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## Massive Hemorrhages in Pregnant Women with Placenta Previa and Accreta: a Transfusiologist's View

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**ABSTRACT** The aim of this study was to estimate volumes of blood loss and infusion and transfusion therapy during Cesarean section in pregnant women with placenta previa and accreta.

**MATERIAL AND METHODS** The study group consisted of 15 patients with placenta previa and accreta. The delivery period was 32–36 weeks. We used clinical and laboratory techniques and special methods of investigation. The analysis of pregnancy course, bleeding volumes, infusion and transfusion therapy, hemostasis system parameters and hemogram was carried out.

**RESULTS** The mean age of pregnant women was 33.8±4.3 years. All pregnant women underwent fundal Cesarean section. In 80% of women, we performed Cesarean section and metroplasty. In 20% of women, Cesarean section and hysterectomy were performed. The volume of intraoperative blood loss ranged from 750 ml to 6,000 ml and averaged 2,471.4±1,528.5 ml.

The volumes of crystalloid solutions were 1,361.53±1,052.40 of Sterofundin, and 688.4±123.5 ml of other solutions. In 80% of patients, Gelofusine was administered (969.66±351.86 ml on the average), as well as Geloplasma (620.8±124.8 ml on the average). The volume of HES solutions 6% 130/04 was 744.4±120.45 ml on the average. FFP in the amount of 1,526.7±762.83 ml was transfused to 60% of women. The mean dose of tranexamic acid was 2.6±0.84 g. The factor rFVIIa was administered in three patients in the dose of 90 mcg/kg. Prothrombin complex concentrate 1200 IU was administered in three patients. The volume of reinfused autoerythrocytes was 793.7±424.17 ml on the average. The volume of donor red blood cells during the operation amounted to 775.12±120.2 ml.

**CONCLUSION** Pregnant patients with placenta previa and accrete represent a high-risk group for the development of massive coagulopathic bleeding and postoperative complications. These patients should deliver on a routine basis at the high-tech institutions of obstetric care. The adequate, timely infusion and transfusion maintenance of surgical intervention with this pathology, using modern blood-saving technologies, transfusion of sufficient volumes of blood components, inhibitors of fibrinolysis, coagulation factors, modern balanced crystalloid and colloidal solutions plays a important role in implementation of organ-preserving tactics.

**Keywords:** pregnancy, placenta previa and accreta, massive hemorrhage, infusion and transfusion therapy, blood safety technologies

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APTT — activated partial thromboplastin time

CBV — circulating blood volume

FFP — fresh frozen plasma

HES — hydroxyethyl starch

INR — international normalized ratio

Despite the development of medical technologies, massive obstetric hemorrhages are still a serious problem, being one of the main causes of obstetric mortality and the development of critical, so-called “near miss” conditions [1, 2]. According to the Ministry of Health of the Russian Federation for 2016, the bleeding ranks second in the structure of causes of obstetric mortality and it is 18.6%. It should be emphasized that there is a tendency to an increase in the frequency of bleeding associated with abruption of a normally located placenta and faulty placentation [3]. The most severe and life-threatening bleeding develops in pregnant women with placenta previa and accreta, they are associated with a high risk to the life of the woman. The direct contribution of placenta accreta to the obstetric mortality rate is quite high at 7%. One of the main factors for increasing the frequency of obstetric bleeding is a significant increase in the incidence of abdominal birth, which is considered as the main factor contributing to abnormal presentation and invasion of the placenta, and causing an increase in the frequency of

placenta accreta [4]. In the Russian Federation, the Caesarean section in 2008 was performed in 19.9%, and in 27.8% of observations in 2016. The more frequently the Caesarean section is performed, the higher is the incidence of placenta previa and accreta. In a patient with a single Caesarean section, the risk of placenta accreta is 3%, and with three Caesarean sections, this risk rises to 40% [5]. Undoubtedly, management of pregnant women with placenta previa and accreta and their delivery requires an interdisciplinary approach, coordination of actions of doctors of various specialties: obstetrician-gynecologists, anesthesiologists-resuscitators, surgeons, transfusiologists, doctors of laboratory services.

