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Association between masked hypertension and late-onset fetal growth restriction at advanced maternal age

Nazli Topfedaisi Ozkan[1], Aylin Onder Dirican[2], Nezaket Kadioglu[1], Gorkem Yildiz[3]

[1]Yüksek İhtisas University School of Medicine , Department of Gynecology and Obstetrics, Ankara, Türkiye
[2]Başkent University School of Medicine , Department of Gynecology and Obstetrics, Konya, Türkiye
[3]Yüksek İhtisas University, Department of Cardiology, Ankara, Türkiye

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Abstract

Fetal growth restriction (FGR) is a major risk factor for complicated pregnancy including stillbirth. The all-pathophysiology results in uteroplacental insufficiency. Hypertension chronic or pregnancy-related complicates the all-prenatal periods. The relationship between fetal growth restriction and hypertension is well-known and this risk increases with maternal age. Late-onset FGR is diagnosed >32 weeks. Masked hypertension (MH) is a phenotype of hypertension when clinic blood pressure is in the normal range in the office but elevated outside the office. This study examined the risk of late-onset FGR and masked hypertension at advanced maternal age. Sixty pregnant women over 40 years old were included in the study who delivered at our hospital with late-onset fetal growth restriction diagnosis. After taking detailed anamnesis from all individuals included in the study, detailed physical examination, obstetric examination and ambulatory blood pressure monitoring (ABPM) were performed. Women with maternal chronic hypertension, pregestational or gestational diabetes mellitus, chronic kidney disease, rheumatoid disease history, tobacco use, cardiac arrhythmia, fetal genetic abnormality or placental abnormality were excluded from the study. The prevalence of masked hypertension was statistically significantly higher in the group with late intrauterine growth. (n:13, 43% vs n:5, 16.7% p=0.02). Office systolic BP (125.5±4.1 mmHg vs 118.5±5.7 mmHg p=0.016), 24-hour systolic BP measurement (125±9 mmHg vs 119.7±5.7 mmHg p=0.03), and ambulatory nocturnal diastolic BP measurement (66.7±10 mmHg vs. 61.±5.5 mmHg p=0.03) was higher in the group with late FGR. Hypertension can lead to complications in the perinatal period. There is a bad association between FGR and hypertension. Masked hypertension should be considered especially in advanced age pregnant individuals with FGR.

Keywords: Late-onset fetal growth restriction, masked hypertension, hypertension in pregnancy

Introduction

FGR results in of fetus failing to reach maximum growth potential are determined by its biological and genetic factors. The condition when the estimated fetal weight (EFW) or abdominal circumference (AC) 10% below the week of gestation is named FGR. The classic Hadlock formula is most common formula for calculating [1,2]. Severe FGR is detected when gestational week measurements are below 3% and fetal umbilical artery Doppler abnormalities are detected [3-5]. Diagnosis of FGR in prenatal care is very important to take preventive actions for decreasing perinatal morbidity and mortality. Early-onset FGR onset of FGR before 32 weeks of gestation without congenital anomalies, is associated with preeclampsia, increased perinatal morbidity and mortality [4]. Late-onset FGR FGR diagnose >32 weeks of gestation with a higher risk of perinatal hypoxic events and more without congenital anomalies [4]. Although perinatal morbidity and mortality are low, neurodevelopment may be affected [4,5]. The difficulty of late-onset FGR in clinical practice; is to try to minimize the risk of stillbirth Excessive obstetric intervention and neonatal sequelae of iatrogenic preterm birth are the other problems of management of late-onset FGR [6]. Advanced maternal age is associated with adverse maternal and

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Corresponding Author: Nazli Topfedaisi Ozkan, [1]Yüksek İhtisas University School of Medicine , Department of Gynecology and Obstetrics, Ankara, Türkiye
Email: drnazliozkan@gmail.com

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fetal outcomes. Lower fertility, using of assisted reproductive therapy, diabetes mellitus and hypertension are severe problems in this age group such as diabetes and [7]. Association between advanced maternal age and perinatal complications such as low-birthweight, preterm birth, stillbirth, chromosomal abnormalities, gestational diabetes, and hypertension are well known [7-10].

