RESEARCH ARTICLE

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Missed abortion and endothelial dysfunction

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Abstract

Objective: The aim of this study to evaluate endothelial dysfunction in missed abortion patients via flow and nitrate mediated brachial artery vasodilatation with ultrasonography. **Introduction:** The incidence of missed abortion among spontaneous miscarriages is high. Endothelial changes, including endothelial dysfunction, are main stage for the beginning and progression of atherosclerosis. It was demonstrated that intra-arterial TNF-α, furin, TGF-β2 causes an acute local vascular inflammation during missed abortion is associated with impaired endothelium-dependent vasodilatation. We evaluated these changes via nitrate and flow mediated vasodilatation before and shortly after surgical evacuation by ultrasonography. We tried to prove that endothelial dysfunction was related to missed abortion and temporary. **Method:** This cross sectional study included 54 missed abortus patient with in first 28 weeks of gestation. They were admitted to bicard clinic hospital for dilatation and curettage. All patients were evaluated by ultrasonography. Measurements of FMD (flow mediated vasodilatation) and NMD (nitrate mediated vasodilatation) obtained 12 h before surgery and with in 24 hour after surgery. After that all measurements statistically compared. **Result:** FMD and blood flow during flow mediated shear stress was impaired before surgery at hospitalization of patients and it improved shortly after surgery (Dilatation and vacuum aspiration). On the contrary NMD and blood flow during nitrate mediated dilatation was normal and not change after surgery. Also postoperative FMD was better than postoperative NMD. **Conclusion:** Missed abortion which may lead a lot of metabolic and inflamatuvary changes in endothelium. And Endothelium dependant vasodilatation is impaired until evacuation of fetus and placenta. Shortly after evacuation endothelial response of NO(Nitric oxide) is increased as a result of this endothelium dependant vasodilatation increased. Nitrate dependant vasodilatation was same before and after evacuation.

Keywords: Flow Mediated Vasodilatation, Nitrate Mediated Vasodilatation, Missed Abortus, Ultrasonography.

OBJECTIVE

The aim of this study to evaluate endothelial dysfunction in missed abortion patients via flow and nitrate mediated brachial artery vasodilatation with ultrasonography before and after surgical evacuation. (Dilatation and vacuum aspiration).

INTRODUCTION

Literature on the etiology, diagnosis, and treatment of missed abortion is clear. Missed abortion during the 1st 28 weeks of gestation is defined as retention in the uterus of an abortus [1-3]. The incidence of missed abortion among spontaneous miscarriages is 2.6-9.4%. Miscarriages have been observed widely and the most common complication of pregnancy, with 12%–24% of all clinically recognized pregnancies ending in miscarriage [4,5]; and approximately a third of all pregnancies, including those not brought to clinical attention, lost through miscarriage [6-9]. Changes in the endothelium, including endothelial dysfunction, are essential for the initiation and progression of atherosclerosis [10,11]. Maternal endothelial dysfunction prior to pregnancy has been suggested to impair the invasion of trophoblasts into the uterine wall, which is necessary for a successful pregnancy. Women with a history of recurrent miscarriages have been found to have higher rates of endothelial dysfunction relative to women who experienced uncomplicated pregnancies and women who have endothelial dysfunction corrected prior to, or early in, pregnancy have improved outcomes [11-15]. But there is a lack of studies about

endothelial function and its relationship with missed abortus. We evaluated 54 miscarriage patients 'endothelium via flow mediated vasodilatation (endothelium dependant) with ultrasonography. Also nitrate mediated vasodilatation (endothelium-independent) as a result of vascular smooth muscle relaxation via increasing guanizine monofosfat activation were evaluated and FMD and NMD were compared pre-postoperatively

METHOD

This cross-sectional study included 54 missed- abortion-patient, mean age (34 ± 2.3). All they were within 1st 28 weeks of gestation and were diagnosed first time as a missed abortion with USG and clinical-laboratory findings. They were admitted to hospital to abortion via surgically. All patients' surgical evacuation (dilatation and vacuum aspiration) were performed under general anesthesia. Patients with hypertension, diabetes, diagnosed cardiovascular disease, usage of vasoactive medication were excluded. All informed consents were obtained. Flow and nitrate mediated vasodilatations of brachial artery were measured at admission time and after abortion within 24 hours later and all measurements statistically compared.