The purpose of this study was to evaluate infusion and transfusion support during Caesarean section in pregnant women with placenta previa and accreta in the implementation of the organ-preserving tactics of surgical treatment.

#### MATERIAL AND METHODS

The study group consisted of 15 pregnant women from 26 to 40 years old with placenta previa and accreta. All pregnant women were promptly delivered to V.I. Kulakov National Medical Research Center of Obstetrics, Gynecology and Perinatology. Clinical, special (ultrasound and pelvic magnetic resonance imaging) and laboratory methods were used in examining women: hemogram was examined with a BT-2100 analyzer (USA); hemostasis system – by the automatic analyzer "Behring Coagulation Timer" (Germany) and "Hellige" thromboelastograph (Germany). The visual and gravimetric method (weighed the operative material and calculated the volume of blood loss using Libov's formula) were used to determine the volume of blood loss. The volume of blood loss on the basis of indicators of Cell-Saver 5+ type apparatus during automatic operation with the production of autoerythrocytes with a hematocrit of 55–60% was calculated according to the formula:

$$VBL = 2 \cdot V_{er} \times K,$$

where VBL is the volume of blood loss (ml); 2 is a constant that takes into account hemoconcentration of the obtained erythrocytes (hematocrit 60%); K is the loss coefficient for hemolysis, loss outside the wound and on the surgical material (1.5 on average) [6].

In order to assess the composition, volume of transfusion fluid and hemostatic preparations, anesthesia records were analyzed. The obtained results were statistically processed using Excel v.8.0® by Microsoft and Statistica for Windows v.5.1® by Stat Soft Inc. (USA) with standard methods of calculating indicators of descriptive statistics, correlation, regression and analysis of variance.

#### RESULTS

The average age of pregnant women with placenta accreta was 33.8±4.3 years. Three patients (20%) had morbid obesity, body mass index was over 30, which today is considered as one of the risk factors for the development of bleeding. An analysis of the anamnestic data revealed that 27% of women had uterine fibroids, one woman had undergone myomectomy. In 33% of patients, there had been inflammatory diseases of the uterus and appendages in history, which also played a role in subsequent irregular placentation during pregnancy [7]. Almost every patient (87%) had a history of endometrial curettage, with an average of 1.8±1.02 procedures. Three women (20%) had a bleeding during previous births, so they were donated blood components. Two patients had antenatal fetal death in a previous pregnancy in the third trimester. In 14 women of the study group, this pregnancy was 3<sup>rd</sup> or 4<sup>th</sup>, and all 14 had the Caesarean section in history (93%), only one patient had the first pregnancy and the first birth. The real pregnancy in 13% of cases occurred with the help of assisted reproductive technologies, which today is considered as a risk factor for placenta previa and accreta [8]. In this group of studies, placenta previa and accreta is confirmed by ultrasound and magnetic resonance imaging data. Operational delivery was carried out in the period of 35 weeks and 4 days±12 days.

The planned Caesarean section was performed in 80% of cases (12 women), emergency section was performed in 20% (3 patients), indicated due to the onset of the first stage of delivery, bleeding and acute hypoxia of the fetus due to the placental abruption. All patients were scheduled for the caesarean section, ligation or temporary occlusion of the main pelvic vessels, and if possible, metroplasty. The operation was carried out with the participation of an obstetrician, a surgeon, an anesthesiologist-resuscitator, a transfusiologist, a laboratory assistant in the conditions of intraoperative reinfusion of autoerythrocytes on a Cell-Saver-5 device (Haemonetics). Leukocyte filters, donor fresh frozen plasma and erythrocyte suspension, tranexamic acid, rFVIIa (Coagil VII), prothrombin complex concentrate were prepared for the operation. In 80% of women, operations were performed under conditions of low-dose combined spinal-epidural anesthesia, since regional anesthesia techniques are the "gold" standard for Caesarean section due to high efficiency and maximum safety [9]. In 20% of cases, the operation was performed under combined general anesthesia.

