

Are maternal metabolic syndrome and lipid profile associated with preterm delivery and preterm premature rupture of membranes?

Shiva Niyaty

Tarbiat Modares University Faculty of Medical Sciences

Lida Moghaddam-Banaem (✉ moghaddamb@modares.ac.ir)

Tarbiat Modares University Faculty of Medical Sciences <https://orcid.org/0000-0002-9849-7451>

Hadis Sourinejad

Tarbiat Modares University Faculty of Medical Sciences

Samira Mokhlesi

Islamic Azad University of Qom

Research article

Keywords: Metabolic Syndrome, Lipid Profile, Pregnancy, Preterm Delivery, Preterm Premature Rupture of Membranes

Posted Date: January 16th, 2020

DOI: <https://doi.org/10.21203/rs.2.20984/v1>

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Version of Record: A version of this preprint was published at Archives of Gynecology and Obstetrics on August 17th, 2020. See the published version at <https://doi.org/10.1007/s00404-020-05738-5>.

Abstract

Background We aimed to evaluate the association of metabolic syndrome (MetS), its components and lipid profile in mid-pregnancy with preterm delivery and preterm premature rupture of membranes (PPROM).

Methods This prospective cohort study was conducted on 203 pregnant women between 24-28 weeks of gestation, undergoing the gestational diabetes screening test with 50 gr glucose challenge test (GCT). Fasting serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were measured during the week after GCT assessment. Information on the participants' pre-pregnancy weight, demographic/ reproductive characteristics, and height and blood pressure (BP) measurements were documented at baseline entry into the study. Metabolic syndrome was defined as the co-existence of 3 or more of the following criteria: Body mass index (BMI) before pregnancy ≥ 30 kg/m², BP $\geq 130/85$ mmHg, GCT ≥ 140 mg/dl, TG ≥ 150 mg/dl, and HDL-C ≤ 50 mg/dl. All participants were followed through routine prenatal care, up to delivery. Any deliveries or rupture of membranes of less than or equal to weeks of pregnancy, were considered preterm delivery and PPRM respectively. Statistical analysis was performed by SPSS V.20, and p-value of less than 0.05 was considered significant.

Results MetS was detected in 10 (4.9%) of participants. Logistic regression analysis showed HDL-C levels, and hypertension had significant effects on spontaneous preterm delivery occurrence [(OR: 0.952, 95%CI: 0.910_0.995), (OR: 1.629, 95% CI: 1.554_1.709) respectively], but no statistically significant results were found for PPRM.

Conclusions Low HDL-C levels and hypertension in mid-pregnancy may increase the occurrence of spontaneous preterm deliveries, indicating that MetS and its components should be monitored more closely in pregnancy.

Background:

In 1998, the World Health Organization (WHO) defined 'metabolic syndrome' (MetS) as a combination of central abdominal (visceral) obesity, glucose intolerance, insulin resistance, dyslipidemia and hypertension (1). This syndrome is a cluster of physiological abnormalities that accelerate the risk of type 2 diabetes and atherosclerotic cardiovascular disease (2). Recently, the diagnostic criteria and etiology of this syndrome have become a controversial topic (3) and its prevalence is a challenging issue worldwide (4). According to one study, the prevalence of metabolic syndrome was considerably higher in Iranian women (55.0%), and men (30.1%), than in French women (6.6%) and men (13.7%) (5).

Despite the increasing prevalence of MetS worldwide in recent years, and consequently an increased prevalence during pregnancy, there is still no established definition for metabolic syndrome in pregnancy (6).

Normal pregnancy is associated with varying degrees of resistance to insulin, dyslipidemia, and inflammatory (7, 8). Studies that have assessed metabolic components in pregnancy have generally used accepted definitions for the adult population (9).

A preterm birth, described as birth at or under 37 weeks of gestation, can lead to adverse consequences for the newborn (10). Although management of preterm infants has much improved, the mortality and morbidity of neonates, even in late preterm labors ($34 \leq \text{labor} \leq 37$) has remained unchanged (11). Preterm premature rupture of membrane (PPROM) is defined as the rupture of membranes in less than or equal to 37 weeks of gestation and usually leads to preterm birth. This condition affects approximately 3% of all pregnancies and occurs in up to 30% of preterm deliveries (12).

