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Pharmacotherapy of Massive Obstetric Bleedings as Alternative to Hysterectomy

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1. Introduction

Modern society with its bad ecology, chronic stress and the prevalence of mental activities over physical no longer treats pregnancy as a physiological state with "natural" course of events but the state that requires intensive medical supervision, active, even invasive, intervention during pregnancy and delivery. In most cases such intervention is the only way to save life for a mother and her child. Therefore, modern obstetrics is primarily a surgical one. With the overall growth of obstetric operations a number of radical interventions to remove the reproductive organ is also increasing .The main cause of hysterectomy and sometimes death of a patient in obstetric practice is massive obstetric hemorrhage (post-partum haemorrhage - PPH). Life-threatening bleeding occurs in about 10% of deliveries worldwide (The Department of Health UK. Why mothers die. A report.., 2004). Obstetric hemorrhage is a major cause of maternal mortality, with 25 - 30% of overall death cases in prergnancy (Bonnar, 2000; Make Every Mather and Child count: the World Health Report.: WHO, 2005). The occurance of massive obstetric hemorrhage in developed and developing countries differs greatly (Ben Hamid et al., 2006; Sheiner et al., 2005). The risk to die from obstetric hemorrhage in developed countries is 1:100 000, while in developing countries the rate reaches 1: 1000 births (Mousa & Alfirevic, 2003). According to WHO bleeding is among the "big five" of causes of maternal mortality that leads to an on-going research to find various methods to stop bleeding, as well as blood transfusion (Baudo et al., 2001).

Cases with heavy bleeding, such as hysterorrhesis, premature detachment placenta increta and uterine atony require intensive resuscitation, and often result in hysterectomy. The problem of PPH treatment can be hardly overestimated in modern science and offers challenges to specialists in obstetrics, hematology and intensive care, in other words it requires inter-disciplinary approach to its solution.

It is known that only 62 - 65 % of vaginal deliveries are accompanied by physiological hemorrhage, and one third of patients lose from 500 ml to 1000 ml of blood and in 3 - 8 % hemorrhage exceeds 1.5 % of body weight and is to be massive and requires infusion of erythrocytes and hysterectomy. Definitions of PPH vary and relate to the patients with

blood loss of 50 % of overall circulating blood within 3 hours, or hemorrhage > 150 ml/minute. WHO defines PPH as a loss of blood in volume of 500 ml or more during or after delivery, or any quantity of blood loss after the delivery which leads to instability of blood circulation (World Health Organization [WHO], 2009).

Most authors believe that uterine atony is the cause (75-90%) of early postpartum hemorrhage (Henrich et al., 2008; Ramanathan & Arulkumaran, 2006; Reynders et al., 2006). In this condition, uterus loses its ability to involution and does not react to medications and other types of stimulation (Roeal College of Obstetricians and Gynaecologists UK. Prevention .., 2009). Disorders of functional state of myometrium are possible due to prolonged labor, due to the of use of medication, reducing uterine tonus, due to greater amount of oxytocin in labor (Grotegut et al., 2011). Obstetric haemorrhage is characterized by suddenness and high temper of blood loss. Besides, reduced adaptive abilities of mother organism upon giving birth, her somatic diseases and pathology in pregnancy easily contribute to the rapid development of coagulopathy, to the shock phenomenon and multiple organ failure (Macphail & Talks, 2004). An increased number of caesarean section worldwide is one of the factors that cause the growth of postpartum haemorrhage (Deneux_Tharaux et al., 2006; Murkin, 2009). According to Ohkuchi et al. (2003), an average blood loss during vaginal delivery was 615 ml, whereas in cesarean section – 1530 ml.

Standard methods of treatment of massive PPH include therapeutic (hemotransfusion therapy and uterotonics) and surgical methods of hemorrhage control (Bouwmeester et al., 2005; Macphail & Talks, 2004; Mousa & Alfirevic, 2007). First aid in obstetric hemorrhage in most countries traditionally employs the use of uterotonics and prostaglandins, manual examination of uterus and birth canals and uterine massage (Abdel-Aleem et al., 2010; Henrich et al., 2008; Price & Lynch, 2005). If uterotonics and manual examination of the uterus prove to be ineffective, more complex surgical technics are traditionally employed - uterine artery ligation, internal iliac artery ligation and hysterectomy.

Many publications and reviews that relate to the problem of obstetric bleeding offer the opportunity and place to discuss new methods to stop postpartum bleeding. In recent years, a series of invasive manipulations is used as a rather effective measure to stop postpartum bleeding, for example - uterine balloon tamponade (Bakri et al., 2001; Dabelea et al., 2007; Penninx et al., 2010), uterine devascularization and compression sutures (Allam & B-Lynch, 2005; Sentilhes et al., 2008a; Sentilhes et al., 2008b), uterine artery embolization (Chauleur et al., 2008; Irion et al., 2008; Vedantham et al., 1997), internal iliac artery and uterine artery ligation (Api et al., 2005; O'Leary, 1995; Papp et al., 2006), that, to some extent, is an alternative to traditional hysterectomy (El-Hamamy & B-Lynch, 2005; Malibary, 2004; Smith & Baskett, 2003).

In the , in a majority of obstetric hospitals hysterectomy still plays a crucial role in the algorithm of surgical treatment of massive obstetric hemorrhage, and causes women to become infertile.

In accordance with nowadays approaches, to save a woman's life as well as her reproductive function in the course of solving the problem of bleedings upon pregnancy, delivery and early postpartum period is a priority. In this regard, research efforts for additional, effective methods of PPH management alternative to hysterectomy, is very important.

Recently advances for stopping PPH and decreasing the need in donor blood become crucial in the field of pharmacological correction of hemostasis as well. In particular, empirical use of recombinant factor VIIa (rFVIIa) is studied in the treatment of obstetric hemorrhage refractory to conventional conservative therapy.

2. Indications and clinical situations for rFVIIa administration

Originally rFVIIa (NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) has been developed for treatment of spontaneous and/or surgical bleeding in patients, suffering from haemophilia A or B with formation of autoantibodies to FVIII or FIX as a result of compensation of their deficiency in the course of replacement therapy (Abshire & Kenet, 2004; Lusher et al., 1998; Negrier & Hay, 2000; Shapiro et al., 1998; Sobieszczyk & Breborowicz, 2006). Now rFVIIa is licensed for the use in a number of countries. In 1999 Food and Drug Administration (FDA), United States of America approved rFVIIa for treatment of hemophilia A or B in patients with inhibitors to FVIII or FIX. Further, in 2005, FDA also approved the use of rFVIIa in patients with congenital deficiency of factor VII (K.A. O'Connell et al., 2006). In Europe rFVIIa is also prescribed to stop bleeding in patients with acquired hemophilia and Glanzmann thrombasthenia (Franchini et al., 2005a; Hedner & Erhardtsen, 2002; Jurlander et al., 2001; Kessler, 2000).

