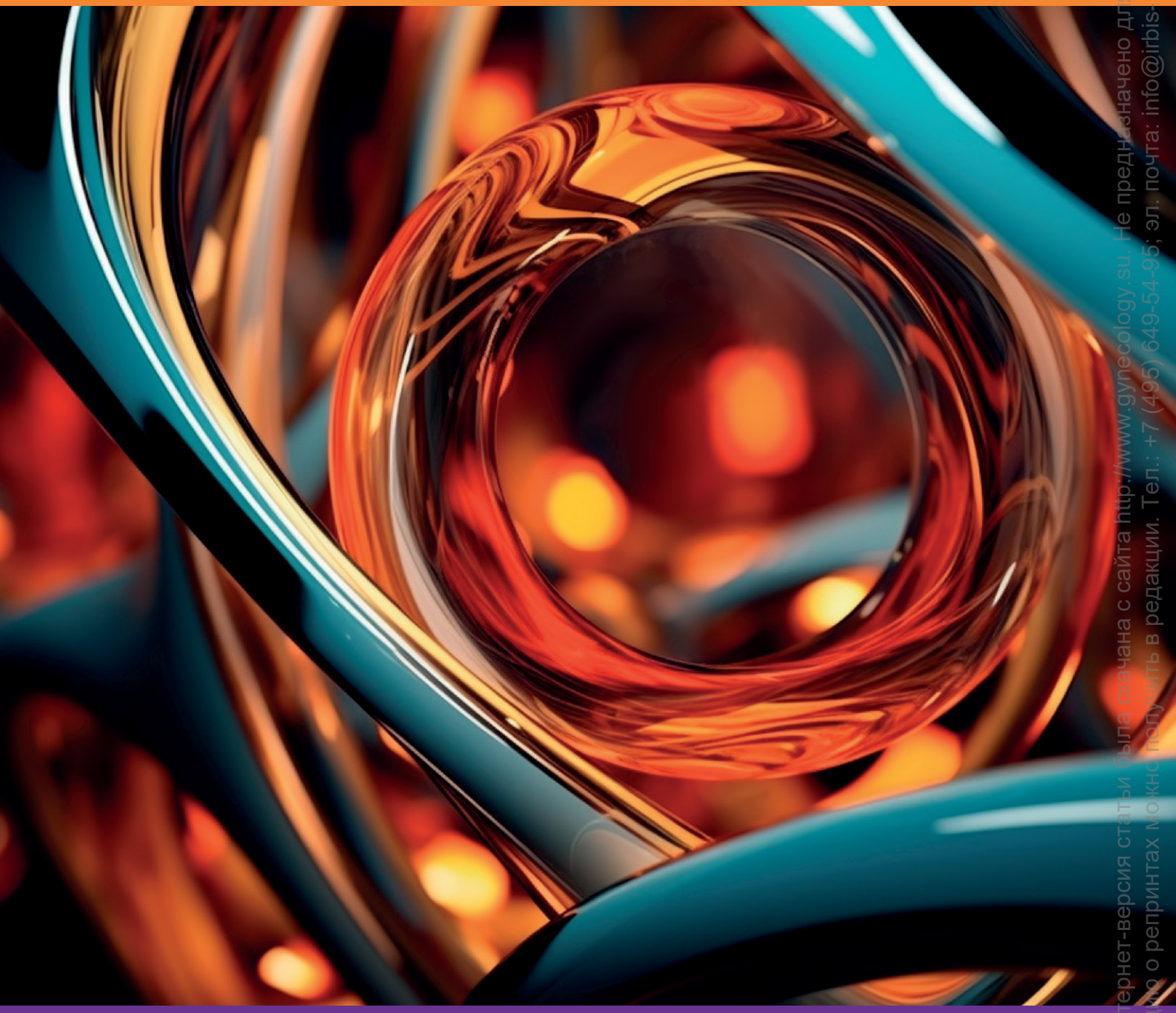
ISSN 2313-7347 (print)
ISSN 2500-3194 (online)

