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Prediction of adverse pregnancy outcomes by first trimester components of metabolic syndrome: a prospective longitudinal study

Running title: metabolic syndrome components and adverse pregnancy outcomes

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Abstract

Purpose: The present study aimed to identify the optimal cut-off values of each component of Metabolic Syndrome (MetS) in the first trimester of pregnancy for the prediction of adverse pregnancy outcomes.

Methods: 1076 pregnant women in the first trimester of gestation were recruited in this prospective longitudinal cohort study. A total of 993 pregnant women at 11-13 weeks' gestation who were followed up until the end of pregnancy, were included in the final analysis. The cut-off values of each component of MetS syndrome in the occurrence of adverse pregnancy outcomes including gestational diabetes (GDM), gestational hypertensive disorders, and preterm birth were obtained with Receiver Operating Characteristic (ROC) curve analysis using the Youden's index.

Results: Among the 993 pregnant women studied, the significant associations between the first trimester MetS components and adverse pregnancy outcomes were as follows: Triglyceride (TG), and Body Mass Index (BMI) with preterm birth; Mean Arterial Pressure (MAP), TG and High Density Lipoprotein-Cholesterol (HDL-C) with gestational hypertensive disorders; BMI, Fasting Plasma Glucose (FPG), and TG with GDM (all p-values<0.05). The cut-off point values for the above-mentioned MetS components were: TG > 138 mg/dl, and BMI < 21 kg/m^2 for the occurrence of preterm birth; TG > 148 mg/dL, MAP > 84, and HDL-C < 84 mg/dl for gestational hypertensive disorders; BMI > 25 kg/m^2, FPG > 84 mg/dl, and TG> 161 mg/dl for GDM.

Conclusion: The study findings imply the importance of early management of metabolic syndrome in pregnancy to improve maternal-fetal outcomes.

Keywords: Pregnancy; Metabolic Syndrome; Gestational Diabetes; Gestational Hypertensive Disorders; Preterm Birth

Abbreviations:

MetS: Metabolic Syndrome

TG: Triglyceride

BMI: Body Mass Index

MAP: Mean Arterial Pressure

HDL-C: High Density Lipoprotein – Cholesterol

FPG: Fasting Plasma Glucose

GDM: Gestational diabetes

Introduction

Metabolic syndrome (MetS) is a cluster of anthropometric and cardio-metabolic abnormalities including central obesity, high blood pressure, hypertriglyceridemia, hypo-HDL-cholesterolemia and insulin resistance (1), and is strongly associated with the increased risk for cardiovascular diseases (CVD), diabetes mellitus (DM) and all-cause mortality (2). Although the exact underlying etiology of the syndrome is unknown, however, both genetic and acquired factors may contribute to the final pathway of inflammation that leads to the syndrome (3). The prevalence of MetS has increased dramatically worldwide and often parallels the incidence of obesity and DM (4). According to Adult Treatment Panel III (ATP III) criteria, Its prevalence of ranged between 9.6 % -55.7% (5).

Normal pregnancy is associated with the increased level of pro-inflammatory and pro-thrombotic factors, insulin resistance, and hyperlipidemic state (6, 7); as a result, pregnancy may be pregnancy predisposed to MetS (8). Although there is no standard definition for MetS during pregnancy, some limited studies suggested that individual metabolic components in pregnancy could increase the adverse pregnancy outcomes (9, 10). In a study by Grieger et al. (2018) reported that more than half of the women who had MetS in early pregnancy developed a pregnancy complication coMAPred to just over a third of women who did not have MetS (11). However, the results of this study may be limited by using Diabetes Federation (IDF) criteria in adults for MetS, since the validity of using non-pregnant adult criteria for the pregnant population is unclear, more over these results are not generalizable to second or third trimesters. Furthermore, they measured random plasma glucose in high risk pregnant women for diabetes which may potentially affect the results (8).

To the best of our knowledge, there have been no established cut-off points for healthy metabolic indices in pregnancy. Studies involving metabolic components in pregnancy have generally used metabolic indices cut-off points of the general adult population (12). Thus, there is a need to define the cut-off values of MetS components in relation to pregnancy complications. The present study aimed to identify the optimal cut-off values of each component of MetS in the first trimester of pregnancy, for prediction of adverse pregnancy outcomes.

Material and Methods

This study was a prospective longitudinal study conducted on 1076 pregnant women in the first trimester of gestation who attended the Jam Bio-Medical Laboratory in Hamadan (a western city in Iran), for their first routine prenatal tests.