Except above listed indications, any use of rFVIIa is reviewed «off-label» and responsibility for its decision remains for the attending physician. For the last decade, the use of rFVIIa, with more specified data about mechanisms of its action has been successfully approved «off-label» to stop other uncontrolled hemorrhages unassociated with haemophilia, to reduce the need for allogenic blood. They included intracranial hemorrhage, bleedings due to coumarin use, hepatic coagulopathy, major surgery and traumas (Aggarwal et al., 2004; Aldouri, 2002; Dutton al., 2004; Eikelboom et al., 2003; Franchini et al., 2007; Ghorashian & Hunt, 2004; Hedner, 2003; Mathew, 2004; Martinowitz et al., 2002; Martinowitz & Michaelson, 2005; Mayo et al., 2004; Mittal & Watson, 2006; O'Connell et al., 2003; Price et al., 2004; Roberts et al., 2004; Sobieszczyk & Breborowicz, 2004; Uhlmann & Eby, 2004; Vincent et al., 2006).

3. World experience of use of rFVIIa in treatment of PPH

The first experience of successful treatment of intractable obstetric bleeding in nonhaemophilic patients with rFVIIa was published by Moscardo et al. in 2001 (Moscardo et al., 2001), who reported that rFVIIa showed high hemostatic effect in life-threatening PPH after caesarean section in women with disseminated intravascular coagulation (DIC) syndrome, impaired liver and kidney failure. Later, Breborowicz et al. (2002) reported the results of the experience of PPH treatment when rFVIIa application helped to avoid hysterectomy in two of six cases.

Hossain et al. (2007) described the results of cohort retrospective study of 34 patients with blood loss more than 1500 ml, 18 of them received rFVIIa treatment. Ahonen et al. (2007) compared results of 26 women receiving rFVIIa with 22 women of control group, with PPH without rFVIIa. In both studies the causes of PPH were: uterine hypotension, abnormal placentation, premature placental detachment, as well as hysterorrhesis or vaginal

laceration were. Before rFVIIa administration women received oxitocics, uterus massage, uterine artery ligation and, in some cases, hysterectomy.

Above-mentioned and other reports were very important, as treatment of life-threatening PPH still remains acute problem. Moreover it can demand hysterectomy with subsequent loss of reproductive function of woman, despite the fact that rendered aid was not included in the number of registered indications for this clinical situation (Franchini et al., 2007).

Presently there is a number of works available for successful empirical rFVIIa application in treatment of massive PPH, with introduced refractory to conservative methods of treatment. (Aggarwal et al., 2004; Ahonen & Jokela, 2005; Ahonen et al., 2007; Boehlen et al., 2004; Bomken et al., 2009; Bouwmeester et al., 2003; Boyer-Neumann et al., 2003; Breborowicz et al., 2002; Brueckner et. al., 2001; Dart et al., 2004; Dutton et al., 2004; Eikelboom et al., 2003; Franchini et al., 2007; Franchini et al., 2008; Hollnberger et al., 2005; Holub et al., 2005; Jansen et al., 2005; Jimenez-Yuste et al., 2000; Kale et al., 2004; Kretzschmar et al., 2003; Macphail et al., 2004; Martinowitz & Michaelson, 2005; Mayo et al., 2004; Merchant et al., 2004; Mittal & Watson, 2006; Moscardo et al., 2001; Mousa & Walkinshaw, 2001; Mousa & Alfirevic, 2003,2007; Nowacka et al., 2005; Palomino et al., 2006; Pepas et al., 2006; Price et al., 2004; Segal et al., 2004; Shamsi et al., 2005; Shander et al., 2005; Sobieszczyk et al., 2002, 2004, 2006; Sokolic et al., 2002; Tanchev et al., 2005; Verre et al., 2006; Vincent et al., 2006; Welsh et al., 2008; Zupancic et al., 2002).

There is also data about rFVIIa efficacy in hemorrhage prevention during delivery in pregnant women with acquired impaired coagulation. (Eskandari et al., 2002; O'Connell et al., 2006).

In Russia the first successful experience in this field took place in 2002 in Clinic of Professor Zinovij Barkagan (Russian Academy of Medical Sciences, Hematological Research Center, Altai department). The patient with severe postpartum hemorrhage and syndrome of massive hemotransfusions underwent a successful treatment and the followed long-term observations led to this publication.

Nevertheless, there is not enough evidence in favor of rFVIIa application in postpartum hemorrhage. According to the last recommendations of World Health Organization the use of rFVIIa should be limited to primary defect symptoms of hemostasis. (World Health Organization [WHO], 2009). The document also indicates that rFVIIa was given a priority interest to treat postpartum haemorrhage, mainly in industrialized developed countries due to its high cost. The broad use of rFVIIa is limited to the evidence in this area reporting that the use of rFVIIa is risky and even life-threatening . Despite the positive recommendations (Ahonen et al., 2007; Welsh et al., 2008) the practice of rFVIIa use in PPH is far from homogeneous (Haynes et al., 2007). Though it's available to be prescribed, experts need to determine its effectiveness, safety in obstetric hemorrhage and dosage recommendations. It is also clear that further accumulation and generalization of rFVIIa administration in obstetric practice may serve as the basis to register indications for its possible prescription in obstetrics.

4. Mechanism of hemostatic action of rFVIIa

FVII of natural origin, as well as a recombinant product, plays a key role in the haemostatic reactions in a human body. According to the cellular model of coagulation (Hoffman, 2003.)

after injury of vascular walls tissue factor (TF) gets into circulating blood to form a complex TF-FVII on the surface of cells containing TF. Complexes of TF-FVII activate factor X, which, in its turn, promotes the transformation of prothrombin to thrombin. A limited amount of formed thrombin activates cofactors V, VIII and XI, as well as platelets accumulated at the site of injury. Activated platelets secrete negatively charged phospholipids (phosphatidylserine) on membrane surface, and FIXa, FVIIIa and FXIa bound to their surface, which leads to further activation of FX and a massive thrombin formation (Monroe et al., 1997). The formation of large doses of thrombin leads to thrombin-activated fibrinolysis inhibitor (TAFI), which protects the fibrin clot from early dissolution (Bajzar et al., 1995). Direct activation of FX on the surface of activated platelets in the absence of TF, which leads to increased thrombin formation, may explain the mechanism of action of rFVIIa in the local cases of acquired coagulopathy due to trauma or surgery (Gabriel et al., 2004; Hedner, 2001; Hoffman et al., 1998; Lisman & De Groot, 2003; Monroe et al., 1997).

5. Original researches

Our research project offers a comparative assessment of rFVIIa effectiveness against (NovoSeven ®; Novo Nordisk A / S, Bagsvaerd, Denmark) PPH, due to the cause of bleeding, blood loss, dynamics of hemostatic disorders and period of drug administration from the start of bleeding. That is the main objective of the research.

