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ORIGINAL ARTICLE

Altered Fetal Cardiac Function in Smoking During Pregnancy

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Abstract Maternal smoking during pregnancy remains a major public health issue and is associated with adverse perinatal outcomes. This study aimed to evaluate fetal cardiac functions in chronic maternal smoking during pregnancy and to compare them with non-smoker pregnant women. Forty-two smoker pregnant women between 24 and 34 weeks of gestation and gestational age-matched 44 non-smoker pregnant women were enrolled in this cross-sectional study. Fetal cardiac functions were measured using conventional Doppler echocardiography. The peak velocities of the mitral valve during early diastole (E) and atrial contraction (A) were measured, and the E/A ratio was calculated. The following time periods were also calculated; isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT), and ejection time (ET). Then, the fetal left ventricle modified myocardial performance index (Mod-MPI) was calculated. No significant differences were noted between the groups in terms of E, A, and E/A ratio z-scores ($p > 0.05$). The ICT and IRT z-scores were found to be significantly higher in the study group compared with those in the control group ($p = 0.001$ and $p = 0.034$). Mod-MPI z-score was also found significantly higher in the study group than in the control group ($p = 0.034$). There was no significant difference between the groups in terms of ET ($p > 0.05$). The signs of systolic, diastolic, and global cardiac dysfunction were demonstrated in fetuses of pregnant women with chronic smoking. It, therefore, merits consideration that the fetal heart is also exposed to the detrimental effects of smoking.

Keywords Maternal smoking · Modified myocardial performance index · Fetal cardiac function · Conventional doppler echocardiography

Introduction

Although there has been a recent declining trend in maternal smoking during pregnancy, it still remains a major public health issue. Unfortunately, 52.9% of smoking women continue to smoke during their pregnancy [1]. Maternal smoking during pregnancy is associated with congenital anomalies, preterm labor, low birth weight, spontaneous abortion and sudden infant death. Besides, offsprings of smoking mothers more commonly present long term behavioral and psychiatric problems [1–3]. Nicotine is the known major bioactive component of cigarette smoke, which essentially contains many chemicals and carcinogens [4]. In persistent smoking during pregnancy, the fetus gets exposed to the detrimental effects of cigarettes via fetoplacental transfer leading to a pathological process that impairs fetoplacental development [5]. Maternal smoking during pregnancy has

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been associated with uteroplacental dysfunction [6]. Fetal cardiac effects have also been reported, including a temporary increase in fetal heart rate and a decline in FHR variability [7, 8].

The Myocardial Performance Index (MPI) was first introduced by Tei et al. to assess adult cardiac functions [9]. MPI is a pulse wave Doppler-derived measurement of both systolic and diastolic heart function [9, 10]. Current literature has a wide range of MPI reference values for assessing left ventricular function. Hernandez-Andrade et al. introduced the modified myocardial performance index (Mod-MPI) taking as reference point Doppler echos of mitral and aortic valve clicks for measuring time periods in the calculation of the MPI. In this way, they reported less variability, better repeatability and improved interobserver agreement in time period measurements [11]. MPI has found itself a place in many studies that assess cardiac function in both normal and complicated pregnancies being claimed as a useful method for a global assessment of cardiac functions in complicated pregnancies [12, 13]. Isovolumetric relaxation time (IRT) is the main component of MPI. IRT is an indicator of diastolic dysfunction presenting an early impairment in cardiac function [14]. Isovolumetric contraction time (ICT) and ejection time (ET), the other components of MPI, are indicators of systolic function [15]. The E wave / A wave peak velocity (E/A) ratio at the mitral valve is another tool used to assess ventricular diastolic function [16].

Functional fetal echocardiography is a non-invasive method for anatomic, functional and hemodynamic assessment of the fetal heart. This study aims at evaluating fetal cardiac functions in chronic maternal smoking during pregnancy, hypothesizing, that smoking, which has detrimental effects on the fetus may also affect fetal cardiac function. The modified MPI was calculated in fetuses of smoking mothers for assessment of fetal cardiac function, and compared to the control group.