In some studies, it has been shown that mothers who have given birth to premature babies suffer from cardiovascular disease and diabetes later in life (13, 14) but the question is whether there is a metabolic syndrome in the mother before and during pregnancy. Most studies have assessed the relationship between metabolic syndrome components such as hypertension, obesity, diabetes, dyslipidemia, and adverse outcomes in pregnancy (6). Results of a study showed that elevated maternal triglyceride levels measured during early pregnancy are associated with an increased risk of induced preterm delivery. In this study, total cholesterol was not associated with any pregnancy complications (15). One study also demonstrated that odds of spontaneous preterm delivery were increased among women with high total cholesterol, LDL and TG (16).

However, few studies have been conducted on metabolic syndrome and preterm birth which are inconsistent. In the study by Grieger et al., the metabolic syndrome of the mother at the onset of pregnancy had no significant relationship with low birth weight and preterm delivery (9), but in the study by Chatzi et al., the risk of preterm delivery in mothers with metabolic syndrome increased approximately threefold (6).

Considering the lack of confirmatory evidence on the association between the metabolic syndrome and preterm birth or PPRM, especially in Iran, we decided to assess metabolic syndrome in mid-pregnancy and determine their associations with the occurrence of preterm delivery and preterm premature rupture of membranes.

Method

This prospective cohort study was performed on 203 pregnant women referred to Niloo and Akbarabadi laboratories in Tehran, from August 2013 through June 2014.

Participants were 18-45 year old pregnant Iranian women with singleton pregnancies, who had been referred to these laboratories for routine gestational diabetes screening test with 50 gr glucose challenge test (GCT), between the 24th - 28th weeks of gestation. Women who were at high risk for preterm delivery due to underlying medical conditions (e.g., chronic hypertension or diabetes) were excluded.

After explaining the study details and obtaining written consent from the women participants, they were enrolled in the study. At the entry, maternal characteristics such as age, parity, educational level, height, weight and pre-pregnancy body mass index (BMI), blood pressure, nutritional complements consumed during pregnancy, family history of diabetes, hypertension, and dyslipidemia were documented.

During the following weeks, venous samples were obtained from the participants in fasting status to measure serum total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels.

As there is no definition of metabolic syndrome in pregnancy, we modified the Metabolic Syndrome Diagnosis Criteria of NCEP-ATP III (17, 18), in which the presence of 3 or more of the following criteria sets the diagnosis of MetS: Central obesity, waist circumference > 88cm or BMI > 30kg/m², triglycerides > 150mg/dl, HDL-C < 50mg/dl, systolic Blood Pressure > 130, diastolic BP > 85 mmHg, and/or fasting blood glucose (FBS) > 105 mg/dl. Since waist circumference increases naturally in pregnancy and is thus inapplicable in this study, we used pre-pregnancy BMI > 30kg/m² instead of waist circumference. FBS was also replaced by impaired GCT results (glucose intolerance). Thus, our diagnosis of MetS in pregnancy was based on the presence of 3 or more of the following criteria: Pre-pregnancy BMI ≥ 30 kg/m², GCT ≥ 140 mg/dl, systolic blood pressure ≥ 130mmhg or diastolic blood pressure ≥ 85 mmHg (taken twice, at least six hours apart), plasma triglyceride levels ≥ 150 mg/dl, and HDL-C levels ≤ 50 mg/dl.

All mothers went through routine prenatal care and were followed up to delivery. Spontaneous preterm birth was defined as intact membranes, regular contractions and cervical changes in the absence of labor induction in mothers with less than or equal 37 weeks of pregnancy that caused delivery. Preterm premature rupture of membranes (PPROM) was defined as rupture of membranes before the initiation of spontaneous contractions in mothers with less than or equal 37 weeks of pregnancy.

All data were registered and analysed by SPSS software V.20. Independent Student T-Test and Chi-Square tests be used to detect significant differences between the preterm birth and term deliveries. Metabolic syndrome, together with its components, and cholesterol and LDL levels were compared between two groups by Fisher's Exact Test.