АКУШЕРСТВО ГИНЕКОЛОГИЯ РЕПРОДУКЦИЯ

Включен в перечень ведущих рецензируемых журналов и изданий ВАК

2025 • том 19 • № 6



OBSTETRICS, GYNECOLOGY AND REPRODUCTION

2025 Vol. 19 No 6

https://gynecology.su

ISSN 2313-7347 (print)
ISSN 2500-3194 (online)

Научный обзор | Review article

https://doi.org/10.17749/2313-7347/ob.gyn.rep.2025.482

Management of coagulopathy related to major obstetric bleeding: narrative review

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Abstract

Obstetric bleeding represents one of the main causes of maternal mortality worldwide. Along with hypertensive disorders it accounts for over half of maternal mortality cases. The implementation of strategies such as the "code red", increased institutionalized deliveries, early transfusions, and early obstetric alert system has reduced mortality. Cases of massive bleeding require admission to the Intensive Care Unit as they can progress to coagulopathy. This narrative review focuses on medications intended for the advanced management of coagulopathy in this population.

Keywords: pregnancy, delivery, postpartum hemorrhage, coagulopathy

For citation: Correa-Pérez L., Olaya-Garay S, Mora-Martínez S. Management of coagulopathy related to major obstetric bleeding: narrative review. *Akusherstvo, Ginekologia i Reprodukcia = Obstetrics, Gynecology and Reproduction.* 2025;19(6):914–922. (In English). https://doi.org/10.17749/2313-7347/ob.gyn.rep.2025.482.

Лечение коагулопатии, связанной с большим акушерским кровотечением: описательный обзор

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Резюме

Акушерские кровотечения представляют собой одну из основных причин материнской смертности во всем мире. Вместе с гипертензивными расстройствами они составляют более половины случаев материнской смертности. Внедрение стратегий, таких как «красный код», увеличение числа институциональных родов, ранние трансфузии и системы раннего предупреждения в акушерстве, привело к снижению смертности. Случаи массивного кровотечения требуют госпитализации в отделение интенсивной терапии, так как они могут усугубляться вплоть до развития коагулопатии. Настоящий описательный обзор фокусируется на лекарствах, предназначенных для более эффективного ведения коагулопатией в указанной группе лиц.

Ключевые слова: беременность, роды, послеродовое кровотечение, коагулопатия

Для цитирования: Корреа-Перес Л., Олайя-Гарай С., Мора-Мартинес С. Лечение коагулопатии, связанной с большим акушерским кровотечением: описательный обзор. *Акушерство, Гинекология и Репродукция.* 2025;19(6):914–922. https://doi.org/10.17749/2313-7347/ob.gyn.rep.2025.482.

Highlights

What is already known about this subject?

- Obstetric bleeding is one of the leading causes of maternal mortality.
- The main etiologies include uterine atony, birth canal lacerations, and thrombocytopathies.
- Prompt medical intervention is crucial to prevent complications.

What are the new findings?

- The authors provide a treatment algorithm based on the recommended time frame for managing postpartum hemorrhage.
- Hemostatic agents must integrate a multimodal approach to treat postpartum hemorrhage.
- Tranexamic acid is mandatory in all postpartum hemorrhages because it reduces mortality by 33 %.

How might it impact on clinical practice in the foreseeable future?

- The implementation of multimodal approaches may reduce postpartum hemorrhage mortality.
- Functional hemodynamic monitoring, appropriate use of blood products, and resource management could positively affect maternal-fetal prognosis.
- The point-of-care diagnostic tests can optimize clinical management and save resources.

Основные моменты

Что уже известно об этой теме?

- Акушерские кровотечения являются одной из ведущих причин материнской смертности.
- Основными этиологическими причинами являются атония матки, разрывы родовых путей и тромбоцитопатии.
- Своевременное медицинское вмешательство имеет решающее значение для предотвращения осложнений.

Что нового дает статья?

- Авторы представляют алгоритм лечения, основанный на рекомендованных временных рамках ведения послеродового кровотечения.
- Гемостатические средства должны быть частью мультимодального подхода к лечению послеродового кровотечения.
- Применение транексамовой кислоты обязательно при всех послеродовых кровотечениях, поскольку она снижает смертность на 33 %.

Как это может повлиять на клиническую практику в обозримом будущем?