Study Participants

The inclusion criteria included: age above 18 years, singleton pregnancy, gestational age of 11-13 weeks, and naturally conceived. Out of 1302 pregnant women referred for prenatal assessments, there were 1076 women that met our inclusion criteria . Those pregnant women with previous history of still birth (n=11) or endocrine disorders including DM and thyroid disorders, or systemic diseases that taking medication during pregnancy (n=38) and those lost to fallow-up (n=18) or reluctance to continue the study (n=13) were excluded. In addition, those pregnancies that terminated before 20 weeks of gestation were excluded from the final analysis (n=11). Finally, a total of 993 pregnant women were included in the current study for final analysis**.** The study flowchart is presented in Figure 1**.**

Study initiation and follow-up:

Upon entry into the study, a standard questionnaire was filled up by face-to-face interviews. The questionnaire included information on demographic characteristics, and medical and reproductive history All participants received standard prenatal care recommended by the American College of Obstetricians and Gynecologists (ACOG) (13) and followed up until the end of pregnancy. Pregnancy outcomes were recorded in details.

Anthropometric and biochemical assessments

Anthropometric variables were obtained using standard techniques. Maternal height (centimeters) and weight (Kg) were measured without shoes using standardized procedures and calibrated equipment. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a validated automatic sphygmomanometer (Beurer, Germany), with an appropriately sized cuff for arm diameter. After resting for five minutes blood pressure was measured in a sitting position 2 times over 10 minutes and the mean value was recorded. Mean Arterial Pressure (MAP) was calculated as: MAP = (SBP + 2DBP)/3 (14)

A venous blood sample was obtained after overnight fasting from all participants. Fasting Plasma Glucose (FPG), Triglyceride (TG), Total Cholesterol (TC), High Density Lipoprotein-Cholesterol (HDL-C) concentrations, Total Cholesterol (TC) levels were measured with the immunoinhibition method (Pars Azmun kit, Iran), Triglyceride (TG) levels were assayed using the glycerol-3-phosphatase oxidase phenol aminophenazone method (Pars Azmun kit, Iran). High Density Lipoprotein-Cholesterol (HDL-C) concentrations were measured by homogeneous enzymatic colorimetric assays (Pars Azmun kit, Iran). Fasting Plasma Glucose (FPG) levels were measured by the glucose oxidase method on Beckman AU 680, (Pars Azmun kit, Iran).

Study outcomes and definition of terms

Outcomes of interest were the occurrence of hypertensive disorders of pregnancy, GDM and preterm birth. Hypertensive disorders of pregnancy included gestational hypertension, preeclampsia, and eclampsia. According to the criteria of the American College of Obstetricians and Gynecologists (ACOG), Gestational hypertension was defined as development of a SBP≥140 mm Hg and/or a DBP ≥ 90 mm Hg without proteinuria after 20 weeks of gestation in previously normotensive women. Preeclampsia (PE) was defined as the development of a SBP≥140 mm Hg and/or a DBP ≥ 90 mm Hg with new-onset proteinuria (≥ 300 mg/24 h) in a random urine sample with no evidence of urinary tract infection. eclampsia was defined as occurrence of generalized seizures, in addition to preeclampsia criteria (15). GDM diagnostic criteria followed the newly accepted criteria with ADA 2020 (Standards of Medical Care in Diabetes). These criteria recommend a diagnostic 75 g oral glucose tolerance test performed at 24-28th week of gestation. The diagnosis of GDM was made when any one value met or exceeded the following values: fasting: 92mg/dl; 1-h: 180mg/dl ; 2-h: 153 mg/dl (16). Preterm birth was defined as delivery prior to 37 weeks of completed gestation

Statistical analysis

Quantitative data were expressed as mean and standard deviation (SD). The cut-off point value of the each components of metabolic syndrome in the occurrence of each adverse pregnancy outcomes was obtained using Receiver Operating Characteristic (ROC) curve along with using Youden's index. Based on the cut-off point for each outcome, individuals were divided into normal and abnormal groups. Binary logistic regression was used to examine the relation between components of MetS and adverse pregnancy outcomes. The results of the binary logistic model are reported as Odds Ratio (OR), 95 % CI and the associated P-value. Data entry and data analysis were performed with SPSS version 20.0 for Windows (SPSS Inc, Chicago, III, USA). The level of statistical significance was set at 0.05.

