American Journal of Medicine and Medical Sciences 2021, 11(9): 635-639
DOI: 10.5923/j.ajmms.20211109.07

Evaluation of the Effectiveness of the Methods for Determining Endothelium Dysfunctions in Pregnant Women with Obstetric Bleeding in Anamnesis

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Abstract In accordance with the purpose and objectives of this study, we studied the clinical course of labor and the postpartum period in 112 pregnant women who had a history of massive obstetric postpartum hemorrhage. At the 1st stage, 112 pregnant women in the 1st and 2nd trimester with a history of postpartum hypotonic bleeding were examined, aged 18 to 45 years, constituting the 1st group. Group II - a control group, consisted of 30 patients, comparable in age, without gynecological pathology, severe somatic diseases and severe metabolic disorders, with a physiological history of pregnancy and childbirth. After examination and identification of the risk group for the occurrence of postpartum hypotonic bleeding, pharmacotherapy is prescribed according to the developed algorithm in group 1A, which will include 52 patients. Group 1B will include 60 patients with the traditional method of management.

Keywords Postpartum atonic bleeding, Endothelial dysfunction, Cuff test, Vascular resistance, Bleeding prognosis, Preeclampsia

1. Introduction

In recent years, in all economically developed countries, the number of consequences of pregnancy and childbirth, in particular obstetric bleeding, has been increasing, which leads to a decrease in the quality of life and an increase in mortality [1,3,6]. According to the World Health Organization (WHO), "... obstetric hemorrhage ranks 3-4th in the mortality rate of women." Massive blood loss during childbirth becomes the cause of death of women, that is, "... in pregnant women, in 20–45% of cases, mortality is due to obstetric bleeding" [4,7,8]. The high frequency of obstetric bleeding during pregnancy and mortality in women, in turn, requires the development of modern approaches to improving the quality of life of women who have suffered massive blood loss during childbirth, and algorithms for managing patients [2,4,6,8]. Identification of endothelial dysfunction, regional hemodynamic parameters in women who have undergone massive blood loss, early signs of blood loss, a decrease in maternal and child morbidity and maternal mortality rates, as well as the establishment of the necessary preventive measures are among the urgent tasks of specialists in this field [2,6,7]. Among the numerous factors of endothelial origin, nitric oxide (NO) and angiotensin converting enzyme are recognized markers of endothelial dysfunction. In addition, in recent years, great importance in the development of endothelial dysfunction has been attributed to endothelin, which is capable, both directly and indirectly, through the generation of nitric oxide and the formation of angiotensin II, to influence the change in vascular tone [1,3,7,8]. In recent years, when discussing the genesis of postpartum hemorrhage, special attention has been paid to endothelial dysfunction and damage to the peripheral vascular system. Even small defects of coagulation during disintegration of the vascular wall against the background of endothelial dysfunction, nitric oxide metabolism can end in the early postpartum period with fatal hemorrhages, while with the integrity of the vessels, bleeding can usually be stopped [3,4]. This greatly complicates the prognosis of PC, timely preclinical diagnosis and the implementation of preventive measures aimed at reducing maternal mortality.

The Aim of our research: introduction of a modern non-invasive method for determining endothelial dysfunction in pregnant women with a history of obstetric bleeding.

Received: Aug. 26, 2021; Accepted: Sep. 8, 2021; Published: Sep. 15, 2021
Published online at http://journal.sapub.org/ajmms

2. Materials and Methods

In accordance with the purpose and objectives of this study, we studied the clinical course of labor and the postpartum period in 112 pregnant women who had a history of massive obstetric postpartum hemorrhage. A

comprehensive clinical study, the study of early complications after massive bleeding was carried out for the period 2018-2020, who were hospitalized in the department of the city maternity complex, which is the base of the Department of Obstetrics and Gynecology of the Bukhara Medical Institute and the regional specialized maternity complex of the city of Bukhara. At the 1st stage, 112 pregnant women in the 1st and 2nd trimester with a history of postpartum hypotonic bleeding were examined, aged 18 to 45 years, constituting the 1st group.

Group II - a control group, consisted of 30 patients, comparable in age, without gynecological pathology, severe somatic diseases and severe metabolic disorders, with a physiological history of pregnancy and childbirth. After examination and identification of the risk group for the occurrence of postpartum hypotonic bleeding, pharmacotherapy is prescribed according to the developed algorithm in group 1A, which will include 52 patients. Group 1B will include 60 patients with the traditional method of management. Patients will be randomized using the envelope method. The effectiveness of pharmacotherapy will be assessed on the basis of examination of nitric oxide metabolites after the end of treatment and analysis of the course of the postpartum period.