- Внедрение мультимодальных подходов может снизить смертность от послеродового кровотечения.
- Функциональный гемодинамический мониторинг, рациональное использование препаратов крови и эффективное управление ресурсами могут положительно повлиять на прогноз для матери и плода.
- Экспресс-диагностические тесты у постели пациента могут оптимизировать клиническое ведение и сэкономить ресурсы.

Introduction / Введение

Obstetric bleeding is one of the leading causes of maternal mortality worldwide and together with hypertensive disorders are the pathologies accounting for mortality in more than half of the cases. Major obstetric hemorrhage is preventable and treatable, yet it continues to lead to extreme maternal morbidity and early maternal death (less than 42 days). Strategies such as "code red", management protocols and drills, as well as the increase in institutionalized delivery, early transfusion and early warning systems in obstetrics accompanied by rapid response teams have decreased mortality; but cases of massive bleeding remain requiring Intensive Care Unit admission and frequently progress to hemorrhagic and dilutional coagulopathy, requiring advanced management. The World Health Organization has spoken out against major obstetric hemorrhage as a clear cause of maternal death worldwide [1, 2].

The pandemic also appears as a time when the availability of blood products is lowered. In 2020, blood banks and blood centers report the lowest rates of donor availability in recent years, which is why the need for the rational use of blood products and the approximation of drugs that in a staggered manner allow control of bleeding and decrease blood loss and prevent the progression of coagulopathy. The current review highlights those drugs which are focused on the advanced management of coagulopathy, considering major obstetric bleeding as acquired hemophilia, i.e., a severe coagulation disorder, due to acute loss of fibrinogen or acute loss of coagulation factors [1, 2].

Materials and Methods / Материалы и методы

A narrative review of the scientific literature published between 2000 and 2023 was conducted with the aim of describing the pathophysiology, therapeutic strategies, and clinical implications of postpartum hemorrhage (PPH). The databases PubMed/MEDLINE, ScienceDirect, and LILACS were queried using controlled Medical Subject Headings (MeSH) terms: “blood transfusion”, “postpartum hemorrhage”, and “tranexamic acid”. This search strategy yielded a total of 7,790 potentially relevant articles.

In the initial screening phase, two of the authors independently assessed the titles and abstracts of the

retrieved articles, applying inclusion criteria focused on clinical relevance, methodological validity, and recent studies. Prioritized were meta-analyses, randomized clinical trials (RCTs), and systematic reviews published in scientific journals ranked in Q_1 and Q_2 quartiles according to the Journal Citation Reports. Exclusion criteria included duplicate publications, studies involving pediatric populations, articles with significant methodological limitations, and those not available in full text. Articles in both English and Spanish were analyzed.

The select articles then underwent a full-text review. In cases of disagreement or uncertainty regarding inclusion, a third author acted as a reviewer and arbiter. This third assessment allowed for consensus to be reached regarding the relevance and quality of the select studies. As a result of this consensus-based selection process, 31 articles were included as the foundation of the review. These select studies represent the most robust and up-to-date evidence available on postpartum hemorrhage, with the emphasis on using blood products, antifibrinolytic agents, and multimodal clinical management strategies.

Background / История вопроса

Every four minutes a woman dies due to postpartum hemorrhage worldwide, which is equivalent to more than 160,000 cases each year and it is known that at least 20 million cases of extreme maternal morbidity due to obstetric hemorrhage occur each year globally, particularly in low-middle income countries. The management of postpartum hemorrhage includes medical management, surgical techniques, pharmaceutical approach, and hematological support [1, 2].

Multiple definitions for the volume of blood loss to classify postpartum hemorrhage have been proposed, however physiologically it is considered that blood loss that causes a physiological change that puts a woman's life at risk could be an ideal definition. The incidence is high and occurs in up to 18 % of births worldwide and the fatality rate depends on rating development of the country and the appropriate management [3].