Results

Table 1 shows the characteristics of the study participants, and pregnancy outcomes. The mean (SD) maternal age and BMI of participants were 28.3 (3.3) years and 24.6 (2.2) kg/m^2 respectively, and 70.1% of them were nulliparous. Gestational diabetes, hypertensive disorders of pregnancy and preterm birth were developed in 108 (10.9%), 85 (8.6%), and 79 (7.9%) of study participants.

Regarding preterm birth, the results of analysis with adjustment for maternal age and history of preterm birth revealed that two components of TG and BMI at the first trimester of pregnancy were significantly associated with

developing of preterm birth (P value < 0.001 for both). There were not any association between FBS, HDL-C and MAP and risk of preterm birth. In this respect, the ROC curve analyses in predicting preterm birth showed that AUCs (SE) for TG were 0.737 (0.024) with the optimal cutoff value of 138.5 mg/dL and AUCs (SE) for BMI were 0.152 (0.027) with the optimal cutoff value of 21.87 (table 2). Table 3 shows the association between components of MetS in early pregnancy and preterm birth. The result of logistic regression analysis revealed that pregnant women with first trimester TG level more than cut off value of 138.5 mg/dl had a 5-fold increased risk of developing preterm birth in the unadjusted model (unadjusted OR: 5.5; 95% CI, 3.1–9.8; P=0.001), even after adjustments for the potential confounders including maternal age and history of preterm birth (adjusted OR: 5.3; 95% CI, 3.1–9.0; P=0.0001). As such, women with first trimester BMI less than 21.87 kg/m^2 had a 5% higher risk of developing preterm birth in both unadjusted and unadjusted models (unadjusted OR: 0.05; 95% CI, 0.034-0.102; P=0001) and (adjusted OR: 0.05; 95% CI, 0.03-0.10; P=0.001).

Regarding hypertensive disorders of pregnancy, the results of analysis with adjustment for maternal age and history of hypertensive disorders of pregnancy revealed that three components of TG, MAP and HDL-C at the first trimester of pregnancy were significantly associated with developing of hypertensive disorders of pregnancy (P value < 0.001 for all). However, there were not any association between FBS and BMI and risk of hypertensive disorders of pregnancy. In this respect, the ROC curve analyses in predicting hypertensive disorders of pregnancy showed that AUCs (SE) for TG were 0.699 (0.032) with the optimal cutoff value of 148.5 mg/dL, AUCs (SE) for MAP were 0.695 (0.030) with the optimal cutoff value of 84.8 and AUCs (SE) for HDL-C were 0.388 (0.034) with the optimal cutoff value of 54.5 mg/dL (table 2). The results of adjusted logistic regression analysis showed that women with first trimester TG levels more than 148.5 mg/dL had a more that 5-fold higher risk of developing hypertensive disorders of pregnancy (adjusted OR: 5.34; 95% CI, 3.16-9.03; P=001). As such, women with first trimester MAP more than 84.8 had approximately 3-fold higher risk of developing hypertensive disorders of pregnancy in both unadjusted and unadjusted models (unadjusted OR: 2.88; 95% CI, 1.78-4.66; P=001) and (adjusted OR: 3.09; 95% CI, 1.93-4.93; P=0.001). In addition, women with first trimester HDL-C levels less than 54.5 mg/dL had a 5% higher risk of developing hypertensive disorders of pregnancy (unadjusted OR: 0.58; 95% CI, 0.36-0.65; P=0.01) and (adjusted OR: 0.54; 95% CI, 0.34-0.86; P=0.001). (table 4).

Regarding GDM, the results of analysis with adjustment for maternal age and history of GDM revealed that three components of BMI, FBS and TG at the first trimester of pregnancy were significantly associated with developing of GDM (P value < 0.001 for all). However, there were not any association between MAP and HDL-C and risk of GDM. In this respect, the ROC curve analyses in predicting GDM showed that AUCs (SE) for BMI were 0.700

(0.029) with the optimal cutoff value of 25.66 kg/m^2, AUCs (SE) for FBS were 0.744 (0.022) with the optimal cutoff value of 84.5 mg/dL, and AUCs (SE) for TG were 0.591 (0.029) with the optimal cutoff value of 161.5 mg/dL (table 2). In this respect, the results of adjusted logistic regression analysis showed that women with first trimester BMI more than 25.66 kg/m^2 had a more that 7-fold higher risk of developing GDM (adjusted OR: 7.41; 95% CI, 4.80-11.46; P=0.001). As such, women with first trimester FBS levels more than 84.5 mg/dL in the first trimester of pregnancy had a more that 5-fold higher risk of developing GDM (adjusted OR: 5.55; 95% CI, 3.61-8.56; P=001). In addition, women with TG levels more than 161.5 mg/dL in the first trimester of pregnancy had a 2.6-fold higher risk of developing GDM (adjusted OR: 2.66; 95% CI, 1.66-4.27; P=001) (table 5).