3. Research Methods

Determination of markers of endothelial dysfunction (endothelin-1, nitric oxide, E-selectin, vascular endothelial growth factor - VEGF, PECAM-1) in peripheral blood was carried out using enzyme immunoassay. Endothelial function is determined by cuff test with reactive hyperemia of the maternal brachial artery (Ostroumova O.D., Dubinskaya R.E., 2005). Complex ultrasound and Doppler study with transabdominal and transvaginal transducer. Study of blood flow in the uterine, spiral and radial arteries, assessment of peripheral resistance by calculating the indices of resistance and pulsation.

4. Results of Research

It was found that in terms of age, frequency and nature of extragenital pathology, anamnestic data, obstetric and gynecological status, the examined women of the first group and the comparison group did not have a statistically significant difference. Of the total population surveyed at the time of the study, 92% of patients were married. When assessing social and living conditions, most of the women, 64%, characterized them as satisfactory, as good as noted by 26%, and as unsatisfactory by 10 patients. About half of the surveyed were housewives - 47.2%, 40.2% belonged to mental workers, 12.6% of women were engaged in manual labor. 14.3% of patients were students of various educational institutions. We analyzed somatic diseases that contributed to the emergence and increase of massive postpartum blood loss in the subjects. It should be noted that various somatic diseases were observed in 67% of pregnant women. From the presented figure, it is not difficult to notice that the age of women in all the studied groups was almost identical, and the groups for this feature were representative. According to the figure, bleeding in all groups was mainly observed in the active reproductive age of 26-30 years. An analysis of the formation of menstrual function in the study groups revealed the following features: in the main group, when taking anamnesis, an early formation of a regular menstrual cycle was revealed, and in the comparison and control group, a somewhat later formation was prevalent. When analyzing the duration of the menstrual cycle, no statistically significant difference was found in the study groups.

When studying the age, the onset of sexual activity showed that in the main group the patients began sexual activity at the age of 21-24 years, and in the comparison group at the age of 25 years or more, in the control group it was more common at the age of 17-20 years.

In the structure of somatic diseases, the leading place is occupied by iron deficiency anemia - 45.3%, in second place - varicose veins - 11.8%, in third place - urinary tract disease - 9.4.6%, etc. According to prospective data, it has been established that postpartum hemorrhage can occur in women without a burdened obstetric and gynecological history. In the structure of concomitant genital pathology, the first place is taken by chronic inflammatory diseases of the uterus and appendages, the second place is bacterial vaginosis, the third place is the pathology of the cervix - erosion of the cervix.

APTT indices were within the normal range only in 29.3% of women in the main group and in more than 75% of women in the comparison group. This indicator was increased in 33.8% and decreased in 36.9% of women who subsequently had bleeding. The INR indicator was within the normal range in all groups. In our studies, an increase in the total activity of prothrombin time was noted (17.46 ± 0.20 - in the main group and 16.52 ± 0.14 - in the comparative group versus 13.1 ± 0.25 - in the control group), a decrease in thrombin time 16.93 ± 0.2 in the main group, 17.03 ± 0.24 in the comparative group versus 18.22 ± 0.21 in the control group).

In order to determine the degree of development or correction of endothelial dysfunction in pregnant women, we used modifications of the method of D. Celemajer et al. - changes in the level of cuff placement, the area of location and an increase in the number of arterial trunks, at the level of which the vasomotor function of the endothelium can be assessed in pregnant women with a history of bleeding ...To do this, we examined the brachial, radial, and common femoral arteries, but good results were obtained when measuring the brachial artery, since during pregnancy, large cuffs are needed to measure the femoral artery. When examining the vasomotor function of the endothelium at the level of the brachial artery, there are two options for applying the cuff: in the upper third of the shoulder above the location zone and the anterior third of the forearm below the location

zone. When examining pregnant women with a history of bleeding in group 1 B, the cuff test gave the following results: pregnant women after receiving traditional therapy, the rate of flow dilatation varied from 5% to 12%. These indicators are considered very low, since this indicates circulatory disorders in the vascular bed and indicates a severe degree of endothelial dysfunction (table 1).