To adjust for confounding variables, we used Logistic Regression Analysis to evaluate some potential factors affecting preterm birth and PPRM, i.e. number of pregnancies, mothers' education, use of multivitamins during pregnancy, history of preterm birth, and metabolic syndrome together with its components. p-value of less than 0.05 were considered statistically significant.

This research was approved by the Ethical Committee of the Faculty of Medical Sciences in Tarbiat Modares University, Tehran, Iran.

Results

A total of 203 pregnant women were enrolled in the study. As many as 18 (8.9%) spontaneous preterm deliveries and 10(4.9%) PPROM cases occurred among the study subjects. Demographic and reproductive characteristics of the study participants are demonstrated and compared between the 2 study groups (preterm and term deliveries) in table 1. Using the Independent Student T-Test and Chi-Square tests, no statistically significant differences were detected between the two groups (Table 1). The only different variable between the two groups, as expected, was gestational age at delivery (34.11 vs. 38.71 weeks for preterm and term deliveries respectively).

MetS was detected in 10 (4.9%) study participants. High cholesterol ($\geq 200\text{mg/dl}$) and TG ($\geq 150\text{mg/dl}$) levels were observed in 75.4 and 82.8% of participants respectively. Metabolic syndrome, together with its components, and cholesterol and LDL levels were compared between preterm birth and term deliveries by Fisher's Exact Test (Table 2). The only statistically significant differences between the two groups were in the impaired GCT results and high LDL levels, both occurring more in the preterm group [(61.1% vs. 37.3%) and (55.6% VS 32.4%) respectively].

Metabolic syndrome, together with its components, and cholesterol and LDL levels were compared between PPROM versus term deliveries by Fisher's Exact Test which revealed no statistically significant differences between the two groups (Table 3).

Logistic Regression showed that HDL levels and hypertension had significant effects on the occurrence of preterm deliveries, with lower levels of HDL and hypertension increasing the occurrence [(OR:0.952, 95%CI: 0.910_0.995), and (OR:1.629, 95%CI: 1.554_1.709), respectively. Regarding PPROM, only mothers' age had a significant impact; as the aged increased , PPROM occurrence decreased (OR: 0.796, 95%CI: 0.661_0.960) (Table 4).

Discussion

In this prospective cohort study of 203 Iranian pregnant women in mid-pregnancy, 8.9% of deliveries were preterm, and prevalence of MetS was 4.9%. This study showed that some of components of MetS related with preterm birth.

This study showed that impaired glucose tolerance (impaired GCT results) was significantly associated with preterm birth. A Turkish study found that the incidence of preterm labor was not altered by GDM status (19), but most studies have suggested that high glucose levels are associated with preterm delivery. Yun et al, in Korea, showed that glucose intolerance and gestational diabetes (GD) were risk factors for preterm labor (20). In addition, Basirat et al. reported that the prevalence of PROM and preterm labor, in Iran, was higher in pregnant women with abnormal GCT results (21). Diverse mechanisms, such as inflammation, infection, stress and some immunologic mechanisms might explain this situation (22).

In this study, lower levels of HDL-C and elevated levels of LDL-C were also significantly associated with preterm birth. These findings are consistent with the results of some other studies (22-24). Some metabolic factors related with inflammation may be associated with increased risk of spontaneous preterm labor. Maternal hyperlipidemia may increase oxidative stress in the fetus, resulting in damage of the umbilical vessel wall and disruption of normal placentation (15, 25). Increasing evidence suggests that elevated plasma lipids may induce endothelial dysfunction. Interaction of maternal components such as neutrophils and oxidation susceptible lipids with placental cells engenders a forwarding cycle of oxidative stress (25). Oxidative stress produces free radicals and lipid peroxidase (26).

In this study, a significant relationship was observed between gestational hypertension and preterm birth. Leda Ghatzi et al., assessed the association between metabolic syndrome components and the risk of preterm birth in Greece, and their findings showed that the most significant risk factor was hypertension (6). Catov et al. suggested that chronic hypertension, diabetes, body mass index, and age were related to the risk of term and preterm SGA births (27). Gilbert reported that mothers with chronic hypertension are at risk of various neonatal morbidities such as low birth weight and prematurity (28). In general, women with hypertension may have an inadequate vascular response and may suffer from a defect in endothelial wall and also abnormal placentation; on the other hand, gestational hypertension, independent of maternal obesity and metabolic disorders, is associated with insulin resistance and dyslipidemia.