All pregnant women first underwent the Caesarean section. Further, ligation of the internal iliac arteries and temporary occlusion of the common iliac artery were performed. Twelve women (80%) had organ-preserving surgery, metroplasty. Three patients (20%) underwent hysterectomy: due to postoperative hypotonic bleeding in one case, due to premature placental abruption with the development of acute massive bleeding and the inability to perform an organ-preserving operation in the second woman and due to deep ingrowth of placenta into the bladder. The average duration of surgery increased due to the complexity of the main stage of operation and amounted to

107.2±38 minutes. In a patient with placental abruption and massive blood loss, the duration of surgery was maximum and amounted to 207 minutes.

Speaking about the volume of blood loss, it should be said that it ranged from 750 to 6,000 ml and averaged 2,471.42±1,528.53 ml. A blood loss in the volume of 750 ml was observed in the patient, where the Caesarean section and planned extirpation of the uterus were initially performed. In the other two women who underwent extirpation of the uterus, the volume of blood loss was much greater and amounted to 4,400 ml and 6,000 ml. In 12 women, the volume of blood loss varied from 1,300 ml to 3,600 ml, on average 2,213.63±1,230.45 ml; they all managed to undergo metroplasty. Thus, the volume of blood loss relative to the volume of circulating blood (CBV) in pregnant women with placenta previa and accreta during operative delivery, despite careful preparation, use of blood-saving technologies, bandaging or temporary clipping of the main vessels, can be very significant (up to 130% CBV), which depends on the degree of ingrowth of the placenta and such an aggravating factor, as premature detachment of the placenta during ingrowth, which is accompanied by rapid and massive blood loss. With the development of obstetric hemorrhage, special attention is paid to adequate infusion and transfusion therapy.

The analysis of the volume and qualitative composition of infusion and transfusion therapy during surgery in 15 women with placenta previa and accreta showed that the volume of crystalloid solutions, in particular Sterofundin, averaged 1,361.53±1,052.40 ml (from 500 to 2,000 ml), other crystalloid solutions (Jonosteril, Ringer, Hartman), on average, 688.4±123.5 ml (from 500 to 1,500 ml). In 80% of women, Gelofusine was used: 969.66±351.86 ml on average (from 500 to 1,500 ml), Geloplasma: on average, 620.8±124.8 ml (from 500 ml to 1,000 ml). The volume of hydroxyethyl starch (HES) 6% 130/04 averaged 744.4±120.45 ml.

With massive blood loss, modern transfusion tactics include avoiding the use of whole blood and the transition to multicomponent therapy. Since there is a significant amount of bleeding during the presentation of placenta and placenta accreta with metroplasty, coagulation and anticoagulation factors are rapidly consumed. When the volume of blood loss is more than 20% of the CBV, a quick introduction of donor fresh frozen plasma (FFP) in the amount of 15–20 ml/kg of body weight should be initiated [10]. In nine patients (60%), FFP was transfused in volumes of 1,526.7±762.83, and 6 women (40%) with an average blood loss of 1,191.6±215.4 ml FFP was not transfused. Of these, concentrate of prothrombin complex (1200 units) was administered in 3 patients. This complex was administered to patients at the initial stage of bleeding, which allowed the operation to be performed without transfusion of FFP. Three women received only infusion therapy and tranexamic acid. Tranexamic acid was administered to all women during surgery at an average dose of 2.6±0.84 g (from 1.5 g to 4 g) intravenously. The total dosage consisted of a prophylactic dose and a dose used for therapeutic purposes. The use of inhibitors of fibrinolysis and proteolysis is necessary to suppress excessive fibrinolysis and prevent the progression of intravascular coagulation of the blood, antiplatelet effect [11, 12].

Separately, it should be said about three patients with massive blood loss, refractory to conventional therapy, where recombinant activated VII coagulation factor (rFVIIa) was introduced. In this group of patients, rFVIIa (Coagil) was administered at the rate of 90 µg/kg, with the development of hypocoagulation, refractory to FFP and fibrinolysis inhibitors. The average blood loss was 2,179.4±965.4 ml. After the introduction of rFVIIa (Coagil), these patients showed a significant decrease in the rate and volume of bleeding, which allowed metroplasty to be performed. Some indicators of the hemostasis system in women of the studied population are presented in Table 1.