In this study we obtained data on 75 patients with PPH in study conducted within the scope of prospective analysis, and 30 patients with PPH for the retrospective analysis. Recruitment campaign in patients was carried out randomly in accordance with internationally recognized protocol in major obstetric clinics in Russian cities - Barnaul, Krasnoyarsk, Bryansk, and Syktyvkar. The criterion for selection of patients for the research was the same pathology - a massive haemorrhage (PPH), which started during pregnancy, delivery and in the postpartum period. By “massive” we understand the blood loss that constitutes more than 1.5% of patient body weight or less, leading to hemodynamic disturbances.

The age range of women participating in this study varied: from 18 to 44, and average age was 28,6 ± 6,3 years. Gestational age at the time of bleeding was also different - from 24 to 43 weeks, average gestational age at delivery was 35,5 ± 5,5 weeks, that is, in the majority of patients (63.8%) bleeding occurred at full-term pregnancy.

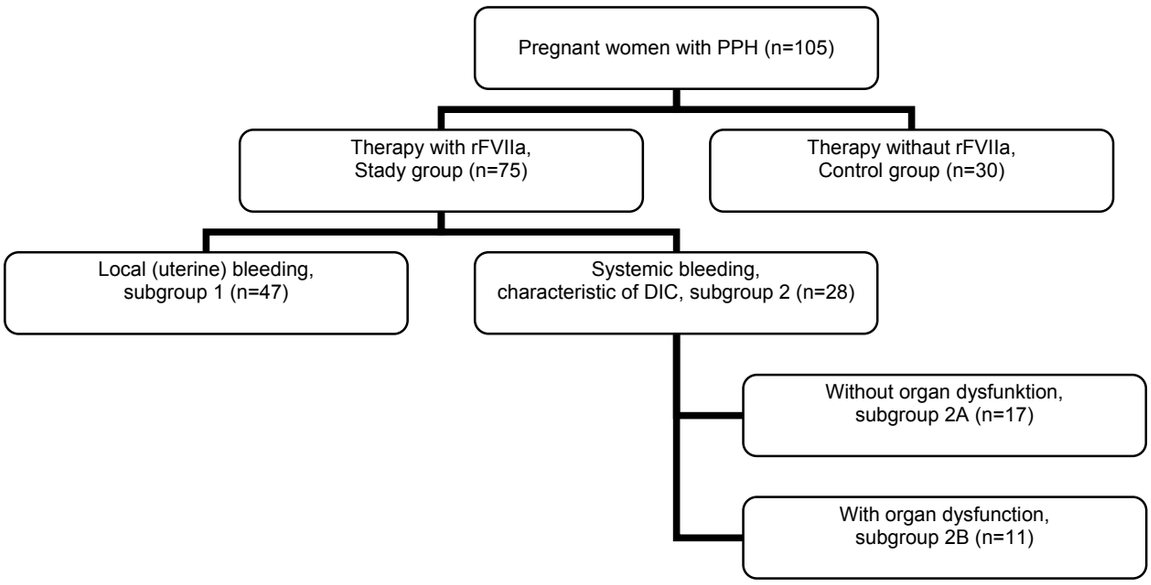
Pregnancy which resulted in spontaneous vaginal birth is found only in 46 women (43.8%), the greater part of pregnant women (56.2%) required surgical delivery by cesarean section (93.2% women), or the use of obstetric forceps (6,8%). In more than half of the observations (56.2%) major bleeding occurred in the postpartum period, approximately in every fourth - during pregnancy (26.7%), almost in every sixth - during delivery (17.1%).

According to the study, all patients were divided into two groups – study group and control group (see pic. 1). The main principle of this division was the use of rFVIIa along with traditional therapy consisting of pharmacologic hemostasis in life-threatening obstetric hemorrhage in 75 patients (study group). rFVIIa was given intravenously at doses ranging from 13,6 to 146,5 mg / kg body weight, an average dose of rFVIIa was 65,4 ± 36,7 mg / kg.

Criteria for enrollment in the study group are: reproductive age 18 - 44 years, the presence of massive obstetric haemorrhage, rFVIIa administration to correct hemostasis. Negative

factor for enrollment: physiological blood loss during delivery or in the postpartum period, the presence of massive obstetric haemorrhage without rFVIIa administration to correct hemostasis. The rFVIIa was used as a supplement to the traditional scheme against PPH.

The control group retrospectively consisted of 30 patients with PPH, and their treatment was delivered according to classical method, which includes the use of drugs that reduce uterus size, uterine massage, manual examination of the uterine cavity, infusion and transfusion therapy with fresh frozen plasma, blood cells - red blood cells and platelets, protease inhibitors, as well as surgical methods of hemostasis, which is consistent with the recommendations of several experts (Ahonen et al., 2010; Franchini et al., 2007; La Belle & Kitchens, 2007; Phillips et al., 2009; Shander et al., 2005; Sobieszczyk & Breborowicz, 2006a; Vincent et al., 2006; Welsh et al., 2008).



Pic. 1. The division of women with PPH into groups / subgroups in the study

The factors for the analysis in the study group: age of patients in the target group, gestational age at the time of massive bleeding, the methods of delivery, as well as obstetric data, reproductive and physical history, which in most patients characterized by the presence of several diseases in their reproductive system, abnormal cardiac and vascular system, presence of chronic infections, viral and toxic liver injury.

Analysis of the characteristics of hemorrhagic syndrome showed similar results in two groups compared to hemorrhage causes, the volume of blood loss, hemoglobin levels and bleeding tempo and other similar factors.

By the clinical manifestations of PPH we divided study group into two subgroups for further in-depth analysis. The first subgroup included 47 women with the classical picture of obstetric haemorrhage. rFVIIa was administered to stop PPH prior to the use of traumatic surgical methods of treatment. The purpose of rFVIIa administration in patients of this subgroup was to stop local uterine bleeding without a laparotomy and to preserve the uterus.

The second group which included 28 patients with obstetric DIC with massive blood loss, according to the criteria,offered by LaBelle & Kitchens (2007). Prior to the introduction of rFVIIa in this group, the classical scheme has been implemented in full, using the known methods of surgery, even a hysterectomy in 16 patients (57.1%). At the same time patients with DIC had systemic bleeding (hematoma under the skin, bleeding from the injection site, gastrointestinal bleeding, hematuria, and others in a variety of combinations), which threatened their lives. Thus, we introduced a special subgroup – 2B, which consisted of 11 patients in whom PPH was complicated with organ dysfunction.

To assess the effectiveness of rFVIIa in treatment PPH we indicated negative factors - early and late. Early negative factors are as follows:

- volume of blood loss ≥ 2.200 ml;
- rate of blood loss> 30 ml / min;
- hemoglobin level ≤ 60 g / l;
- period of time from the beginning of bleeding to rFVIIa administration > 120 min in the study group (the comparison group - the time from the beginning of bleeding to its termination);

Late negative factors -total hysterectomy and death of both mother and fetus.

In patients with PPH, with general clinical examination and measurement of parameters of blood loss, an analysis of core indicators of hemostasis was performed (Practical hemostasis and thrombosis, 2005). The number of platelets in blood, measurement of activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen concentrations according to Clauss were subject to the analysis.Moreover, the activity of antithrombin in plasma was evaluated by amidolytic method. Laboratory studies were conducted prior to bleeding, during (prior to use rFVIIa), and after 1-5 hours, 24 hours and 2-5 days after rFVII administration.