In this study, no significant relationship was observed between metabolic syndrome and preterm birth and PPROM. Similarly, in a study by Baliutavičienė et al., gestational age in women who had three components of metabolic syndrome (impaired glucose tolerance, obesity, and hypertension) with healthy women was not different (29). Furthermore, in the study by Grieger et al., diagnosis of MetS was not associated with increased risk at lower gestational ages (9). However, in the study by Lei et al., metabolic abnormalities in pregnancy were associated with adverse pregnancy such as preterm labor (30). The reason for the difference in the results of these studies is that there is no single definition for the metabolic syndrome in pregnancy and different measurements have been carried out to diagnose the metabolic syndrome.

This study provides a new insight into the metabolic syndrome and its components in mid-pregnancy (24th-28th weeks of gestation) and any possible association with preterm birth; To our best knowledge, no such investigation has hitherto been conducted in Iran, measuring and evaluating precisely all these components in addition to lipid profiles in mid-pregnancy and following subjects up to delivery.

A major limitation was the lack of a standard definition for gestational metabolic syndrome. Studies that have assessed metabolic components in pregnancy have generally used a pregnancy-modified version of accepted definitions for the adult. In the study by Grieger et al., random plasma glucose and abdominal circumference were considered as metabolic syndrome criteria (9). In the study by Stekking et al., such as our study, abdominal circumference was not considered as a criterion of obesity, although obesity was defined as a body mass index higher than 30 kg/m² prepregnancy (31). However, in our study instead of

performing a fasting blood sugar test (FBS), glucose challenge test (GCT), was used. Appropriate definitions of metabolic syndrome have yet to be defined in pregnancy and the utility of using previously defined variables from the non-pregnant adult population is unclear. Thus, we used a pregnancy-modified version of NCEP-ATP III definition of metabolic syndrome for a general population, which needs further investigations to be confirmed.

Also, the sample size of this study is not large enough to draw definitive conclusions. Further research is needed with larger samples/cohorts for clarification and confirmation of these associations. The protective effect of metabolic syndrome observed on preterm birth needs further investigations too.

Conclusion

To conclude, our findings can be used to identify pregnancies at higher risk of preterm deliveries earlier, and to implement appropriate measures to prevent them.

Abbreviations

MetS: Metabolic Syndrome

PPROM : Preterm Premature Rupture Of Membranes

GCT: Glucose Challenge Test

LDL-C: Low-Density Lipoprotein Cholesterol

HDL-C: High -Density Lipoprotein Cholesterol

TG: Triglyceride

BP: Blood Pressure

WHO: World Health Organization

BMI: Body Mass Index

FBS: Fasting Blood Glucose

Declarations

Ethics approval and consent to participate

This research was approved by the Ethical Committee of the Faculty of Medical Sciences in Tarbiat Modares University, Tehran, Iran. Informed written consent was obtained from all participants.

Consent for publication

consent for publication was obtained from all participants.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This study was performed as the thesis project for an M.Sc. degree in midwifery in Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran. No external funding sources were provided for this study.

Authors' contributions

SN: Project development, Data Collection, Manuscript writing

LM: project administration, writing-review and editing, supervision

HS : Data Collection, Manuscript writing

SM: : data analysis, writing-review and editing

Acknowledgements

We are grateful to the participants in the study.

Tables

Table 1: Comparison of the demographic and reproductive characteristics of participants (n =203)

Characteristics	Study Group (n=203)		
	Preterm delivery (n=18)	Term delivery (n=185)	p-value
Maternal age (years)	30.22±5.31	29.35±4.56	¹ .450
Years of education	13.22±3.82	13.38±4.30	¹ .878
BMI (kg/m2)	24.10± 4.30	24.16±3.2	¹ .947
Gestational age at birth (weeks)	34.11±2.67	38.71±0.977	1<0.001
Number of pregnancies			
1	10(55.6%)	109(58.9 %)	² .782
≥2	8(44.4 %)	76(41.1 %)	
Job(Occupation)			
Housewife	11(61.1%)	115(62.2%)	² .930
Occupied(Employed)	7(38.9%)	70(37.8%)	
Type of delivery			
NVD	5(27.8%)	43(23.2%)	² .666
C/S	13(72.2%)	142(76.8%)	
Use of supplements during pregnancy			
Folic acid	15(83.3%)	132(71.4%)	² .782
Iron	10(55.6%)	131(70.8%)	² .180
Calcium	7(38.9 %)	83(44.9%)	² .626
Multivitamins	11(61.1%)	114(61.6%)	² .966

Data are defined as mean± SD or n (%), as appropriate.