Table 1

**Indicators of hemostasis in patients with placenta accreta at different stages of the study**

Research phase	PLT × 10 <sup>9</sup> /l	Fibrinogen, g/l	Prothrombin, g/l	INR, units	APTT, sec	D-dimer, mcg/l
Before surgery	222±61.8	5.27±0.79	102.5±8.5	1±0.04	28.9±3.3	2,378±1,848
After surgery	163.1±76.2*	3.5±1.7*	91.07±37.1	1.04±0.08**	34.9±8.8**	3,587±2,693
3 days after surgery	250.7±102.5*	5.31±1.6**	107.3±14.2	1.1±0.07	34.6±5.7	1,844±1,760

Notes: statistical significant changes in comparison to the initial data: \* p<0.01, \*\* p <0.05. APTT – activated partial thromboplastin time; INR – international normalized ratio; PLT – platelets count in the blood unit volume

After the operation, hemostasis indicators showed a decrease in blood coagulation potential (decrease in blood levels of fibrinogen, prothrombin, elongation of activated partial thromboplastin time), which required transfusion of FFP, tranexamic acid and administration of hemostatic preparations. The D-dimer level indicator initially had high numbers in all patients, which is common for placenta previa and accreta. On the day of the operation, due to blood loss, its increase was noted with a subsequent tendency to decrease during therapy (p>0.05).

All women underwent hardware intraoperative reinfusion of erythrocytes. The volume of reinfused autoerythrocytes ranged from 240 ml to 1,380 ml and averaged 793.7±424.17 ml with a hematocrit of 55–60%. During the operation, donor erythrocytes were required only by three (20%) women, who had the highest degree of blood loss (3,600 ml, 4,400 ml, 6,000 ml) in an average volume of 775.1±120.2 ml. Indicators of the level of red blood cells, hemoglobin and hematocrit are presented in Table 2.

Table 1

**Indicators of the level of erythrocytes, hemoglobin and hematocrit in patients with placenta accreta at different stages of the study**

Research phase	Erythrocytes, x10 <sup>12</sup> /l	Hemoglobin, g/l	Hematocrit
Before surgery	3.8±0.3	111.1±9.9	0.34±0.02
After surgery	3.24±0.7*	92.2±19.1*	0.28±0.05*
3 days after surgery	3.37±0.59	96.2±12.3	0.3±0.04

Notes: statistical significant changes in comparison to the initial data p<0.01

The analysis of the obtained data showed that after the operation a significant decrease in the hemoglobin and red blood cells levels was noted, as well as a decrease in hematocrit. In the postoperative period, all patients were given anti-anemic therapy with intravenous iron preparations, and in two women, whose blood loss was 4,400 ml and 6,000 ml, washed red blood cells were transfused in an average volume of 720.1±110.2 ml. On the 3<sup>rd</sup> postoperative day, the patients showed an increase in hematocrit, hemoglobin and red blood cells.