Basic management of postpartum hemorrhage / Базовое лечение послеродового кровотечения

The management of major obstetric bleeding includes the management of first, second, and third trimester hemorrhages, as well as postpartum hemorrhage. Management requires definitive surgical measures (curettage in incomplete abortion, laparotomy and salpingectomy, intrauterine tamponade with a Backri's balloon, bimanual uterine massage, hemostatic sutures, or hysterectomy, among other alternatives) as well as the administration of drugs: uterotonics (oxytocin, misoprostol, methylergometrine) and tranexamic acid for the management of the primary cause, which have been evidence-validated and supported with extensive literature reviews [4, 5]. Simultaneously, appropriate medical management and surgical techniques are carried out to control the bleeding in the uterus, tonics, and bimanual massage to correct the atony, the administration of dynamic water supply and hematological support required for such bleeding patients. In Colombia, since the appearance of the "code red" as a comprehensive, organized and protocolized management strategy, lower mortality as well as temporary and clear management of major obstetric hemorrhage have been evidenced. The greatest impact of the "code red" strategy is the generation of zero time and medical and surgical measures with appropriate decisions and interventions every twenty minutes in a golden hour context [5, 6]. The use of tranexamic acid has been validated in several studies and is currently considered mandatory for the management of all obstetric hemorrhages. In this regard, the WOMAN trial, demonstrated that ⅓ of deaths from obstetric hemorrhage are prevented, among other benefits that apply to all causes of postpartum hemorrhage [7, 8].

Hemoderivates in obstetric hemorrhage / Гемодериваты при акушерских кровотечениях

Simultaneously with the dynamic water supply with warm crystalloids, the first intervention is presented as the transfusion of packed red blood cells, considering that 1 unit of packed red blood cells increases hemoglobin usually by 1 g/dl and hematocrit by 3 %. Said erythrocytes should ideally be O negative if the patient did not have previous typing and screening, but if unavailable, O positive should be administered in order not to delay blood repletion [3].

Platelet transfusion can be performed by apheresis where a single donor generates through plateletpheresis at the equivalent of 5 or 6 individual platelet units. Platelets can come in a unit form obtained from whole blood collected from various donors. To achieve the number of units required by the patient, they are stored individually, and the patient may require 4 to 6 units of platelets for bleeding control [3].

Mass transfusion protocols include platelet transfusion, fresh frozen plasma and, depending on fibrinogen levels, include replacement of this. In the bleeding obstetric patient, the idea of plasma transfusion contains all the coagulation factors required for hemostasis and prevents dilutional coagulopathy if only packed red blood cells were used, plasma fibrinogen level is insufficient in the case of hypofibrinogenemia [7].

Including fibrinogen replacement using units of blood products to massive transfusion protocols should be accompanied by plasma transfusion to replete other coagulation factors. Clearly, plasma risk includes volume overload, transfusion reactions, and transfusion-associated infectious diseases. Cryoprecipitate contains

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250–325 mg of fibrinogen and minimal amounts of other clotting factors; the downside is the risk of viral transmission and significantly varied fibrinogen levels [7].

In 2019, a clinical practice guide for the management of blood products in obstetrics entitled the consensus of the NATA (Network for the Advancement of Patient Blood Management, Hemostasis and Thrombosis) was produced in association with FIGO (International Federation of Gynecology and Obstetrics). As a collaborative effort, the ESA (European Society of Anesthesiology) and EBCOG (European Board and College of Obstetrics and Gynecology) advanced to improve the use of blood products in pregnancy and the puerperium [9].

The first initiative is to define primary postpartum hemorrhage with blood loss > 500 ml within the first 24 hours regardless of the type of delivery and to consider severe hemorrhage with a blood loss > 1000 ml in 24 hours with signs or symptoms of hypovolemia, and define life-threatening massive bleeding that exceeds 2,500 ml blood loss or hypovolemic shock regardless of delivery route [3].

In addition, it also speaks out against the routine use of antepartum autologous donation; the guide provides numerous recommendations for the prevention and management of obstetric hemorrhage; as well as recommendations for specific interventions to correct bleeding. It emphasizes to avoid colloids and a restrictive use of crystalloid resuscitation (1–2 ml crystalloid for every 1 ml of bleeding) as well as recommends administration of calcium and tranexamic acid and primarily avoiding hypothermia [9].

It is proposed to prefer expedited tests at the bedside or to seek strategies to speed up clinical laboratory results and, apply them if there are tests at the bedside (Point-of-Care, POC) such as thromboelastography (TEG) or thromboelastometry (ROTEM) [10–12]. Fibrinogen level below 2 g/L in the scenario of postpartum hemorrhage should be managed with cryoprecipitate or with fibrinogen concentrate to achieve physiological range [13].