5.1 Statistical analysis

The results were statistically computed in Excel software by methods of calculations of indicators in descriptive statistics. Data analysis in small groups during the distribution was carried out by methods of nonparametric statistics, using Fisher angular transducer, criterion $\chi 2$ with Bonferroni correction, as well as T-score according to Wilcoxon (Wilcoxon F. et al., 1963). Assessment of the efficacy of rFVIIa for treatment of PPH was conducted according to the generally accepted criteria in evidence-based medicine, such as Absolute risk reduction (ARR), Relative risk (Rr), Relative Risk Reduction (RRR), Number needed to treat (NNT), Confidence interval (CI).

5.2 Study results

Upon the analysis of pregnancy complications in patients in the compared groups we obtained interesting results (Table 1). Complicated course of pregnancy due to the taken nosology was characteristic in patients with obstetrical DIC and organ dysfunction rather than in patients with uterine bleeding. Thus, systemic bleeding in the setting of massive obstetric blood loss (subgroup 2A) was more frequent than in patients with local hemorrhage (subgroup 1) and antenatal fetal death.

Pathology form	Study group (n=75)						P value
	Subgroup 1 (n=47)		Subgroup 2 (n=28)				
			Subgroup 2A(n=17)		Subgroup 2B(n=11)		
	abs.	%	abs.	%	abs.	%	
Pathologic placentation	7	14,89	4	23,53	1	9,09	≥0,05 ≥0,05 ≥0,05
Uterine scar	8	17,02	3	17,65	3	27,27	≥0,05 ≥0,05 ≥0,05
Premature detachment of physiological placenta	7	14,89	3	17,65	3	27,27	≥0,05 ≥0,05 ≥0,05
Preeclampsia	2	4,26	1	5,88	4	36,36	P_{1-2B} = 0,001
Intrauterine growth retardation syndrome	5	10,64	1	5,88	3	27,27	P≥ 0,05
Fetus prenatal infection	14	29,79	8	47,06	8	72,73	P_{1-2B} = 0,008
Antenatal fetal death	7	14,89	2	11,76	6	54,55	P_{1-2B} = 0,004 P_{2A-2B} = 0,01
Total number of women with pregnancy complications	30	63,83	15	88,24	11	100,00	P_{1-2B} = 0,01

Table 1. Complications of pregnancy in women with pharmacological correction of hemostasis by rFVIIa

In a particularly severe clinical cases, namely in patients with severe DIC syndrome and the presence of multiple organ failure (subgroup 2B), the frequency of such pathological conditions like preeclampsia, intrauterine infection and antenatal fetal death as a consequence of placental dysfunction occurred more frequently than in the two other subgroups.

With regard to today's medical science and the latest scientific advances, it is likely that the high incidence of gestational complications such as preeclampsia, placental insufficiency with antenatal fetal death, are often caused by and associated with severe disorders of hemostasis, hereditary and acquired thrombophilia. High frequency of these complications in the subgroup of patients with massive blood loss, obstetrical DIC and organ dysfunction is consistent with the abovementioned.

Pregnancy pathologies partly determined the character of complications during delivery and the postpartum period, which caused the development of PPH (Table 2).

Pathology form	Study group (n=75)				
	Subgroup 1 (n=47)		Subgroup 2 (n=28)		
	abs.	%	abs.	%	P value
Uterine atony	17	36,17	6	21,43	0,08
Pathologic placentation	6	12,77	1	3,57	0,072
Premature detachment of physiological placenta	7	14,89	6	21,43	0,1
Coagulopathy caused by somatic diseases	3	6,38	2	7,14	0,1
Coagulopathy caused by pregnancy complications	7	14,89	1	3,57	0,045
Retained placenta	6	12,77	5	17,85	0,1
Obstetric trauma	1	2,13	4	14,30	0,022
Amniotic fluid embolism	0	0,00	2	7,14	-
Obstetric sepsis	0	0,00	1	3,57	-

Table 2. Causes of massive obstetric hemorrhage in women with pharmacological correction of hemostasis

Analysis of the characteristics of a hemorrhagic syndrome in the study group showed significant differences in subgroups (Table 3). Thus, the total volume of blood loss and blood loss before the drug administration in subgroup with local (uterine) bleeding were significantly lower than in subgroup 2 with the development of DIC.

Criteria of comparison	Study group (n=75)				P value
	Subgroup 1 (n=47)		Subgroup 2 (n=28)		
	X ± m		X ± m		
Volume of blood loss prior to rFVIIa administration, ml	1368,09 ± 77,14		2230,82 ± 198,20		0,01
Total volume of blood loss, ml	1740,21 ± 114,45		2605,16 ± 402,68		0,01
Blood loss rate, ml/min	30,89 ± 3,97		29,91 ± 7,81		0,1
Haemoglobin level at the moment of rFVIIa administration, g/L	71,48 ± 2,73		56,28 ± 4,07		0,05
Time from beginning of hemorrhage to rFVIIa administration, min	119,47 ± 22,82		318,02 ± 26,6		0,001
rFVIIa dose, mkg/kg	55,47 ± 4,24		70,37 ±-4,77		0,05
Repeated rFVIIa administration, number of cases	11	23,40%	8	28,55%	0,01
Volume of blood loss after rFVIIa administration, ml	340,21 ± 62,28		688,77 ± 88,80		0,001

Table 3. Indicators of blood loss and characteristics of the use of rFVIIa in patients with PPH in the study group

Time from the beginning of bleeding to rFVIIa administration was significantly higher among patients with obstetric DIC (subgroup 2). Obviously this is due to the fact that rFVIIa is considered by obstetricians and emergency physicians as a backup means to stop PPH after using known hemostatic technologies, including hysterectomy. However, one should pay attention to the fact that the dosage of rFVIIa in patients with DIC and pattern of administration were higher in patients with local (uterine) bleeding (subgroup 1). Despite this fact, PPH in subgroup 2 continued the use of rFVIIa, and estimated blood loss was higher compared to subgroup 1.

Effectiveness of rFVIIa in treatment PPH was assessed according to the prior given criteria of negative factors. The absolute number of early negative factors in the compared groups / subgroups is presented in Table 4.

Criteria of negative factors	Study group (n=75)				Control group (n=30)
	Subgroup 1 (n=47)	Subgroup 2(n=28)			
		Subgroup 2A (n=17)	Subgroup 2B (n=11)	Total	
	abs.	abs.	abs.	abs.	abs.
Volume of blood loss ≥2.200 ml	2	8	3	11	5
Blood loss rate >30 mL/min	15	5	1	6	4
Haemoglobin level in blood ≤ 60 g/L	13	8	8	16	15
Time from beginning of hemorrhage to rFVIIa administration > 120 min	10	6	7	13	19
Volume of blood loss after rFVIIa administration, >300 ml	14	10	7	17	2

Table 4. Early negative factors in women with PPH, depending on the use of rFVIIa in the therapy

Estimate of efficiency according to the blood loss criterion in patients of subgroup 1 (with local uterine bleeding) showed a relative risk reduction by 75%, according to the criterion of depth of anemia – by 45% and with the early administration of the preparation (less than 120 minutes since the beginning of bleeding) – by 66%, indicating a high clinical efficacy of rFVIIa in treatment of PPH not complicated by DIC (Table 5). To avoid adverse outcomes on all reflected criteria from 4, 5 to 7, 8 patients are needed to be treated in this group.