Table 1. Indicators of the cuff test in patients of group 1B

FULL NAME. Patient	Brachial artery diameter before test (D) and flow rate (V).	1 minute after 4 minutes of compress	2- minute	3- minute	4- minute	Flow dilatation rate%
patient 1	D= 4,5 mm. V= 85 cm/sec.	D= 3,1 mm. V= 120 cm/sec.	D= 3,4 mm. V= 110 m/sec.	D= 3,5 mm. V= 72 cm/sec.	D= 4,0 mm. V= 70 cm/sec.	12%
patient 2	D= 4,6 mm. V= 89 cm/sec.	D= 3,5 mm. V= 110 cm/sec.	D= 3,9 mm. V= 116 m/sec.	D= 4,0 mm. V= 72 cm/sec.	D= 4,2 mm. V= 70 cm/sec.	9,0%
patient 3	D= 4,8 mm. V= 88 cm/sec.	D= 3,6 mm. V= 135 cm/sec.	D= 3,7 mm. V= 100 m/sec.	D= 4,2 mm. V= 76 cm/sec.	D= 4,4 mm. V= 70 cm/sec.	9,0%
patient 4	D= 4,4 mm. V= 87 cm/sec.	D= 3,6 mm. V= 117 cm/sec.	D= 3,7 mm. V= 110 m/sec.	D= 4,2 mm. V= 69 cm/sec.	D= 4,1 mm. V= 62 cm/sec.	7,0%
patient 5	D= 4,6 mm. V= 87 cm/sec.	D= 3,7 mm. V= 120cm/sec.	D= 3,9 mm. V= 105 m/sec.	D= 4,0 mm. V= 72 cm/sec.	D= 4,1 mm. V= 70 cm/sec.	11%
patient 6	D= 4,7 mm. V= 88 cm/sec.	D= 3,2 mm. V= 130 cm/sec.	D= 3,5 mm. V= 111 m/sec.	D= 4,0 mm. V= 71 cm/sec.	D= 4,2 mm. V= 70 cm/sec.	11%
patient 7	D= 4,7 mm. V= 78 cm/sec.	D= 3,6 mm. V= 121 cm/sec.	D= 3,7 mm. V= 110 m/sec.	D= 4,0 mm. V= 70 cm/sec.	D= 4,2 mm. V= 70 cm/sec.	11%
patient 8	D= 4,8 mm. V= 80 cm/sec.	D= 3,7 mm. V= 121 cm/sec.	D= 3,9 mm. V= 111 m/sec.	D= 4,2 mm. V= 79 cm/sec.	D= 4,2 mm. V= 69 cm/sec.	12,5%
patient 9	D= 4,6 mm. V= 81 cm/sec.	D= 3,6 mm. V= 124 cm/sec.	D= 3,9 mm. V= 112 m/sec.	D= 4,0 mm. V= 65 cm/sec.	D= 4,4 mm. V= 65 cm/sec.	5,0%
patient 10	D= 4,7 mm. V= 84 cm/sec.	D= 3,5 mm. V= 132 cm/sec.	D= 3,9 mm. V= 106 m/sec.	D= 4,0 mm. V= 82 cm/sec.	D= 4,2 mm. V= 69 cm/sec.	11%
patient 11	D= 4,7 mm. V= 89 cm/sec.	D= 3,3 mm. V= 132 cm/sec.	D= 3,7 mm. V= 110 m/sec.	D= 4,0 mm. V= 75 cm/sec.	D= 4,4 mm. V= 71 cm/sec.	9,0%
patient 12	D= 4,6 mm. V= 88 cm/sec.	D= 3,4 mm. V= 130 cm/sec.	D= 3,7 mm. V= 110 m/sec.	D= 4,0 mm. V= 75 cm/sec.	D= 4,2 mm. V= 68 cm/sec.	9 %

In group 1, the prevention of the development of bleeding was carried out.

L-arginine (Tivortin) - 3 g / day. within 3 weeks from 18 weeks of gestation, at 24 weeks and 30 weeks, thus, three courses of 3 weeks are carried out with a break of 3 weeks. Therapeutically justified beginning of prophylaxis at any stage of pregnancy up to 34 weeks of pregnancy. The appointment of L-arginine helps to restore the level of nitric oxide, which is the main lever of influence on the vascular endothelium.

The vascular tone (total vascular resistance, blood pressure), atrombogenicity of the vascular wall, the activity of platelets and the blood coagulation system, the inflammatory, oxidative process, as well as the structural preservation of the layers of the vascular wall, depend on the adequate functioning of endothelial cells.

The conversion of L-arginine to nitric oxide is key to maintaining the normal functioning of the endothelium, incl. activity of physiological compensatory angiogenesis. L-arginine, simultaneously with the improvement of the functional state of the endothelium, increases the level of vascular endothelial growth factor in the blood serum, which indicates the activation of physiological compensatory angiogenesis. Tivortin (4.2% solution for infusion) is injected intravenously at a rate of 10 drops per minute in the first 10-15 minutes, then the rate of administration was increased to 30 drops per minute. The daily dose of the drug is 100 ml. The duration of treatment is 10 days. When examining pregnant women with a history of group 1 B bleeding, a cuff test after the first course of treatment with Tivortin showed the following results: pregnant women after receiving 1 course of our proposed treatment, the rate of flow dilatation varied from 13% to 14.5%. These indicators are considered very close to normal, since this indicates a sufficient effectiveness of our therapy with L-argin in violation of blood circulation in the vascular bed and indicates the restoration of endothelial dysfunction (table 2).