Discussion

The results of this large prospective study in Middle-East Asian population revealed that MetS components at the first trimester of pregnancy, independent of potential associated risk factors, were significantly associated with increased risk of adverse pregnancy outcomes in later pregnancy. Moreover, we presented the optimal cut-off points for each MetS component in early gestation for predicting those major adverse pregnancy outcomes in Iranian population.

Previously, some studies reported that MetS components during pregnancy are associated with adverse pregnancy outcomes (17-24). However, some of those studies were cross-sectional and with most studies focusing on the third trimester. Meanwhile, results of studies on MetS components abnormalities in early pregnancy for predicting major adverse pregnancy outcomes are limited and controversial. As such, the cut of values for each component and magnitude of those increased risks need still to be clearly identified.

In this respect the first trimester levels of TG more than 138 mg/dl and BMI less than 21 kg/m^2 could increase the risk of preterm birth. Based on our finding, first trimester TG is a strong and BMI is a relative predictor for the development of preterm birth, with area under curves (AUC) in ROC curve analyses of 0.737 and 0.152 respectively. However, the number of underweight pregnant women was small, which may explain why no strong association was found for them. Our results suggested a considerable effect first trimester TG and BMI on prediction of preterm birth, which may provide valuable information on early pregnancy screening and contribute to perinatal health care.

As well, first trimester level of TG more than 148 mg/dL, MAP more than 84 and HDL-C less than 54 mg/dl could increase the risk of hypertensive disorders of pregnancy in the second and third trimester of pregnancy. Accordingly, MAP and TG were strong predictive factors (AUC of 0.695 and 0.699, respectively) and HDL was

a relative predictor for hypertensive disorders (AUC of 0.388). These findings suggest that dyslipidemia may be a potential factor in the etiology of hypertensive disorders of pregnancy, and may serve as a marker of increased risk for it.

Additionally, the first trimester BMI more than 25.6 kg/m^2, FPG more than 84 mg/dl, and TG more than 161 mg/dl could increase the risk of developing GDM later in pregnancy. In our study, the first trimester BMI and FPG are strong (AUC of 0.700 and 0.744, respectively) and TG is moderate predictors in development of GDM (AUC of 0.591). These data suggest that overweight and obesity before pregnancy and first trimester of gestation could be a major determinant of GDM, that lead to increased insulin resistance and islet b-cell depletion, so that b-cells cannot secrete enough insulin to compensate for insulin resistance caused by pregnancy, leading to the occurrence of GDM (25).

Although, the exact underlying pathophysiology of those finding are not clearly understood, however some mechanisms have been suggested. Altered maternal lipid metabolism during the course of a pregnancy are a normal part of pregnancy physiology which leads to an early accumulation of lipids in maternal tissue and the development of hyperlipidemia in the latter half of pregnancy (26). Those are necessary for placental steroid production and promote the accumulation of maternal fat storage to serve a source of calories for the mother and fetus during the later stages of pregnancy (27). Meanwhile, we found that there is strong association between serum level of TG in the first trimester of pregnancy and some major adverse outcomes, as each unit increase TG level in early pregnancy could increase the risk of preterm birth, hypertensive disorders of pregnancy and GDM. In agreement with our findings, in a large meta-analysis including 74 studies, it was revealed that women who developed preeclampsia have increased levels triglycerides during all trimesters of pregnancy (28). In another meta-analysis, Jiang et al. (2017) demonstrated that higher level of TG and lower levels of HDL-C were associated with preterm birth (29). As such, in a recent published meta-analysis, Ryckman et al. (2015) found that TG levels the at first, second and third trimesters of pregnancy were significantly elevated in women with GDM coMAPred with those without GDM (30, 31). And also our findings are consistent with previous literature as hypertriglyceridaemia is thought to be one of the key drivers of fetal macrosomia (30, 32).