The guidelines published by the NATA 2019 highlight against the administration of clotting factor concentrates. Regarding fibrinogen reflection therapy, it considers that fibrinogen is the first factor to decline to critical levels in massive bleeding. In patients who have been resuscitated with packed crystalloid and colloid red blood cells, it has been shown in settings other than postpartum hemorrhage that fibrinogen replacement reduces bleeding and transfusion requirements, and that postpartum hemorrhage alone shows a related bleeding severity with fibrinogen levels and those range below 2 g/L increase the risk of postpartum hemorrhage with a positive predictive value of 100 % [14, 15].

Role of fibrinogen in the coagulation cascade / Роль фибриногена в каскаде коагуляции

The new coagulation cascade consists of three phases: phase 1 – initiation, phase 2 – amplification, and phase 3 – propagation. The coagulation cascade allows thrombin to convert fibrinogen into insoluble fibrin to which factor (F) XIII binds. At phase 1 called the initiation phase, the interaction of tissue factor with FVIIa and FX that becomes FXa activates transition from prothrombin to thrombin, followed by amplification, wherein the interaction between platelets, thrombin, FIX and FX results in the thrombin explosion, and the platelet clot is generated [16]. In the propagation phase, activated FIX and FVIIIa bind to platelets, generating more FXa and further enhancing the conversion of prothrombin to thrombin as well as fibrinogen to fibrin. In addition, the thrombus becomes stabilized with the support of FVIII and FVIIa [3].

When an obstetric patient presents bleeding and has decreased fibrinogen levels, there are two options: management with cryoprecipitates or fibrinogen concentrate [16]. In pregnancy, fibrinogen is elevated as part of the hemostatic response to pregnancy, with levels at term ranging between 5 and 7 g/L. So even a patient with obstetric bleeding at normal fibrinogen levels is actually characterized a prominent fibrinogen consumption [16]. Among the physiological changes related to pregnancy is a progressive increase in fibrinogen levels and its normal value doubles for the third trimester [17].

Fibrinogen concentrate and prothrombin complex human / Концентрат фибриногена и протромбиновый комплекс человека

Fibrinogen concentrate / Концентрат фибриногена

Fibrinogen concentration should not be managed empirically, without having performed a measurement of serum fibrinogen levels for decision-making [18, 19]. The rational use of cryoprecipitates and fibrinogen concentrate emerges to understand how fibrinogen levels are usually very low in obstetric hemorrhage, compared to uterine atony or intra-abdominal hemorrhage, large volumes of clots can form and quickly consume all the available fibrinogen. It is considered as a rule, 10 bags of cryoprecipitate will increase a fibrinogen in an adult person by 1 g/L. On the other hand, fresh frozen plasma is an insufficient source of fibrinogen and in case of verified hypofibrinogenemia additional supplies are required. Fibrinogen plays a fundamental role in hemostasis; it is a soluble glycoprotein produced in the liver and is considered an acute phase reactant. Fibrinogen is to facilitate platelet aggregation mediated by surface glycoproteins [15, 19].

Several studies have shown the importance for lowering blood fibrinogen during bleeding. The study by B. Charbit et al. collected blood samples in early obstetric hemorrhage. The regression analysis showed that a sole fibrinogen concentration at the time of the initial bleeding significantly predicts the hemorrhage severity and thus

levels less than 2 g/L predict about severe bleeding and that > 4 g/L has a negative value to predicting severe bleeding [20, 21].

L. de Lloyd also demonstrated an inverse relationship between fibrinogen concentration and severity of postpartum hemorrhage [13, 22]. The FIB-PPH trial randomized 249 patients to receive placebo versus 2 g of fibrinogen as preventive treatment for postpartum hemorrhage without finding an inter-group difference or showing a difference between the need for transfusion, however this population had normal fibrinogen > 4.5 g/L in both groups at the onset of bleeding [23]. The FIDEL trial, a randomized controlled and blinded study that administered fibrinogen concentrate early in postpartum hemorrhage when uterine tonics such as oxytocin and intravenous prostaglandins had failed, apparently found no advantage in using fibrinogen without hypofibrinogenemia [24, 25].