In contrast, in women with systemic bleeding due to underlying DIC (subgroup 2) absolute risk reduction was negative (Table 6). This suggests that the incidence of negative factors in the study group is higher than in the control group. The reduction of relative risk in patients of subgroup 2 accounted for 26%, suggesting that there is clinical effect from the use of rFVIIa, especially with the early introduction of preparation (≤ 120 min).

Factors	ARR	NNT	Rr	RRR	CI (95%)
Volume of blood loss ≥2.200 ml	0,128	7,8	0,25	75%	0,274; 0,018
Blood loss rate >30 mL/min	-0,189	-5,3	2,45	-1,45	-0,043; -0,335
Haemoglobin level in blood ≤ 60 g/L	0,224	4,5	0,55	45%	0,370; 0,078
Time from beginning of hemorrhage to rFVIIa administration >120 min	-0,418	-2,4	0,34	66%	0,272; 0,564

Table 5. The effectiveness of rFVIIa administration in patients with local uterine bleeding (subgroup 1)

Factors	ARR	NNT	Rr	RRR	CI (95%)
Volume of blood loss ≥2.200 ml	-0,222	-4,5	2,31	-1,31	-0,028; -0,416
Blood loss rate >30 mL/min	-0,084	-11,9	1,65	-65%	0,110; 0,278
Haemoglobin level in blood ≤ 60 g/L	-0,071	-14,1	1,14	-14%	0,123; 0,265
Time from beginning of hemorrhage to rFVIIa administration >120 min	-0,166	-6,0	0,74	26%	0,028; 0,360

Table 6. The effectiveness of rFVIIa administration in patients with PPH in the setting of DIC (subgroup 2)

This fact has motivated us to carry on more detailed analysis of the effectiveness of preparation in subgroups of women with DIC (Table 7).

The effectiveness of rFVIIa in systemic bleeding with simultaneous presence of organ dysfunction (in subgroup 2B) in prevention of large volume of blood loss was uncertain. According to the criterion of blood loss rate we obtained positive values of ARR, NNT, and RRR index was 31% in these patients, which corresponds to a positive clinical effect of rVIIa application in the "fast" bleeding. However, to prevent one negative factor in these cases 25 patients should be treated. At the same time, in systemic bleeding without development of organ dysfunction (subgroup 2A) with early introduction of rFVIIa clinical efficacy was even greater (RRR = 44%).

Thus, according to the results of this analysis we can conclude that the clinical efficacy of rFVIIa in treatment of PPH is the highest in patients with local (uterine) bleeding and only according to the selected criteria with the early rFVIIa administration in patients with the development of obstetrical DIC.

Factors	ARR (2A)	ARR (2B)	NNT (2A)	NNT (2 B)	Rr (2A)	Rr (2B)	RRR (2A)	RRR (2B)	CI (95%) (2A)	CI (95%) (2B)
Volume of blood loss ≥2.200 ml	-0,3	-0,1	-3,30	-10,0	2,76	1,59	-1,76	-59%	0,028; 0,416	-0,085; -0,285
Blood loss rate >30 mL/min	-0,164	0,04	-6,1	25,0	2,26	0,69	-126%	31%	0,032; -0,36	0,225; -0,145
Haemoglobin level in blood ≤ 60 g/L	0,03	-0,22	33,3	-4,5	0,94	1,44	6%	-44%	0,226; -0,166	-0,035; 0,405
Time from beginning of hemorrhage to rFVIIa administration >120 min	-0,278	0,006	-3,6	166,7	0,56	1,01	44%	-1%	-0,082; -0,474	0,191; -0,179

Table 7. The effectiveness of rFVIIa administration in women with PPH, complicated by obstetrical DIC (subgroup 2A and 2B)

We also took into account the absolute number of late adverse outcomes in compared groups/subgroups that are shown in Table 8.

Criteria of negative factors	Groups / subgroups of patients				
	1 (n=47)	2A (n=17)	2B (n=11)	2 (n=28)	Control group (n=30)
	abs.	abs.	abs.	abs.	abs.
Maternal mortality	0	0	6	6	2
Perinatal mortality	4	7	3	10	3
Total hysterectomy	9	8	12	20	19

Table 8. Late adverse outcomes in the groups / subgroups of women with PPH

Below, we provide separate analysis for each criterion, except for the maternal mortality, as it was not registered in subgroup 1.

We did not obtain any data about the effect of rFVIIa administration in treatment of PPH on frequency of perinatal mortality in study groups (Table 9).

Absolute risk reduction for this criterion was indicated in women with DIC, but relative risk reduction was not indicated, so it is obvious that administration of rFVIIa has no significant effect on fetal loss. In contrast, we obtained positive clinical results for the total hysterectomy criterion, although somewhat different in the subgroups of study group (Table 10).

It is quite understandable that women with a local (uterine) bleeding according to the total hysterectomy criterion had negative rate of absolute risk reduction. This suggests that in

Values	Local (uterine) bleeding (subgroup 1)	Obstetric DIC, in general (subgroup 2)	Systemic bleeding without organ dysfunction (subgroup 2A)	Systemic bleeding with organ dysfunction (subgroup 2B)
ARR	-0,01	0,26	0,08	0,54
NNT	-67,1	3,9	13,1	1,9
Rr	0,85	3,57	1,76	6,36
RRR (%)	15	-2,57	-76	-5,36
CI 95% (+)	-0,030	0,514	0,153	1,073
CI 95% (-)	-0,104	0,131	-0,013	0,368

Table 9. The effectiveness of rFVIIa administration in women with PPH, according to the criterion of perinatal mortality

control group hysterectomy was performed much more frequently in order to stop bleeding than in the group with local (uterine) bleeding. Indicator for relative risk reduction in patients with massive local (uterine) bleeding recommended rFVIIa in their therapy was 70%, which was consistent with clinical effect to preserve healthy reproductive function. When we studied each case of hysterectomy in patients with local (uterine) bleeding (9 cases, or 19.1%) separately we found out that the use of rFVIIa was not effective in patients who had bleeding caused by pathologic placentation (placenta increta in 5 cases out of 9) and the development of Kuveler's uterus (4 cases out of 9) due to premature detachment of placenta.