Materials and Methods

Forty-two smoker pregnant women between weeks 24 and 34 of gestation were enrolled in this cross-sectional study as the study group. The control group consisted of gestational age-matched 44 non-smoker pregnant women. The study protocol was reviewed and approved by the local ethics committee. Informed consent was obtained from all patients prior to enrollment, according to the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh. The participants in the study group who smoked more than 10 cigarettes a day abstained from smoking at least 6 hours before the ultrasound examination to offset the acute effects of smoking.

All ultrasound examinations were performed by a maternal-fetal medicine specialist in the absence of fetal movements using a Toshiba Aplio 500 (Toshiba Medical Systems, Co., Ltd., Otawara, Japan) ultrasound machine equipped with a 3.5-MHz convex transducer. After fetal anatomy assessment, fetal biometry, amniotic fluid index, umbilical artery, middle cerebral artery (MCA) and mean uterine artery Doppler indices were measured. Mod-MPI measurements were performed as originally described by Hernandez-Andrade et al. [11]. After obtaining an apical four-chamber view, the ultrasound probe was swept apically, and the origin of the aorta was visualized. The Doppler sample was placed at a location to include both the lateral wall of the ascending aorta and the internal leaflet of the mitral valve, where the clicks corresponding to the opening and closing of the two valves were clearly visualized. The Doppler settings were adjusted to the size of the sample volume of 3 mm, wall motion filter 300 Hz and sweep speed 5 cm/s. The insonation angle of the ultrasound beam was kept below 15 degrees and no angle correction was applied. The peak velocities of the mitral valve during early diastole (E) and atrial contraction (A) were measured, and the E/A ratio was calculated. The following time periods were also measured; ICT, IRT, and ET (Fig. 1). Then Mod-MPI was calculated by using the formula (ICT + IRT)/ET. The measurement of all velocities was made from the same cardiac cycle.

Multiple pregnancies, the presence of fetal structural or chromosomal anomaly, obstetric complications (e.g., fetal growth restriction, oligohydramnios, preeclampsia), and maternal co-morbidities (e.g., chronic hypertension, diabetes mellitus) were defined as exclusion criteria.

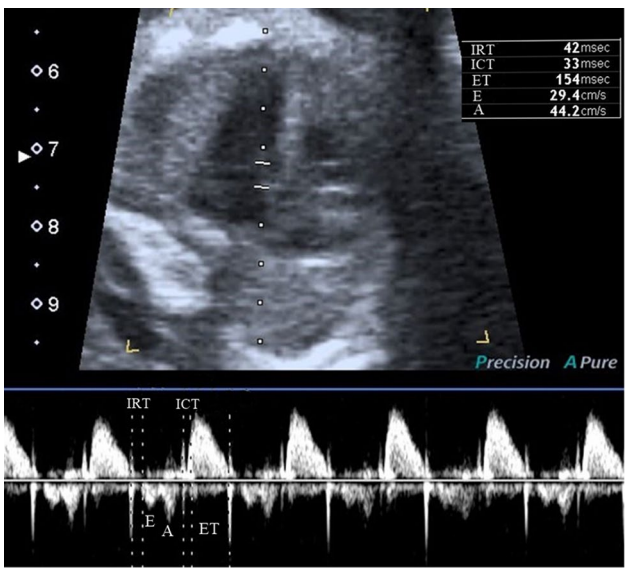

Fig. 1 Conventional Doppler echocardiography measurement of isovolumetric relaxation time (IRT), isovolumetric contraction time (ICT), ejection time (ET), E wave and A wave peak velocities

Statistical Analysis

All analyses were performed using the Statistical Package for Social Science (SPSS) software, version 24 (Chicago, IL, USA). Conformity of data to normal distribution was evaluated using the Shapiro-Wilk test, and the homogeneity of variance was assessed using Levene's test. Doppler indices and the calculated fetal cardiac function parameters were converted into z-scores. The variables with normal distributions were compared between the groups using the independent samples t-test and were expressed as mean ± SD. The Mann-Whitney U test was used to analyze non-normally distributed variables among the two groups, and the results were expressed as median and minimum-maximum. A two-tailed p value < 0.05 was considered statistically significant.