In this respect, some researchers argued that increased TG level coincide with reduced insulin sensitivity may play an important role in occurrence of adverse pregnancy outcomes (33). Further, although maternal serum TG does not appear to cross the placenta, however association between enhanced insulin resistance and hypertriglyceridemia may explain the relationship between maternal TG levels and fetal overgrowth (33, 34). Additionally, the increased TG level is considered as an activator of oxidative stress and inflammation. Emerging

evidence suggests that elevated plasma TG level and its related remnants could progressively produce toxic free radicals and lipid peroxides that may potentially damage endothelial cells. This damage are *per se* associated to the wide range of incidence of feto-maternal and neonatal complications such as pregnancy hypertensive disorders and preterm birth (35, 36).

Furthermore, based on ROC and logistic regression analysis of our data, we were able to determine an acceptable cut-off value of TG for predicting adverse pregnancy outcomes at a later gestational age. In this respect, TG values more than 140-160 mg/dL could strongly predict preterm birth, hypertensive disorders of pregnancy, and GDM. In agreement**,** Chatzi et al. (2009) suggested that women with TG >150 mg/dl in early pregnancy had higher risk for preterm birth (37). In another studies, it was reported that first-trimester of TG >177 mg/dl could be the critical risk factor associated with preeclampsia (38) and TG >160 mg/dL could valuably predict GDM (39). However, small differences between finding if different studies may be related to different population characteristics such as racial and ethnic diversity.

In addition, we found that lower level of HDL-C is associated with higher risk of hypertensive disorders of pregnancy. HDL-C plays a positive role in protecting the maternal vascular endothelium during pregnancy (40). It has anti-thrombotic, anticoagulant, anti-inflammatory and anti-atherosclerotic properties by accepting cholesterol from lipid-laden macrophages and stimulators of the production of nitric oxide (41). In line with this finding, Spracklen et al. (2014) in a large and well-designed meta-analysis reported that preeclampsia was associated with lower levels of HDL-C, regardless of gestational age at the time of blood sampling (28).

As well, we showed that HDL-C < 54 mg/dL could acceptable predict hypertensive disorders of pregnancy. In another study, Li et al. (2021) reported that HDL-C < 78 mg/dL could valuable predict pre-eclampsia (42). Although different ethnicity of population may be important, but This discrepancy may be due to this fact that the authors in this study assessed the predictive value of HDL-C in the second trimester of pregnancy (42).

Nowadays, more and more researchers have shown the role of first-trimester fasting plasma glucose in GDM. It is hypothesized that higher FPG concentrations in early gestation may lead to aggregated insulin resistance induced by diabetogenic placental hormones in the second trimester of pregnancy and subsequent GDM. However, our finding confirmed previous literature regarding increased risk of GDM among women with higher FPG levels in first trimester of pregnancy. In this respect, Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study results indicated there is a strong, continuous association of maternal glucose levels (even below those diagnostic of diabetes) with increased risk of adverse perinatal outcomes (43). Furthermore, several researchers examined

whether first-trimester FPG is also consistently associated with increased risk of GDM and support previous findings (44-47).

In our study, results of ROC curve analysis suggested that first- trimester of FPG more than 84 mg/dL could significantly predict the occurrence of GDM in second trimester of pregnancy. However, according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) standard, Agarwal et al. pointed out that 80 mg/dL (with sensitivity of 95.4%) is recommended as the cutoff value for FPG (48). The AUC calculated by Zhu et al. was 0.836 and the sensitivity was 87.8%, which also indicated that the first-trimester FPG of 80 mg/dL is a good predictor for GDM (49). As well, Kouhkan et al. (50) demonstrated that FBS $\geq$ 84.5 mg/dl in the first-trimester of the pregnancy (with sensitivity of 74%) could significantly predict GDM. Different studies all highlighted the usefulness and importance of using FPG alone for the diagnosis of GDM**.**