Values	Local (uterine) bleeding (subgroup 1)	Obstetric DIC, in general (subgroup 2)	Systemic bleeding without organ dysfunction (subgroup 2A)	Systemic bleeding with organ dysfunction (subgroup 2B)
ARR	-0,44	0,08	0,09	0,07
NNT	-2,3	12,4	10,6	13,8
Rr	0,30	1,13	1,15	1,11
RRR (%)	70	-13	-15	-11
CI 95% (+)	-0,884	0,162	0,188	0,145
CI 95% (-)	-0,531	-0,045	-0,074	-0,017

Table 10. The effectiveness of rFVIIa administration in women with PPH, according to the total hysterectomy criterion

Further, we compared clinical manifestations of PPH to effects of rFVIIa in women under study who have abnormal changes in hemostatic system, and the research data gives the foundation for the formation of hemorrhagic syndrome, and to assess the effectiveness and safety of pharmacological correction of bleeding.

Based on coagulation results almost all patients (subgroups 1, 2) had the relative hypofibrinogenemia and hypocoagulation a few days prior to developing PPH (compared

to the physiological norm for this gestational age) (Tables 11-13). We can assume that these changes can reduce the so-called physiological hypercoagulability in pregnancy and may serve as the pathological basis for the formation of severe hemorrhagic syndrome during delivery.

The manifestation of PPH was associated with thrombocytopenia, hypocoagulation on PT and dynamic lowering of fibrinogen concentrations. Later, the first hours after infusion of rFVIIa the termination or reduction of bleeding (see Table 11-13) was followed by depression of thrombocytopenia and hypofibrinogenemia which is to be the natural course, as the platelets and fibrinogen are the basis of a blood clot.

Haemostatic markers	The indicator for normal pregnancy in III trimester	In patients 1-7 days prior to administration of rFVIIa	During bleeding	After rFVIIa administration			
				In 30 min	In 1 – 5 hours	In 24 hours	In 2-5 days
Platelets, $x10^9/l$	146-429	194,7±10,37	177,6± 8,2	109± 4,2	114± 7,9	146± 9,48	161± 5,8
PT, ratio	0,87	0,96	1,16	1,02	0,87	1,05	0,94
APPT, ratio	0,91	0,97	0,93	0,96	1,07	1,00	0,90
Fibrinogen, g/l	3,7-6,2	3,42± 0,16	2,15± 0,14	2,09± 0,13	2,02± 0,01	2,55± 0,12	3,09± 0,17
Antithrombin, %	82 - 116	93± 4,4	86± 3,5	87± 4,8	67,67± 1,8	91,38± 1,59	89,56± 2,9

Table 11. The dynamics of hemostasis in women of subgroup 1 (with local bleeding and uterine hypotension) before and after application of rFVIIa (X ± m); * - according to Abbassi-Ghanavati et al. (2009).

These shifts in patients of subgroup 1 were defined on the basis of shortening of PT and noticeable reduction of antithrombin activity. This indicates systemic, caused by rFVIIa interference increase of procoagulant properties of blood, along with moderate reduction of its anticoagulant potential, leading to clinically diagnosed hemostasis. Later, after 24 hours and more extended period of time , all abnormal changes appeared to be decreasing.

Haemostatic study of the second subgroup in women with obstetric DIC, showed direct (see the results for subgroup 1 given above), but more deep disorders of studied hemocoagulation markers in the period preceding and during PPH (Tables 12).

To determine the intensity, focus and accuracy of changes in hemostatic system in women after rFVIIa administration, we used a T-Wilcoxon test (Wilcoxon F, et al 1963). We analyzed changes in the pattern of bleeding, after 1-5 hours and 24 hours after the injection. The results were the following: the intensity of positive shift (in the direction of normal hemostasis) significantly prevails over the intensity of negative shift according to the following parameters: in patients with local uterine bleeding - protrombin time (P = 0.01), 24 hours after the administration, number of platelets (P = 0.05) 24 hours after the administration; level of fibrinogen (P = 0.05), 24 hours after the administration, in patients

with DIC reliable shift only in number of platelets (P = 0.05) 24 hours after the administration . For all other parameters changes are not significant, and in patients with DIC there is no effect or negative shift in prothrombin time.

Haemostatic markers	The indicator for normal pregnancy in III trimester *	In patients 1-7 days prior to administration of rFVIIa	During bleeding	After rFVIIa administration			
				In 30 min	In 1–5 hours	In 24 hours	In 2-5 days
Platelets, $x10^9/l$	146-429	166,7±5,18	136,1± 8,8	65±5,9	62,67± 6,8	81,5± 9,2	104,7± 16,3
PT, ratio	0,87	1,31	1,04	1,2	1,3	1,6	1,1
APPT, ratio	0,91	1,9	1,0	0,81	0,89	1,0	1,5
Fibrinogen, g/l	3.7-6.2	3,07±0,32	2±0,09	-	1,27± 0,006	3,75± 0,55	2,94± 0,2
Antithrombin, %	82 - 116	108±0,75	59±6,2	55±0,2	42±0,15	82±0,09	91,86±2, 2

Table 12. Hemostasis markers in patients with obstetrical DIC (subgroup 2) before and after rFVIIa administration (X ± m)

Haemostatic markers	Subgroup 1			Subgroup 2		
	During bleeding	After rFVIIa administration		During bleeding	After rFVIIa administration	
		In 1-5 hours	In 24 hours		In 1-5 hours	In 24 hours
Platelets, $x10^9/l$	177,6±8,2	114±7,9	146±9,48	136,1±8,8	62,67±6,8	81,5±9,2
PT, ratio	1,16	0,87	1,05	1,04	1,3	1,6
Fibrinogen, g/l	2,15±0,14	2,02±0,01	2,55±0,12	2±0,09	1,27±0,006	3,75±0,55
Antithrombin, %	86±3,5	67,67±1,8	91,38±1,59	59±6,2	42±0,15	82±0,09

Table 13. The dynamics of main hemostatic markers in women with PPH after rFVIIa administration (X ± m)

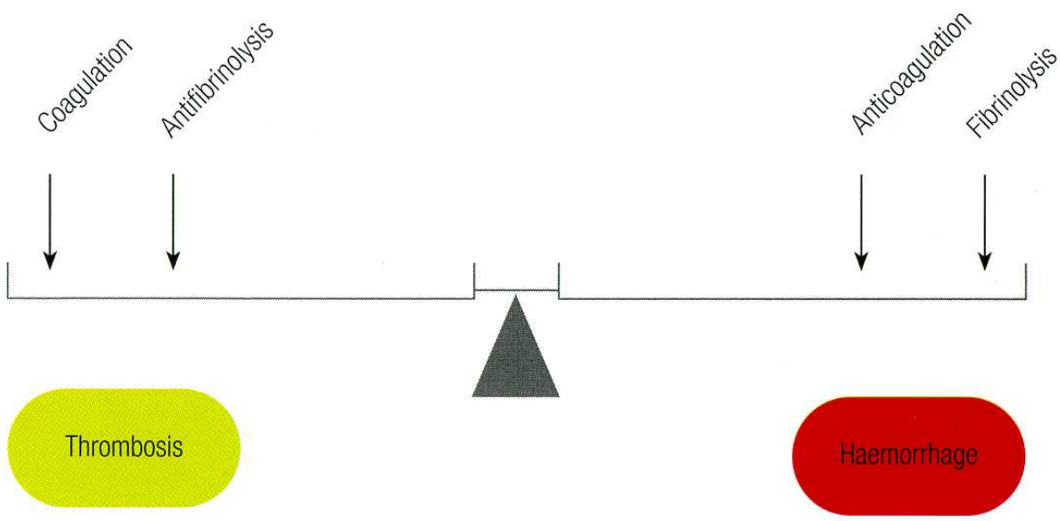
With all the results shown, as well as the fact of the massive reduction of anticoagulant potential (antithrombin activity) in DIC-related PPH and rFVIIa administration , a higher risk of developing or enhancing organ dysfunction associated with blockade of microcirculation can be indicated in this subgroup, which is described and mentioned in a number of publications devoted to the study of aseptic and septic DIC (Eisele & Lamy, 1998; Macphail & Talks, 2004; Schouten et al., 2008; Vinazzer, 1995).