Results

The demographic characteristics and perinatal outcomes of the groups are shown in Table 1. No significant differences were noted between the groups in terms of maternal age, gravida, parity, body mass index (BMI) and gestational age at ultrasound examination ($p > 0.05$). The birth weight was found to be significantly lower in the study group compared with those in the control group ($p < 0.001$). There were no significant differences between the groups in terms of the gestational age at delivery and APGAR scores ($p > 0.05$).

Doppler indices and the results of cardiac function measurements are shown in Table 2. The z-scores of the umbilical artery pulsatility index (PI) and MCA PI values were significantly higher in the study group compared with those in the control group ($p = 0.007$ and $p = 0.009$, respectively). There were no significant differences between the groups in terms of E, A, and E/A ratio z-scores ($p > 0.05$). The study group had significantly more prolonged ICT and IRT than in the control group ($p = 0.001$ and $p = 0.034$, respectively). No significant difference was noted between the groups in terms of ET z-score ($p > 0.05$). The Mod-MPI z-score was found significantly higher in the study group than in the control group ($p = 0.034$). There was no significant difference between the groups in terms of fetal heart rate ($p > 0.05$).

Table 1 Demographic characteristics and perinatal outcomes of the groups

	Control (n = 44)	Smokers (n = 42)	p value
Age (years)	29.8 ± 4.6	29.4 ± 5.6	0.729
Gravida (n)	2.5 (1–6)	3 (1–6)	0.260
Parity (n)	1.5 (0–3)	1 (0–4)	0.786
BMI (kg/m^2)	25.8 ± 2.6	26.9 ± 3.4	0.129
GA at ultrasound examination (weeks)	26.4 (24–34)	27.1 (24.1–34)	0.312
GA at delivery (weeks)	39.1 ± 0.8	38.8 ± 0.7	0.097
Birth weight (g)	3404.1 ± 240.2	3181.4 ± 251.1	**< 0.001**
1-min Apgar score	8.5 (6–9)	8 (6–9)	0.305
5-min Apgar score	10 (7–10)	9 (8–10)	0.168

BMI body mass index, *GA* gestational age. Data are expressed as means (± SDs) or medians (minimum-maximum). Bold p values refer to statistically significant results

Discussion

Fetal Mod-MPI values, as an indication of global cardiac function, were found significantly high in the smoker's group, when compared to the control group in this study, which aimed to assess the cardiac functions of the fetuses exposed to chronic maternal smoking. Likewise, ICT, as an indication of systolic cardiac function, and IRT, as an indication of diastolic cardiac function, were also found significantly higher.

Fetal Mod-MPI values were found high in pregnancies complicated with fetal growth restriction, cholestasis and diabetes and were associated with fetal global cardiac dysfunction [17, 20]. To the best of our knowledge, this study is the first to evaluate fetal cardiac function by Mod-MPI in chronic maternal smoking during pregnancy. The main limitations of this study are its cross-sectional design and the small number of participants.

Maternal smoking is associated with several adverse pregnancy outcomes [3]. Nicotine freely and rapidly crosses the placenta. The concentration of nicotine and its

Table 2 The Doppler indices and the results of cardiac function measurements

Variable	Control (n = 44)	Smokers (n = 42)	p value
UA PI z-score	− 0.28 ± 0.82	0.29 ± 1.08	**0.007**
Mean UtA PI z-score	0.03 ± 0.92	− 0.04 ± 1.08	0.719
MCA PI z-score	− 0.27 ± 0.9	0.28 ± 1.02	**0.009**
E z-score	− 0.14 ± 0.83	0.14 ± 1.14	0.182
A z-score	− 0.02 ± 0.81	0.02 ± 1.17	0.838
E/A ratio z-score	− 0.17 ± 0.86	0.18 ± 1.1	0.091
ICT z-score	− 0.36 ± 0.67	0.37 ± 1.14	**0.001**
IRT z-score	− 0.22 ± 0.77	0.23 ± 1.15	**0.034**
ET z-score	0.12 (− 2.7–1.4)	− 0.51 (− 1.71–2.03)	0.821
Mod-MPI z-score	− 0.22 ± 0.81	0.23 ± 1.12	**0.034**