Hypertension either chronic or pregnancy induced are the leading causes of neonatal and maternal morbidity and mortality [11,12]. Therefore, blood pressure measurement is an important part of pregnancy care. However, the blood pressure measured in the office does not always coincide with the blood pressure that the patient has in daily life. Masked hypertension is a relatively unknown clinical condition in which a patient measures high blood pressure at home but has normal blood pressure in the clinic and is therefore often not diagnosed. Studies in non-pregnant women have shown that masked hypertension is as common as white coat hypertension. Unlike white coat hypertension, which has a lower risk of cardiovascular consequences than chronic hypertension, masked hypertension can lead to cardiovascular damage like chronic hypertension [13]. Thus, masked hypertension can have serious consequences for the pregnant woman and the fetus, as hypertension itself increases the risk of placental insufficiency, and intrauterine growth retardation in the mother [11].

Data about masked hypertension in pregnancy is not clear. Routine use of ABPM is not recommended [14-16]. The main purpose of this study is to investigate the effect of masked hypertension on late-onset FGR.

Material and Methods

This is a retrospective cohort study. A total 60 women over the age of 40 who had a singleton delivery at ≥36 weeks' gestation were included in the study. Data were extracted from prenatal follow-up files and maternal discharge data linked to infant birth certificate records. This study was conducted with the understanding and the consent of each participant, and was approved by the local ethics committee, date and number of aprroval document is march 2021 3916.

Thirty singleton pregnancies with late-onset FGR were accepted as the patient group, and 30 pregnant women without FGR were accepted as the control group. Women with maternal chronic hypertension, pregestational or gestational diabetes mellitus, chronic kidney disease, rheumatoid disease history, tobacco use, cardiac arrhythmia, fetal genetic abnormality or placental abnormality were not included in the study. After taking detailed anamnesis from all individuals included in the study, detailed physical examination, obstetric examination and ambulatory blood pressure monitoring (ABPM) were performed.

The third-trimester visit, at 30+0 to33+6 weeks' gestation, included USG (Voluson™ E6, GE, USA) to assess fetal growthbased on the EFW [2]. FGR is defined as the EFW or abdominal circumference 10% below the week of gestation and defined using the classic Hadlock formula [2]. The diagnosis of FGR was confirmed by the obstetrician who was not involved in the research process. The cardiologist who evaluated the accuracy and validity of the ABPM results is not aware of the obstetric evaluation of the individuals included in the study. All subjects underwent BP measurement by twenty-four-hour ABPM (BR-102 plus Schiller, Switzerland). The measurement interval of BP during the day is 15-20 minutes and 30-60 minutes intervals at night, and the average of blood pressure for 24 hours, day and night. A minimum of 14 awake readings and 6 sleep measurements was required for an ABPM session to be considered adequate [17]. For this analysis, a normal clinic BP was defined as <140/90 mmHg, a normal awake ABP was defined as <135/85 mmHg, a normal night (sleep) ABP was defined as <120/70 mmHg and a normal 24-hour ABP was defined as <130/80 mmHg [17].

Analyses

Continuous parametric and non-parametric data were calculated respectively, as mean ± standard deviation or median (25th and 75th percentile). Discontinuous variables are presented as number (%). Continuous variables were analyzed using the unpaired Student's t-test and the Mann–Whitney U-test for normally and non-normally distributed continuous data, while categorical variables were analyzed using the Pearson $\chi 2$ test. The observed measurements of EFW were expressed as the respective Z-scores corrected for gestational age. Statistical analyzes were performed using Statistical Package for Social Science (SPSS Inc., for Windows version 15.0).

Results

Between February 2021 and February 2023, 60 eligible women were recruited to this study. Characteristics of the study participants are shown in Table 1. The clinical characteristics of both groups were similar. The mean age of the patient and control groups were similar. Fasting blood glucose, blood total cholesterol, HDL, LDL, triglyceride, creatinine, hemoglobin, ferritin values and obstetric histories were similar in both groups (Table 1). In the echocardiographic examination performed by the cardiologist, no serious valve pathology, structural heart disease, which would adversely affect the course of pregnancy, was observed in both groups. Left ventricular ejection fraction, left ventricular septum and lateral wall thickness, left atrium and aortic root measurements were similar (Table 2).

