The conception. A.K., H.R.B., M.E.Kh.; Design of the work. A.K., R.H., A.A., R.Ch.; The acquisition and analysis. A.K., A.A., F.M.; Interpretation of data. A.K., A.A., R.Ch.; Have drafted the manuscript and revised it. All authors have read and approved the manuscript.

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