UA umbilical artery, *UtA* uterine artery, *MCA* middle cerebral artery, *E* early diastole, *A* atrial contraction, *ICT* isovolumetric contraction time, *IRT* isovolumetric relaxation time, *ET* ejection time, *Mod-MPI* modified myocardial performance index. Data are expressed as means (± SDs) or medians (min-max). Bold p values refer to statistically significant results

metabolite cotinine is significantly higher in amniotic fluid, placental tissue and fetal serum than in maternal serum [21]. The effect of nicotine on the cardiovascular system is mediated through endogenous nicotinic acetylcholine receptors (nAChR) [22]. Smoking has acute cardiovascular effects such as an increase in myocardial contractility, and temporary elevation in heart rate and blood pressure [23]. Blood pressure and heart rate of chronic smoker adults were found to be higher than the non-smokers under ambulatory blood pressure monitoring [24]. Endothelin-1 (ET-1) is a potent vasoconstrictor and smokers have elevated levels of ET-1 [25]. In this study, the increase in the umbilical artery and MCA PI values found in the fetuses exposed to chronic habitual smoking can possibly be associated with the vasoconstrictor effects of cigarettes and their metabolites on cerebral and umbilical vessels.

Shao et al. concluded that nicotine inhalation in pregnant rats resulted in a temporary decrease and irregular fluctuations in uterine artery blood flow in association with cardiac arrhythmia and high magnitude irregular fluctuations of systemic blood pressure as well. They suggested that sudden elevation of nicotine levels in arterial blood first stimulated and later desensitized autonomic nAChRs resulting in cardiac dysfunction [26]. Whereas, Oakes et al. demonstrated right ventricular systolic pressure increase and right ventricular hypertrophy, with no change in the left ventricle when mice were exposed to chronic nicotine inhalation. They concluded that changes in systemic and pulmonary blood pressure could result in right ventricular remodeling and pulmonary hypertension [27]. It was demonstrated that acute nicotine exposure at doses similar to those in habitual smoking, increased DNA synthesis in vascular smooth muscle cells and facilitated proliferation [22]. Nicotine induces fibrosis in several organs by increasing collagen and fibronectin. Since nicotine is a vasoconstrictor, it results in both fetal hypoxia and reduction in placental nutrient transport by way of decreasing uteroplacental flow. In addition to nicotine, cigarette smoke contains several gases such as carbon monoxide, hydrogen cyanide and nitrogen oxide. These gases cause both placental and fetal tissue hypoxia by acting through different mechanisms [28].

Alam et al. evaluated cardiac functions in smoker adults with both conventional Doppler echocardiography and Doppler tissue imaging and demonstrated that there was a significant change in left ventricular diastolic function [29]. Similarly, Barutçu et al. reported that acute smoking caused a significant change in both left and right ventricular diastolic function in healthy adults [30]. Sorensen and Borlum reported that acute maternal smoking caused a temporary increase in fetal heart rate, however, no significant change in fetal cardiac functions [31]. ICT, as an indication of systolic dysfunction, and IRT, as an indication of diastolic dysfunction, were found significantly high in this study and thus it may be suggested that both systolic and diastolic left ventricular functions of the fetuses exposed to chronic smoking during pregnancy were affected. Similarly, the increase in left ventricular Mod-MPI values, as reported in this study, confirmed the detrimental effects of smoking on the fetal heart, as an indication of global cardiac dysfunction. Several studies in the literature have demonstrated detrimental effects of smoking on the fetus. As shown in this study, increased Mod-MPI values can be considered as one of the indicators that the fetal heart is also exposed to these detrimental effects of smoking. In order to encourage patients to cease smoking, these negative effects of smoking on the fetal heart can be included in prenatal counseling. In addition to this, intrauterine exposure to smoking may also adversely affect the cardiac function of individuals in their future lives, by causing adverse fetal cardiac programming.

Implications for Clinical Practice

In this study, it was observed that maternal smoking might have detrimental effects on fetal cardiac function. Including these adverse effects in prenatal counseling may provide additional benefits for the mother to cessation smoking.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Consent to Participate Written informed consent was obtained from all individual participants included in the study.

Consent for Publication Written informed consent regarding publishing their data was obtained from all participants included in the study.

Ethical Approval This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the local ethics committee of our university with the decision number 2019/1007.

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