The prevalence of masked hypertension was statistically significantly higher in the group with late-onset FGR (13%-43% vs 5%-16.7% p=0.02). Office systolic blood pressure measurement (125.5±4.1 mmHg vs 118.5±5.7 mmHg p=0.016), 24-hour systolic blood pressure measurement (125±9 mmHg vs 119.7±5.7 mmHg p=0.03), and ambulatory nocturnal diastolic blood pressure measurement (66.7±10 mmHg vs 61.±5.5 mmHg p=0.03) were higher in the group with FGR (Table 3).

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Table 1. Clinical characteristics of the study population according tol te-onset fetal growth restriction (FGR) or normal growth

	Normal Growth	Late-onset FGR	p
Age (mean, year±SD)	42.6±1.6	42.6±1.7	N/S
Gravida (median)	2 (0-3)	2 (0-3)	N/S
Fasting blood glucose (mean mg/dL±SD)	99.4±2.6	98.4±3.5	N/S
Total cholesterol (mean mg/dL±SD)	200±45	197.8±39.1	N/S
HDL cholesterol (mean mg/dL±SD)	46.8±15.2	51.5±15.5	N/S
Trigliseride (ortalama mg/dL±SD)	143.7±65.3	133.3±51.7	N/S
LDL cholesterol (mean mg/dL±SD)	122±41.8	116.3±32.1	N/S
Creatinine (mean mg/dL±SD)	1.1±0.07	1.0±0.08	N/S
Hemoglobin (mean mg/dL±SD)	11.7±1.9	11.7±1.7	N/S
Ferritin (mean mg/dL±SD)	32.6±14.9	36.9±12.6	N/S
Body mass index (mean kg/m2±SD)	25.3±2.2	26.1±2.1	N/S

HDL: high density lipoprotein, LDL: low density lipoprotein

Table 2. Transthoracic echocardiographic features of the groups

	Normal Growth	Late-onset FGR	p
Left ventricular ejection fraction (mean±SD)	64.6±1.5	63.1±2.4	N/S
Left ventricular end-diastolic posterior wall thickness (mean mm±SD)	10±1	10±1	N/S
Left ventricular end-diastolic posterior wall thickness (mean mm±SD)	9±0.7	10±1	N/S
Left atrial diameter (mean mm±SD)	34±3	35±2	N/S
Aortic diameter (mean mm±SD)	28±1	28±2	N/S

Table 3. Office and ambulatory blood pressure measurements of the groups

	Normal growth	Late-onset FGR	p
Office heart rate (mean, beats/min±SD)	80.6±9	81.7±10.1	N/S
Office systolic blood pressure (mean mmHG±SD)	118.5±5.7	125.5±4.1	0.016
Office diastolic blood pressure (mean mmHG±SD)	75.4±6.6	77.2±6.1	N/S
Ambulatory heart rate (mean, beats/min±SD)	74.8±9	73.2±9	N/S
24-hour systolic blood pressure (mean mmHG±SD)	119.7±5.7	125±9	0.03
24-hour diastolic blood pressure (mean mmHG±SD)	66.4±8.7	69.1±8.8	N/S
Day-time systolic blood pressure (mean mmHg±SD)	123.7±6.9	124.8±6.7	N/S
Day-time diastolic blood pressure (mean mmHg±SD)	71.8±8.4	76±11	N/S
Night-time systolic blood pressure (mean mmHg±SD)	110.6±5.5	107.5±9.7	N/S
Night-time diastolic blood pressure (mean mmHg±SD)	61.±5.5	66.7±10	0.03
Masked hypertension (n, %)	5 (6.7%)	13 (43%)	0.02

Discussion

Hypertension during pregnancy is one of the leading causes of maternal and perinatal morbidity and mortality (11).