The diameter of the target artery is measured by high-resolution external vascular ultrasound in response to an increase in blood flow (causing shear-stress) during reactive hyperemia (induced by cuff inflation and then deflation). This leads to endothelium-dependent dilatation; the response is contrasted with that to sublingual nitroglycerin, an endothelium-independent dilator as a result of vascular smooth muscle relaxation.

All measurements were done 12 hours before surgery and within 24 hours after surgery. Patients were studied in the fasting state; vasoactive medications were withheld for 24 h before the study. After 5 min of rest, the brachial artery was located above the elbow, and a longitudinal image of 6 to 8 cm was taken as the resting scan. A blood pressure cuff was placed on the forearm and inflated to 300 mm Hg for 4.5 min. The cuff was deflated, and after ~1 min, the second or FMD scan was obtained, which represents the endothelial-dependent dilation due to shear-induced endothelial nitric oxide production. The second rest scan was acquired after 15 min of rest, and endothelial-independent dilation was measured by calculation of the vasodilator response to exogenous nitrate 3 min after administration of 400 µg of sublingual nitroglycerin. The percent diameter changes for FMD and nitrate-mediated dilation was calculated in relation to its respective rest scan. All measurements statistically compared.

STATISTICAL ANALYSIS

All results are expressed as the mean ± SEM. Univariate analysis was performed using Student t-test. Categorical data were compared against a chi-squared distribution. Linear regression analysis was used to determine the relationship between continuous variables. A p value <0.05 was regarded as significant.

RESULTS

All results were statistically compared before and after abortion. Flow mediated vasodilatation namely endothelial-dependant brachial artery vasodilatation before surgery was (7.29± 0.39 %) and improved shortly after (10.23±0.40 %) surgical removal of fetal and placental tissues.(p<0.001) Also Increase in peak blood flow was statistically significantly improved after operation (334.7±8.9ml/min, 549 ±7.7ml/min, p<0.001) respectively And There were statistically meaningful increase in base line arterial diameters after surgery (3.78 ± 0.11 mm, 4.57± 0.12 mm, p=0.003) and blood flow (196.8± 6.4 ml/min, 297± 5.7ml/min, p= 0.012) respectively.(Table 2) Base line measurements arterial diameter and blood flow also nitrate mediated dilatation and peak blood flow during nitrate mediated hyperemia have statistically no significant differences after and before surgery. (Table 3) FMD and NMD before and after evacuation of fetal and placental material were compared in table 1 and there were statistically significant differences. Postoperative FMD (10.23±0.40 %) were significantly higher than postoperative NMD (7.0± 0.39 %, p=0.002) and There was no statistically significant difference between preoperative NMD and FMD. (6.99± 0.38 %, 7.0± 0.39%, p= 0.06)

Table 1: Comparison of FMD and NMD before and after evacuation of fetal and placental material

	Nitrate Mediated NMD Vasodilatation % (N=54)	Flow Mediated FMD Vasodilatation % (N=54)	P-VALUE
PREOPERATIVE	6.99± 0.38	7.29± 0.39	0.06
POSTOPERATIVE	7.0± 0.39	10.23±0.40	0.002

Table 2: Brachial Arterial Data of Flow mediated vasodilatation. (Endothelial-dependent dilation)

	PREOPERATİVE	POSTOPERATİVE	P-VALUE
Baseline arterial diameter(mm)	3.78 ± 0.11	4.57± 0.12	0.003
Baseline blood flow (ml/min)	196.8± 6.4	297± 5.7	0.012
Increase in peak blood flow during flow mediated hyperemia (%)	334.7±8.9	549 ±7.7	<0.001
Flow-mediated dilatation of brachial artery (%)	7.29± 0.39	10.23±0.40	<0.001