Table 2. Indicators of a cuff test in patients of group 1A

FULL NAME. Patient	Brachial artery diameter before test (D) and flow rate (V).	1 minute after 4 minutes of compress	2- minute	3- minute	4- minute	Flow dilatation rate%
Patient 1	D= 4,7 mm. V= 75 cm/sec.	D= 3,2 mm. V= 125 cm/sec.	D= 3,5 mm. V= 100 m/sec.	D= 3,7 mm. V= 75 cm/sec.	D= 4,1 mm. V= 72 cm/sec.	13%
Patient 2	D= 4,5 mm. V= 85 cm/sec.	D= 3,1 mm. V= 120 cm/sec.	D= 3,4 mm. V= 110 m/sec.	D= 3,5 mm. V= 72 cm/sec.	D= 3,9 mm. V= 70 cm/sec.	14%
Patient 3	D= 4,7 mm. V= 88 cm/sec.	D= 3,6 mm. V= 112 cm/sec.	D= 3,8 mm. V= 116 m/sec.	D= 3,9 mm. V= 72 cm/sec.	D= 4,1 mm. V= 70 cm/sec.	13%
Patient 4	D= 4,9 mm. V= 85 cm/sec.	D= 3,4 mm. V= 110 cm/sec.	D= 3,8 mm. V= 116 m/sec.	D= 4,1 mm. V= 72 cm/sec.	D= 4,3 mm. V= 70 cm/sec.	13%
Patient 5	D= 4,8 mm. V= 84 cm/sec.	D= 3,6 mm. V= 125 cm/sec.	D= 3,9 mm. V= 110 m/sec.	D= 4,0 mm. V= 70 cm/sec.	D= 4,1 mm. V= 70 cm/sec.	14,5%
Patient 6	D= 4,8 mm. V= 80 cm/sec.	D= 3,6 mm. V= 119 cm/sec.	D= 3,7 mm. V= 105 m/sec.	D= 4,0 mm. V= 82 cm/sec.	D= 4,2 mm. V= 71 cm/sec.	13%
Patient 7	D= 4,7 mm. V= 79 cm/sec.	D= 3,6 mm. V= 124 cm/sec.	D= 3,8 mm. V= 116 m/sec.	D= 4,1 mm. V= 72 cm/sec.	D= 4,3 mm. V= 70 cm/sec.	13%
Patient 8	D= 4,7 mm. V= 79 cm/sec.	D= 3,6 mm. V= 124 cm/sec.	D= 3,8 mm. V= 116 m/sec.	D= 4,1 mm. V= 72 cm/sec.	D= 4,3 mm. V= 70 cm/sec.	13%

Considering the effectiveness of 1 course of therapy for pregnant women at the age of 18-20 weeks, they showed reliable results and this allowed us to continue 2 courses and the prophylactic administration of L-arginine to prevent re-bleeding.

On the basis of the conducted studies, a non-invasive method was developed and the method for assessing the degree of endothelial dysfunction in pregnant women with a risk of obstetric bleeding was optimized. Evaluation of the degree of endothelial dysfunction is assessed by a cuff test in pregnant women with a risk of bleeding, and our proposed treatment leads to an improvement in which the rate of flow dilatation (PPI) increases by more than 15% of the initial value, In addition, therapeutically justified initiation of prophylaxis at any gestational age up to 34 weeks of gestation in women at risk of bleeding.

5. Conclusions

1. In the 2nd trimester and at the beginning of the 3rd trimester of pregnancy in women with a history of obstetric bleeding, it is necessary to conduct a non-invasive method for determining the violation of vascular dysfunction: a cuff test with reactive hyperemia of the mother's brachial artery and a complex ultrasound and Doppler study of the uterine arteries.
2. A normative endothelium-dependent reaction can be considered a dilatation of the PA, in which the flow dilatation index (PPD) increases by more than 15% of the initial value, a lesser dilatation or vasoconstriction of the vessel should be considered pathological. The results of the study showed that in all 63% of women with a high risk of increased blood loss and obstetric bleeding, with the preventive differentiated use of L-arginine (Tivortin) during pregnancy, in contrast to traditional prevention of bleeding, PA dilatation was noted, with which the flow dilation index (FPD) increases by more than 15% from the initial value.
3. Studies have shown that the indices of the cuff test when carrying out only one course of therapy with L-arginine (Tivortin) do not give a definitively positive result, since PA dilation was noted, in which the flow dilatation indicator (PPD) increased by more than 10% of the initial values.
4. In order to improve vascular pathologies, L-arginine (Tivortin) g - 3 g / day is necessary. within 3 weeks from 18 weeks of gestation, at 24 weeks and 30 weeks, thus, three courses of 3 weeks are carried out with a break of 3 weeks. Therapeutically justified beginning of prophylaxis at any stage of pregnancy up to 34 weeks of pregnancy.

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