Blood pressure is a continuous variable and there is actually no specific distinction between normal and abnormal values. However, specific blood pressure limits have been established for diagnosis, prognosis and the decision to initiate treatment (18-21). Chronic hypertension is the most common chronic disease in general practice. It is seen in approximately 10% of women of reproductive age [18]. Chronic hypertension is defined when diagnosed before or during the first 20 weeks of pregnancy and lasting more than 12 weeks after delivery with repeated measurements of systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg [19]. Complicates 2.36% of pregnant women [20]. Gestational hypertension is defined as pregnant women without chronic hypertension who have systolic blood pressure measurements ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after the 20th week of pregnancy, often near term, in the absence of proteinuria. In this condition hypertension resolves before the 12th week postpartum. The identification of these two clinical conditions associated with pregnancy is based on repeated office blood pressure measurements [20].

Masked hypertension is a clinical condition seen in approximately 15% of individuals with normal office blood pressure

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measurements. The prevalence is higher in young people, male gender, smokers, and individuals with anxiety and work stress. The diagnosis of MH is when a patient has an office BP level <140/90 mmHg and ABPM parameters are in the hypertensive range (24-hour mean BP ≥130/80 mmHg and/or day-time mean ≥135/85 mmHg and/or night-time mean ≥120/70 mmHg) is placed [21]. These patients face the same total cardiovascular risk seen in stage I hypertensive individuals [22]. Mental stress, smoking, heavy alcohol intake, insomnia, metabolic syndrome, diabetes mellitus and chronic kidney disease are risk factors for masked hypertension [23].

Late-onset FGR is defined as the onset of FGR at 32 weeks or more without congenital anomalies. It is leads to increased perinatal mortality in both term and preterm infants. Infants with FGR are also at risk for significant long-term morbidity, including growth abnormalities and suboptimal neurodevelopment. Also, individuals with FGR may be prone to cardiovascular disease, hypertension, and chronic kidney disease in adulthood [11]. Maternal vascular diseases (such as chronic hypertension), kidney diseases, diabetes mellitus, collagen vascular diseases and antiphospholipid syndrome are risk factors for FGR [11,12]. Some of the conditions that are among the maternal risk factors also play a role in the development of masked hypertension.

Blood pressure measurement in pregnant women is mostly based on single measurements in conjunction with routine pregnancy checkups. Two recent studies have shown that close control and treatment of gestational hypertension significantly reduces the risk of severe hypertension in the pregnant woman [24,25]. Home blood pressure measurements carried out by the pregnant woman herself are not time-specific and therefore do not necessarily give a real picture of the pregnant woman's blood pressure throughout the day. 24-hour blood pressure measurement is not currently included in the assessment of hypertension in pregnant women. Masked hypertension is possibly a precursor to persistent hypertension in pregnancy and is therefore only detected when other complications such as preeclampsia or fetal growth retardation are manifested. Also, older pregnancies are more likely to have elevated blood pressure. The risk of masked hypertension should also be considered in this group.

In our study, pregnant women with placental and fetal risk factors were not included. Also, women with a diagnosis of chronic disease were not evaluated within the scope of the study. Although the number of pregnant women included in the study was small, the prevalence of masked hypertension was found to be statistically significantly higher in the current sample of the group with late-onset FGR. Even if office measurements are normal, it may be appropriate to investigate the presence of masked hypertension in this group. If masked hypertension is common in pregnant women who are in the risk group, this may mean that we overlook hypertension that requires treatment and therefore expose the pregnant woman to serious complications in the long term as well as unnecessary complications in pregnancy. It cannot be excluded that masked hypertension over a long period of time may lead to increased risks for the fetus in the form of intrauterine growth retardation and preterm delivery.

Currently, there are no evidence-based guidelines on whether to treat masked hypertension, but lifestyle changes focused on diet and exercise are recommended. Conditions which could possibly have been prevented or improved with blood pressure-lowering treatment [26].

However this study has some limitations to be discussed. First, this is a preliminary study with a small sample from one single center. Second, a limited number of patients were evaluated. Despite these limitations, our findings provide additional information to the few data on this topic in the literature.

Conclusion

In conclusion, masked hypertension should be kept in mind in pregnant women who occasionally have high blood pressure but are clinically normotensive. Masked hypertension should also be kept in mind, especially when fetal growth restriction is detected. We need more studies on 24-hour ABPM compared to the blood pressure measured in the clinic, especially in high-risk pregnant women.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical Approval
The approval of the ethics committee was taken from local comitee. Date and number of aprroval document is 2014 399192.

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