Table 3: Brachial Arterial Data of Nitrate mediated vasodilatation. (Endothelial-independent dilation)

	PREOPERATİVE	POSTOPERATİVE	P-VALUE
Baseline arterial diameter(mm)	3.58 ± 0.11	3.67± 0.12	0.75
Baseline blood flow (ml/min)	196.8± 6.4	197± 5.7	0.97
Increase in peak blood flow during nitrate mediated hyperemia	259.7±8.1	281±9.7	0.06
Nitrate-mediated dilatation of brachial artery (%)	6.99± 0.38	7.0± 0.39	0.31

DISCUSSION

In our study that was showed FMD mediated dilatation which are well known risk factors for arteriosclerosis was impaired in missed abortus patients. Interestingly FMD was improved after surgical removal of placenta and fetal structures. But Nitrate mediated vasodilatation didn't affect from surgical evacuation of fetal structures [14-16].

There is no study about showing endothelial dysfunction and missed abortus albeit there are a lot of studies FMD and pregnancy, preeclampsia, eclampsia. Oestrogen therapy in postmenopausal women is associated with lower the risk of cardiovascular events, and the augmented release on endothelium-derived nitric oxide by estrogens has been suggested to be one of the mechanisms for the cardio protective effects [15,16].

There are many of factors that promote endothelial dysfunction when present at abnormal levels by acutely inhibiting key Ca^{2+} signaling events and chronically promoting the breakdown of endothelial cell-cell contacts. Increasingly, our understanding of how the contributions of the placenta, immune cells, and the endothelium itself promote the endocrine milieu of preeclampsia is becoming clearer. In one study it was described in detail how the complex endocrine environment of preeclampsia affects endothelial cell function, why this has contributed to the difficulty in fully understanding and treating this disorder, and how a focus on signaling convergence points of many hormones may be a more successful treatment strategy [16-18].

But recently some articles published about missed abortion and endothelial dysfunction and they stated that endothelial dysfunction may related to material which is emitted to systemic circulation from fetal and placental tissues and hormonal changes [18]. Etiopathogenesis of prolonged retention of an abortus can result in fetal maceration or mummification and missed abortion is associated with intrauterine infections, severe abnormalities, inhibition of uterine contraction, or impairment of the hormonal balance. The most frequent complications of missed abortion are uterine hemorrhage, infection, and malignant transformation [19-21].

In immunohistochemical examination, the immunoreactivities of furin, TNF-α, and TGF-β2 were found to be higher in syncytiotrophoblastic cells in the missed abortion group than in the normal pregnancy group in one study [13]. And it had been demonstrated that Intra-arterial TNF-α causes an acute local vascular inflammation that is associated with impaired endothelium-dependent vasomotion as well as a sustained and substantial increase in endothelial t-PA release. TNF-α has potentially both adverse vasomotor and beneficial profibrinolytic effects on endothelial function [21-23].

In our study we were demonstrated that endothelial dysfunction during missed abortus temporary and it can be improved after evacuation of fetal structures via dilatation and curettage. We estimated flow mediated endothelial dysfunction via USG method. Also, we found nitrate dependent endothelial dysfunction was not impaired. Which means NO response of endothelium normal but NO synthesis inadequate during missed abortion. Shortly after evacuation NO synthesis improves and FMD is restored this short disturbance of FMD can play role in etiopathogenesis of missed abortion and as a result of that some kind of drugs which are targeting endothelial dysfunction can be used to prevent missed abortion. But our study had some shortcomings. Some of that study scale is small and we were

not evaluated NO plasma levels. Large scale studies with immunohistochemical evaluation needed so that FMD's role will be clear in ethiopathogenesis of missed abortion.

ABBREVIATION LIST

FMD: Flow Mediated Vasodilatation
NMD: Nitrate Mediated Vasodilatation
NO: Nitric Oxide
TNF-α: Tumor necrosis factor-α
TNF-β2: Tumor necrosis factor-β2
T-PA: Tissue plasminogen activator

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