However, it is well-established that maternal overweight and obesity are associated with several feto-maternal and neonatal outcomes (51-54). However, we showed that one unit increase in first-trimester BMI could significantly increase the risk of preterm birth and GDM. Although there is no unifying mechanism responsible for the adverse outcomes associated with maternal higher BMI, but it is argued that women with higher BMI have increased first trimester IR and disturbed insulin signaling pathways (55, 56), which becomes manifest clinically in late gestation as GDM (57). Moreover, inflammatory milieu with enhanced oxidative stress concentration caused by higher BMI levels leads to a cascading series of events such as endothelial dysfunction that seems to be contribute to altered fetal and maternal functioning in late of pregnancy (58). As well, we showed that BMI level higher than 25 kg/m^2 could acceptable predict GDM. In agreement, Nishikawa et al. reported that applying a BMI cut-off of 25 kg/m^2 would identify 68% of South Asian women with diabetes in pregnancy(59). Kouhkan et al showed that BMI cut-off value in GDM development was 23.5 kg/m^2 with a sensitivity of 48.50% and specificity of 73.05% (50). Unadjusted or adjusted for different confounders, different ethnicity, different incidence of adverse outcomes may influence the findings of different studies. However, evidence regarding the association of maternal BMI and preterm birth is conflicting. Although some studies suggest that maternal BMI does not influence the rate of preterm birth (60, 61), other studies have found reduced rates of preterm birth in higher BMI level (62-64) and some reported that obesity could increase the risk of preterm birth (65, 66). However, In agreement with our findings, some studies have reported that the women with a lower BMI had a greater risk of preterm deliveries. Ehrenberg et al. described a population of 15,196 patients in which low BMI less than 19.8 kg/m^2 at conception and low BMI at the time of birth were associated with an increased risk for preterm birth (67). Han et al. in a meta-analysis of 78 studies, involving 1025794 women, reported that singletons born to underweight

women have higher risks of PTB (overall, spontaneous and induced) and LBW than those born to women with normal weight (adjusted RR: 1.32, 95% CI: 1.10-1.57) (56). It should be noted that we could not perform analysis for obese women, since the number of pregnant women with obesity in our sample population was rare. However, we hypothesized that maintaining or obtaining a healthy BMI level for early pregnancy women could substantially reduce the likelihood of preterm birth.

In uncomplicated pregnancies, arterial blood pressure pattern usually consists of a steady decrease in blood pressure during the first half of pregnancy, then an increase until the time of delivery (68). Some studies have demonstrated a higher predictive power when MAP is measured during the first trimester of pregnancy (69-71). In agreement, results of our study showed that one-unit increase in first-trimester maternal MAP could significantly increase the risk of pregnancy hypertensive disorders. As such, mayrink et al. (2019) reported that early-onset preeclampsia cases had higher mean arterial blood pressure levels at 20 weeks of gestation (68). Nevalainen et al reported MAP is related to maternal vascular adaptation and has been shown to be elevated already in the first trimester of pregnancy in women who develop PE later in pregnancy (72). As well, we showed that first-trimester MAP > 86.5 was the optimal threshold for predicting of hypertension disorders with a sensitivity of 58.5 and a specificity of 69.2%. In agreement, Zhu et al. in a a prospective cohort study among Asian population reported that For predicting preeclampsia, MAP had AUCs of 0.86 at 11–14 weeks of gestation (70).

The strengths of the present study include its prospective design also and use of detailed and validated data for the MetS components in early pregnancy. All measurements were carried out at the same laboratory. Blood pressures were recorded twice. Previous study suggested that when the average of two recordings were used for calculating MAP, the performance of screening tended to improve with an increasing number of recordings (73). Moreover, based on medical documents of participants, adverse pregnancy outcomes were clearly defined. Nevertheless, limitations of study need to be mentioned. There are several socio-demographic and lifestyle variables that may potentially affect the risk of adverse pregnancy outcomes.

However, the exclusion of women with a diagnosis of GDM or chronic hypertension in early pregnancy may underestimate the associated risk of those outcomes. Additionally, results of this study may be limited to Iranian ethnicity.

Conclusion

In conclusion, the results of this large prospective study in revealed that MetS components at the first trimester of pregnancy, independent of potential associated risk factors, were significantly associated with increased risk of adverse pregnancy outcomes in later pregnancy. Furthermore, based on ROC and logistic regression analysis of our data, we have presented an acceptable cut-off values of each component of MetS for predicting adverse pregnancy outcomes at a later gestational age. However, the search for optimal first-trimester each component of MetS is critical, since it can help to identify women at risk of developing adverse outcomes early in their pregnancies. As such, those detection, in turn, can provide an opportunity for an early targeted intervention to reduce related complications.

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Declarations

Author contributions:

Moghaddam-Banaem: Conceptualization, Methodology, Supervision, Writing- Reviewing and Editing. **Asltoghiri**: Data collection, Writing- Original draft , Investigation, Resources**. Behboudi-Gandevani:** Methodology, Writing Original Draft**. Ramezani Tehrani:** Visualization**,** Project administration, Reviewing and Editing manuscript**. Rahimi Froushani**: Software, Validation, formal analysis. All authors approved the final draft of manuscript.

Compliance with ethical standards

Conflict of interest: There is no conflict of interest to disclose by the authors.