**DISCUSSION**

The ingrowth of the placenta is a formidable obstetric pathology, which is based on the mechanism of the pathological invasion of chorionic villi. This pathology tends to increase due to the high frequency of Caesarean section operations and is associated with a high risk to a woman's life due to the possible development of massive life-threatening bleeding, that is, these blood losses are predictable. In this study, the average volume of blood loss was 2,471.42±1,528.53 ml, but in two patients the volume of blood loss was more significant, especially in a patient with premature detachment of the ingrown placenta, and was 6,000 ml, which required emergency surgery and extirpation of the uterus, a significant transfusion of FFP, donor erythrocytes and introduction of activated coagulation factor VII. A multidisciplinary team should always be involved in the delivery of such pregnant women, since it is associated with the routine preparation of donor blood components, a large volume of FFP, erythrocyte-containing components, thromboconcentrate, hemostatic drugs, hardware reinfusion of autoerythrocyte cells, which is the key to successful treatment of massive bleedin. Speaking about the infusion and transfusion therapy of massive blood loss, it should be noted that balanced crystalloid and colloid solutions are currently used to replenish the CBV. It should be said with certainty that crystalloids do not need to be opposed to colloids, and vice versa. On the contrary, they should be considered as "two sides of the same medal" when used in infusion therapy algorithms [14]. Currently, iso-osmolar, polyionic electrolytes with reserve alkalinity (Ringer's solution, Ringer-acetate, Sterofundin isotonic, Jonosteril) are used in cases of obstetric hemorrhages. Considering the risk of hyperchloremic acidosis in the case when the use of crystalloids is indicated, instead of 0.9% NaCl solution, balanced salt solutions should be used which are similar in electrolyte composition to blood plasma and do not cause water-electrolyte and acid-base disorders. Speaking about the use of colloidal solutions, it should be remembered that modern colloidal solutions have a different volemic effect, the ratio of the growth rate of the CBV to the volume of the introduced colloid in percent, the effect on the hemostatic system and the function of kidneys. From colloidal solutions, gelatin derivatives, albumin and HES are more commonly used today. The sodium content in them is on average 130–155 mmol/l, the colloid osmotic pressure is created by macromolecular substances, the colloids are distributed in the intravascular space, and the duration of the volemic effect is much longer than with the use of crystalloids, the kidney excretion is much slower than with the use of crystalloids [ 15]. Regarding HES solutions, the European Medicines Agency, the Association of Medical Communities of Germany concluded that HES requires a rigorous indications and monitoring therapy, including an assessment of the risk-benefit ratio. HES solutions should be used only to ensure adequate hemodynamic stability in case of hypovolemia. Colloidal solutions (6% HES and gelatin) can be used along with crystalloids to fill the volume in the perioperative period, in the treatment of hypovolemia due to acute blood loss, if administration of crystalloid solutions is insufficient [16, 17].

When conducting transfusion therapy with massive blood loss, a significant amount of FFP is transfused as the main supplier of coagulation and anticoagulation factors, components of kinin-kallikrein and fibrinolytic systems with their inhibitors [10]. Optimal results were obtained with the planned Caesarean section and metroplasty, where the complex infusion and transfusion program using modern blood-saving technologies, the introduction of large amounts of fresh frozen plasma, fibrinolysis inhibitors, a concentrate of prothrombin complex, activated blood coagulation factor VII, thorough preparation for surgical intervention, i. e. with a multidisciplinary approach to the delivery of pregnant women with the placenta accreta, allowed to implement organ-saving tactics in 80% of women of reproductive age. Undoubtedly, the question of the preservation or removal of the uterus is largely predetermined by the degree of ingrowth and the technical ability to conduct metroplasty, experience and competence of an interdisciplinary operating team. The introduction of modern hemostatic drugs: the rFVIIa factor, a concentrate of the prothrombin complex, makes it possible to reduce the volume of donor FFP, they are an important addition to hemostatic therapy [18, 19]. The efficacy of the rFVIIa drug is estimated to be quite high and in the form of a

significant reduction or complete cessation of bleeding is 90–95%, and in the form of uterus preservation it is up to 80% of cases [20, 21]. The introduction of rFVIIa is also regulated by the Procedure for the provision of specialized medical care approved by the Ministry of Health of the Russian Federation for bleeding in the placental and postnatal periods, for bleeding due to placenta previa, and the guidelines of the Russian Society of Obstetricians and Gynecologists and the clinical protocol “Prevention, treatment and maintenance algorithm for obstetric bleeding” [11, 22].

Speaking of transfusion of erythrocyte-containing blood components, it should be noted that today the procedure of hardware intraoperative reinfusion of autoerythrocyte plays a significant positive role in the recovery of globular volume with massive obstetric hemorrhage, which minimizes the use of donor erythrocytes, and in some cases completely eliminates them, prevents possible hemotransfusions, and also helps reduce the duration of hospital stay and preserve the quality of life for women with complicated pregnancy. [23]

## CONCLUSION

Pregnant women with placenta previa and accreta represent a high risk group for the development of massive coagulopathic bleeding and postoperative complications. These patients should be delivered in a planned manner in institutions of the third level of obstetric care. The adequate, timely infusion and transfusion to ensure prompt intervention in this disease using modern balanced crystalloid and colloid solutions, blood saving technology, transfusion of sufficient quantities of high-quality blood components, the introduction of fibrinolysis inhibitors and coagulation factors are very important in realization of conserving tactics in women of childbearing age with the placenta accreta.

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