BMI: body mass index; C/S: caesarian section; NVD: natural vaginal delivery

¹. Based on Independent Student T-Test

². Based on Chi-Square Test

Table 2: Distribution of metabolic syndrome, its components, and lipid profiles among preterm and term deliveries

Components N (%)	Study Group (n=203)		
	Preterm delivery (n=18)	Term delivery (n=185)	p-value (fishers' exact test)
BP≥130/85mmhg	1 (5.6)	14 (7.6)	1.000
BMI≥30kg/m2	1 (5.6)	11 (5.9)	1.000
GCT≥140 mg/dl	11 (61.1)	69 (37.3)	0.016
TG≥150 mg/dl	16 (88.9)	152 (82.2)	0.744
LDL≥130 mg/dl	10 (55.6)	60 (32.4)	0.046
HDL≤50 mg/dl	0 (0.00)	4 (2.2)	1.000
Cholesterol≥200 mg/dl	16 (88.9)	137 (74.1)	0.251
MetS	2 (11.1)	8 (4.3)	0.288

BP: Blood pressure; BMI: body mass index; GCT: glucose challenge test; TG: triglycerides; LDL: low density lipoprotein

HDL: high density lipoprotein; MetS: metabolic syndrome

Table 3: Distribution of metabolic syndrome, its components, and lipid profile among PPRM and term deliveries

Components N (%)	Study Group (n=203)		
	PPROM (n=10)	Term delivery (n=185)	p-value (fishers' exact test)
BP \geq 130/85mmhg	2 (20)	13 (6.7)	0.162
BMI \geq 30kg/m ²	0 (5.6)	12 (6.2)	1.000
GCT \geq 140 mg/dl	6 (60)	74 (40.4)	0.088
TG \geq 150 mg/dl	8 (80)	160 (82.9)	0.684
LDL \geq 130 mg/dl	6 (60)	64 (33.2)	0.096
HDL \leq 50 mg/dl	0 (0.00)	4 (2.1)	1.000
Cholesterol \geq 200 mg/dl	9 (90)	144 (74.6)	0.456
MetS	1 (10)	9 (4.7)	0.464

* PPROM: preterm premature rupture of membranes

Table 4: Logistic regression analysis of potential effective factors on preterm birth and PPROM

Variables	Preterm birth			PPROM		
	Odds Ratio	95% Confidence Interval	p-value	Odds Ratio	95% Confidence Interval	p-value
Age (years)	.988	.863_1.131	.860	.796	.661_.960	.017
Number of pregnancies	1.258	.608_2.603	.536	1.372	.691_3.797	.267
Education (years)	1.118	.970_1.287	.123	.998	.813_1.226	.987
History of preterm delivery	.136	.015_1.202	.073	6.452	.358_116.30	.206
Multivitamin consumption	.851	.253_2.857	.794	1.41	.286_7.02	.670
Impaired glucose challenge test	.105	.103_1.241	.105	4.320	.739_25.23	.104
Hypertension	162.92	1.554_1.709	.032	4.809	.270_85.78	.285
Metabolic syndrome	.027	.101_1.982	.249	.206	.003_12.96	.454
Cholesterol (mg/dl)	1.013	.992_1.035	.231	.993	.968_1.018	.577
HDL (mg/dl)	.952	.910_.995	.030	1.020	.966_1.076	.476
LDL (mg/dl)	.981	.957_1.005	.119	1.019	.988_1.050	.237
Triglycerides (mg/dl)	.993	.984_1.001	.088	1.006	.995_1.016	.292
Body mass index (kg/m ²)	1.085	.916_1.285	.345	.907	.731_1.125	.374

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