Ethics approval: The study proposal was approved by the Medical ethics committee of Tarbiat Modares University, Tehran, Iran. (ETHICS ID: IR.MODARES-REC.1397.007).

Informed consent: A written, informed consent was obtained from all participants after explaining about the purpose of the study

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Table 1: Demographic characteristics, and reproductive and obstetrics history of study participants (n=993)

Characteristics	**Mean (SD) or N (%)***
Maternal age at enrollment (years)	28.3 (3.3)
Pre-pregnancy BMI (kg/m2)	24.6 (2.2)
Years of educations	13.8 (2.0)
Occupation	
Housewife	784 (79.0)
Occupied (employed)	208 (21.0)
Number of pregnancies	
1	703 (70.9)
≥ 2	289 (29.1)
Gestational age at birth (weeks)	39.5 (1.3)
Type of delivery	
NVD	645 (65.0)
C/S	347 (35.0)
Hypertensive disorders of pregnancy	
Gestational hypertension	42 (4.3)
Preeclampsia	43 (4.3)
Preterm labor	79 (8.0)
Gestational diabetes	108 (10.9)

*Continuous variables are presented as mean (SD) and categorical variables as n (%). BMI: body mass index, C/S: cesarean section, NVD: normal vaginal delivery

Table 2. Prediction of adverse pregnancy outcomes by cut-off values of the first trimester metabolic syndrome components

Adverse pregnancy outcomes	Metabolic syndrome components	Cut-off values	Youden Index	Area Under Curve	S.E
Preterm birth					
	TG	138.5	121.1	0.737	0.024
	BMI	21.87	39.7	0.152	0.027
Hypertensive disorders of pregnancy					
	MAP	84.8	128.3	0.695	0.030
	TG	148.5	137.6	0.699	0.032
	HDL-C	54.5	88.4	0.388	0.034
Gestational diabetes					
	BMI	25.66	132.1	0.700	0.029
	FPG	84.5	140.4	0.744	0.022
	TG	161.5	114.8	0.591	0.029

BMI: body mass index, MAP: Mean arterial pressure , FBS: Fasting blood sugar, TG: triglyceride, HDL-C: High density lipoprotein-cholesterol

Table 3: The logistic regression analysis results of the investigated association between components of metabolic syndrome in early pregnancy and preterm birth *

	B	S.E	Odds Ratio (95%CI)	Adjusted Odds Ratio (95% CI)**
Maternal Age	-0.025	0.041	0.976(0.901-1.057)	0.993 (0.927-1.064)
Preterm history	.840	0.683	2.316(0.607-8.838)	1.978 (0.669-5.850)
BMI (kg/m^2)	**-2.839**	**0.283**	**0.059(0.034-0.102)**	**0.059 (0.035-0.101)**
TG (mg/dl)	**1.715**	**0.292**	**5.557(3.135-9.849)**	**5.346 (3.163-9.037)**

Bold values indicate statistical significance, BMI: body mass index, TG: triglyceride.
* LOG (p/1-p) = -1.078 -0.025 (Age) + 0.840 (Preterm history) -2.839 (BMI) + 1.715 (TG)
**adjusted for maternal age and preterm history

Table 4: The logistic regression analysis results of the investigated association between components of metabolic syndrome in early pregnancy and hypertensive disorders of pregnancy*

	B	S.E	Odds Ratio (95%CI)	Adjusted Odds Ratio (95% CI)**
Maternal Age	.022	0.037	1.022(0.951-1.099)	1.042 (0.975-1.113)
history of hypertensive disorders of pregnancy	0.524	0.923	1.728(0.283-10.542)	4.352 (0.831-22.777)
MAP	**1.059**	**0.246**	**2.883(1.781-4.669)**	**3.093(1.937-4.938)**
TG (mg/dl)	**1.522**	**0.243**	**4.580(2.845-7.372)**	**5.1028 (3.161-7.995)**
HDL (mg/dl)	**-0.530**	**0.245**	**0.589 (0.364-0.951)**	**0.546 (0.346-.861)**

Bold values indicate statistical significance; BMI: body mass index, MAP: Mean arterial pressure, TG: triglyceride, HDL-C: High density lipoprotein–cholesterol
* LOG (p/1-p) = -3.858 + 0.022 (Age) + 0.524 (Hypertension history) + 1.059 (MAP) + 1.522 (TG) -0.530 (HDL)
**adjusted for maternal age and history of hypertensive disorders of pregnancy