It is known that antithrombin acts as heparin cofactor and related to the most important inhibitors of blood clotting, it accounts approximately 80% of anticoagulant potential (LaBelle & Kitchens, 2007; Opal et al., 2002; Practical hemostasis and thrombosis, 2005; Rublee et al., 2002). When antithrombin activity in plasma falls below 70% the risk of

pathological clotting progressively increases, and it is greater, the greater the anticoagulant deficiency. Decrease in antithrombin activity to the level of 30-50% of the physiological norm leads to a generalized, unrestrained thrombinemia and massive thrombosis in vessels of any size. In this case, antithrombin half-life shortens dramatically, and can be only a few hours (especially with therapeutic doses of heparin) (Vinazzer, 1995).

Decrease in antithrombin activity in patients below 70% in different types of pathology requires replacement therapy to recover the physiological norm (about 80-120%) (LaBelle & Kitchens, 2007; Schouten et al., 2008; Schwartz et al., 1989). To cover antithrombin small supply, commercial products of anticoagulants or fresh frozen plasma (FFP) can be used. Note, however, that the massive transfusion of FFP (20-25 ml/kg) may lead to hypervolemia and risk of interstitial pulmonary edema, if symptoms of renal failure and the termination of bleeding occur. In these cases, we believe, we can use combined application of antithrombin preparation and FFP (dose of 7-10 ml/kg).

We also believe that support of sustainable balance of pro- and anticoagulant systems of hemostasis in patients with systemic bleeding after rFVIIa administration will reduce the risk of thrombotic events, lessening or strengthening of potential multiple organ failure (Pic. 2).



Pic. 2. Systematic hemostasis interaction in oder to balance coagulation / anticoagulation and fibrinolysis / antifibrinolysis, which when altered, results in haemorrage or thrombosis (after Buenso S.R., 2007)

If to look back at the reactions of hemostatic system to the introduction of rFVIIa in women with obstetric DIC and PPH, we conclude that PT, on average data, was not shortened, but in most cases, lengthened or remained normal at the time of registration of bleeding. In our view, the lack of shortening of PT in first two hours after rFVIIa administration may serve as a predictor of its low hemostatic activity, as well as the little impact of repeated injections of rFVIIa.

It was previously shown that the use of rFVIIa has the worst hemostatic effect in patients with severe coagulopathy, acidosis and hypothermia (Aggarwal et al., 2004; Bomken et al., 2009; Dutton, 2004; Eikelboom et al., 2003; Martinowitz & Michaelson, 2005; Mayo et al.,

2004; Mittal & Watson, 2006; O'Connell et al., 2003). It was shown in these studies that effective pharmacologic hemostasis with use of rFVIIa can be expected with the following parameters of blood:

- prothrombin time <1.5 hours upper limit of normal;
- Clauss fibrinogen> 1.0 g / L;
- platelet count > 50 × 10^9 / L;
- along with the above laboratory indices pH > 7.1 is also desirable for optimal effect;
- exclusion of hypothermia.

In the course of the research we have corrected the present parameters with the means of transfusion therapy, which was aimed at the recovery of hemostatic abilities in the blood, maintenance of the acid-base balance and the quantity of red blood cells to oxygenize tissues. It should be noted that in our research the volume and components of such a therapy were practically the same in the study and control groups. At the same time patients of the study group experiencing PPH and DIC (subgroup 2) received the bigger volume of the transfusion therapy as compared to subgroup 1 (table 14). The information we obtained about changes in hemostasis during haemostatic therapy allows us to estimate the importance of such studies in pregnant women and offer recommendations how to treat patients with PPH as evidenced by a number of experts (Ahonen et al., 2010; Bomken et al., 2009; Franchini et al., 2007; Sobieszczyk & Breborowicz, 2004).

Criteria of comparison	Study group (n=75)		P value
	Subgroup 1 (n=47)	Subgroup 2 (n=28)	
	X ± m	X ± m	
Total volume of transfusions, ml	2937,2 ± 630,1	5340,8 ± 1207,0	0,05
FFP, ml	1381,1 ± 314,9	2975,6 ± 702,7	0,01
Red blood cells, ml	1003,2 ± 213,7	1725,4 ± 770,1	P>0,05
Platelets concentrates, U	0	4,13 ± 1,1	-

Table 14. Transfusion therapy in women to study group

Among the questions raised above we were interested in the possibility of arterial and venous thrombosis development during treatment with rFVIIa. In the analysis of 75 cases of rFVIIa treatment of women with PPH, represented by Franchini et al. (2007) there were no evidence of venous thrombosis. The recent work of Bomken et al. (2009) also demonstrated the absence of thrombosis during treatment with rFVIIa, in spite of the increasing thrombogenicity inherent to physiological pregnancy. In addition, several reports indicated a low risk of venous thromboembolism in previously healthy patients, even with the development of DIC (Martinowitz & Michaelson, 2005; Moscardo et al., 2001.). In general, the majority of thrombotic events due to the application of rFVIIa, have arterial origin and are determined in patients with pre-existing thrombogenic risk factors (Biss & Hanley, 2006.). Nevertheless, as well as the number of authors, and according to materials of existing international recommendations (Franchini et al., 2007; Lim et al., 2004; Martinowitz & Michaelson, 2005; Ohkuchi et al., 2003; Vincent et al., 2006; Welsh et al., 2008; World Health

Organization [WHO], 2009), we recommend care in using this systemic haemostatic medicine in women with high risk of thromboembolism, such as cancer, including reproductive organs, air embolism, antiphospholipid syndrome, and thromboembolic syndrome present in history and in close blood relatives. In these cases it is vital to apply therapy or medication for thromboprophylaxis.