Table 5: The logistic regression analysis results of the investigated association between components of metabolic syndrome in early pregnancy and gestational diabetes mellitus*

	B	S.E	Odds Ratio (95%CI)	Adjusted Odds Ratio (95% CI)**
Age	-0.026	0.035	0.975(0.910-1.043)	1.004 (0.946-1.066)
History of GDM	**2.734**	**0.951**	**15.389(2.388-99.149)**	**8.400 (1.674-42.152)**
BMI	**1.594**	**0.236**	**4.922(3.097-7.820)**	**7.431(4.807-11.466)**
FPG (mg/dl)	**1.742**	**0.239**	**5.709(3.572-9.125)**	**5.559 (3.610-8.560)**
TG (mg/dl)	**0.561**	**0.276**	**1.753 (1.021-3.011)**	**2.669 (1.666-4.275)**

Bold values indicate statistical significance, BMI: body mass index, GDM: gestational diabetes mellitus, FPG: Fasting Plasma Glucose, TG: Triglyceride,
*LOG (p/1-p) = -2.723 – 0.026(Age) + 2.734 (GDM history) + 1.594 (BMI) + 1.742 (FPG) +0.561 (TG)
** adjusted for maternal age and history of GDM

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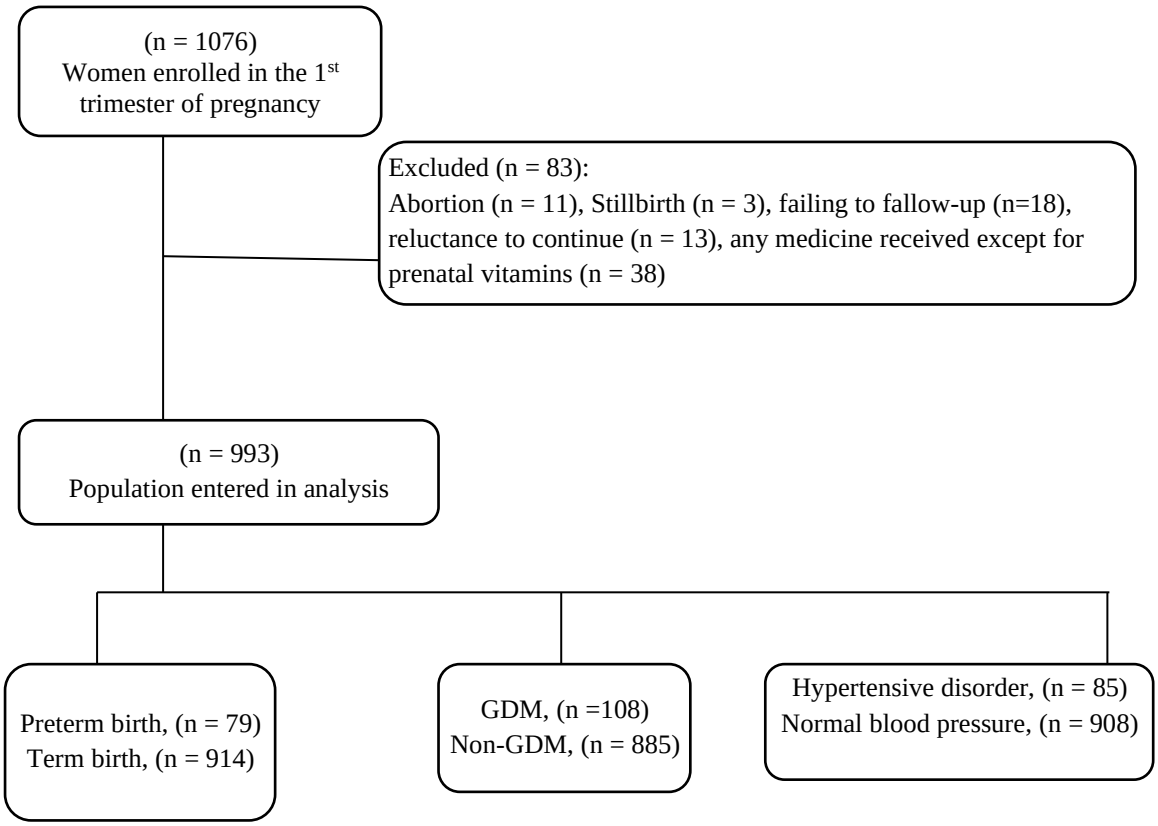

Figure 1.flowchart showing the exclusion criteria

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