6. Discussion

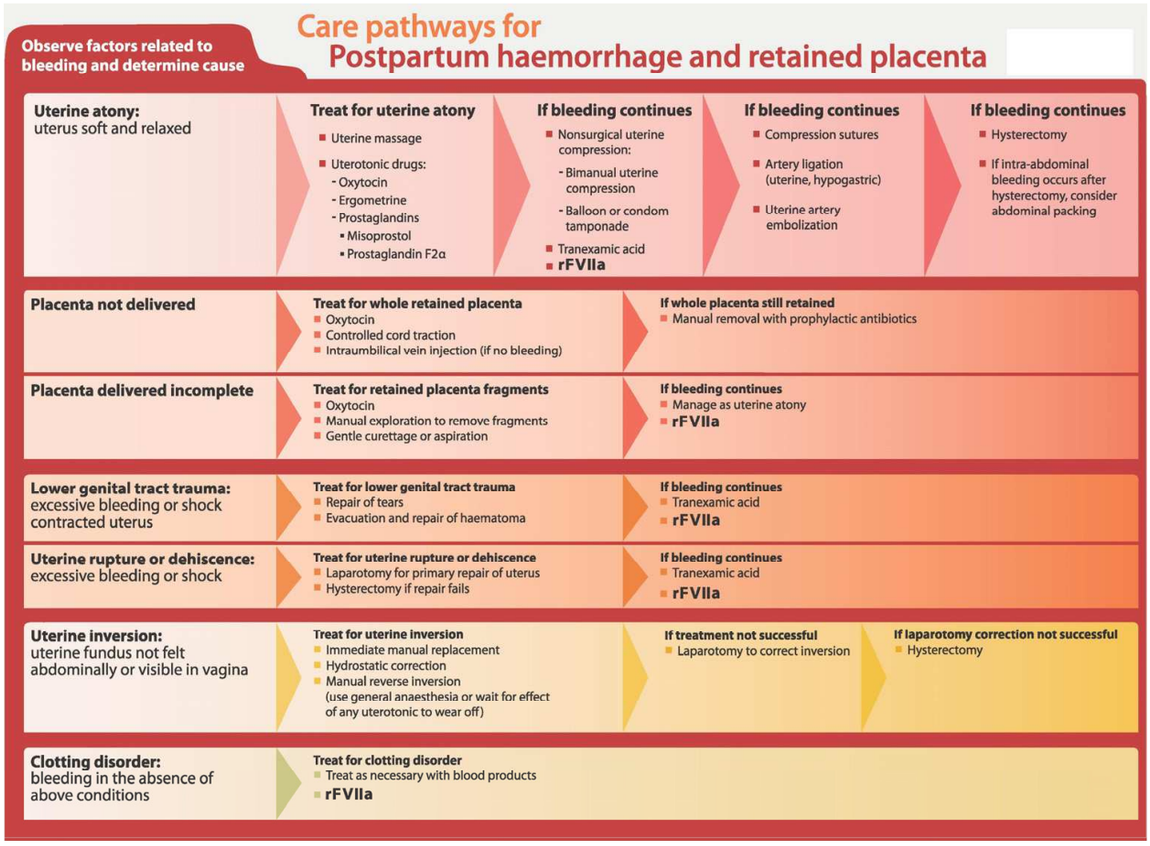
In general the data that we obtained suggests that rFVIIa is a highly efficient hemostatic means to treat women with PPH, who are unable to respond to classical methods of haemostatic therapy. In accordance with the effectiveness criteria used in the present study women with massive local (uterine) bleeding, caused by uterine hypotony and atony in which the use of rFVIIa prescribed to avoid hysterectomy in most cases (80.9%) proved to have haemostatic effect, with no lethality among patients. Women with PPH due to the abruptio placentae combined with Kuveler's uterine and placenta increta had relatively lower hemostatic effectiveness. On the other hand patients with obstetrical DIC (without organ dysfunction) and PPH the use of rFVIIa can also be justified due to health reasons, though relatively less effective. In cases of obstetrical DIC, massive bleeding and developing of organ dysfunction haemostatic effect of rFVII is extremely doubtful.

Cases of failure of pharmacological correction of bleeding with rFVIIa can be attributed to resistance, for various reasons, of the blood coagulation system to activation of redundant quantity of factor VIIa (Franchini et al., 2007; Selo-Ojeme & Okonofua, 1997; Shander et al.,2005; Sobieszczyk & Breborowicz, 2004), as well as by the presence of organ dysfunction, which led to adverse outcome in 6 out of 11 women (54.5%) in our observations.

It is important to note that the use of rFVIIa in massive bleeding leads to further consumption of platelets and fibrinogen, which is consistent with the modern explanation of the mechanism of its hemostatic action, but to reduce the risk of development or strengthening of possible multiple organ failure in obstetrical DIC it is important to recover the deficit not only of platelets and clotting factors, but also of physiological anticoagulants. The optimal tactics in the period after rFVIIa administration is 3-7 days of corrective replacement therapy of fresh frozen plasma (at a dose of 7-10 ml / kg) in combination with antithrombin preparation, to restore the activity of the latter, tentatively, to 100-120% of normal levels. The role of efficient and high-quality laboratory diagnostics of dynamics and basic parameters of coagulation (platelet count, PT, fibrinogen concentration and antithrombin activity) goes without questioning.

Based on this data, we include rFVIIa in a scheme of therapy of obstetric hemorrhage, proposed by WHO, for the prevention of invasive and radical interventions in the treatment of PPH vital for haemostas management (World Health Organization [WHO], 2009) - See Pic. 3.

We also believe that the use of tranexamic acid in the therapeutic tactics proves to be effective in cases of PPH, due to local uterine bleeding. However, the threat of emerging or strengthening of organ dysfunction or venous thromboembolism based on fibrinolytic reaction suppression seems substantial and dangerous to mother's life.



Pic. 3. Potential role of rFVIIa in treatment of PPH to reduce the number of radical operative interventions

7. Conclusion

We state that the resources of our own and those available publicly in regard to this issue received in non-controlled and nonrandomized studies, otherwise is impossible because of ethical reasons in obstetric practice of critical conditions (Bomken et al., 2009). Nevertheless, the accumulation and subsequent analysis of cases of rFVIIa administration in treating PPH will contribute to creating overall and clear recommendations for specialists in this field.

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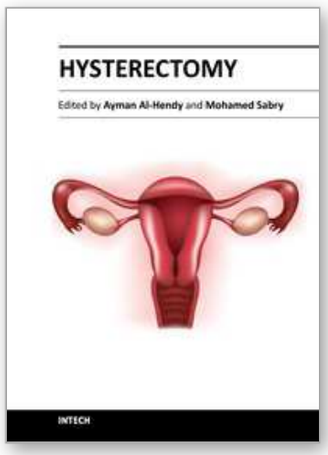

Hysterectomy

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This book is intended for the general and family practitioners, as well as for gynecologists, specialists in gynecological surgery, general surgeons, urologists and all other surgical specialists that perform procedures in or around the female pelvis, in addition to intensives and all other specialities and health care professionals who care for women before, during or after hysterectomy. The aim of this book is to review the recent achievements of the research community regarding the field of gynecologic surgery and hysterectomy as well as highlight future directions and where this field is heading. While no single volume can adequately cover the diversity of issues and facets in relation to such a common and important procedure such as hysterectomy, this book will attempt to address the pivotal topics especially in regards to safety, risk management as well as pre- and post-operative care.

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