Fibrinogen concentrate is derived from human plasma which is subjected to a pasteurization process to reduce viral transmission to be stored in a lyophilized form containing 900 to 1300 mg of fibrinogen generally dispensed as 1 g per vial and can be stored at room temperature environment long-term and reconstituted in 50 ml sterile saline solution. As risks of fibrinogen administration are presented as very low-rate allergic reactions and the risk of thromboembolic events (< 1:20000), it is therefore considered as a safe drug.

The goal of replacing fibrinogen in postpartum hemorrhage requires first identifying patients with fibrinogen deficiency and then correcting it either with cryoprecipitates or with fibrinogen concentrate. The introduction of TEG and ROTEM allow a rapid approach and is considered a very useful bedside test (POC) that guides management in major bleeding. S. Mallaiah's group conducted a study guided by ROTEM for the administration of fibrinogen concentrate and included in their study, but obtaining such products from blood bank is a time-consuming; subsequently they introduce a protocol in which fibrinogen concentrate was administered in fibrinogen deficiency defined by FIBTEM < 7 mm or between 7–12 mm with active bleeding [26]. This group proposed a change from the 1:1 Red Blood Cell Transfusion:Plasma strategy to a 1:1 Red Blood Cell Transfusion:Concentrated fibrinogen strategy guided by the ROTEM diagnosis of hypofibrinogenemia. In this protocol, there was found a reduction in the total number of blood components transfused, although excepting packed red blood cells. They observed a decline in the number of patients requiring more than 6 units of ERT ($p = 0.015$), a reduction in the total use of blood products ($p < 0.0001$), and less transfusion-related cardiac overload (TACO), but not lowering hysterectomy rates or the number of Red Blood Cell Transfusion [27, 28].

OBS2 obstetric bleeding study assesses the experience after fibrinogen administration guided by ROTEM, being a double-blind randomized controlled clinical trial that enrolled 663 women with postpartum hemorrhage and administered either fibrinogen or placebo in case of FIBTEM < 15 mm. In this study, no difference in number of blood products transfused in the two arms or in other outcomes in secondary analysis were found [27, 28].

Prothrombin complex human / Протромбиновый комплекс человека

Human prothrombin concentrate is a complex of four factors derived from vitamin K; consisting of FII, FVII, FIX and FX, associated with low doses of heparin and antithrombin III; approved for the treatment of life-threatening bleeding associated with the consumption of oral anticoagulants type vitamin K antagonists, it has also been used for trauma bleeding and there are case reports on its efficacy in major obstetric bleeding. However, current guidelines do not approve its use in settings outside clinical trials, out of concern about side effects that could outweigh the benefits. However, its use in obstetric hemorrhage requires to be further investigated [29].

Conclusion / Заключение

Obstetric hemorrhage requires a comprehensive approach that includes medical and surgical management, uterotonics, cause identification and correction, tranexamic acid, fluid resuscitation, and transfusion of blood products. Fibrinogen concentrate and prothrombin concentrate are therapeutic options to be considered for transfusion. In the scenarios of unavailable blood products and currently with the emergence of the pandemic, it is necessary to have alternatives to blood products given that there are scarce resources, and the current access to blood products is low, with the shortage of fresh frozen plasma and cryoprecipitates being more noticeable.

Recommendations / Рекомендации

1. The authors provide a treatment algorithm based on the recommended time frame for managing postpartum hemorrhage (**Fig. 1, 2, 3, 4**).
2. Standardized management of postpartum hemorrhage and massive transfusion protocol are essential [10].
3. Hemostatic agents must integrate a multimodal approach to treat postpartum hemorrhage that consists of medical, surgical, Uterotonic, water supply with warm crystalloids, transfusion of blood products. In hypofibrinogenemia, the administration of fibrinogen or cryoprecipitates can be considered based on availability [4, 5, 30].
4. Tranexamic acid is mandatory in all postpartum hemorrhages because it reduces mortality rate by 33 %, as demonstrated in the WOMEN Trial [8, 31].
5. Measurement of fibrinogen level is required to predict bleeding severity [10].

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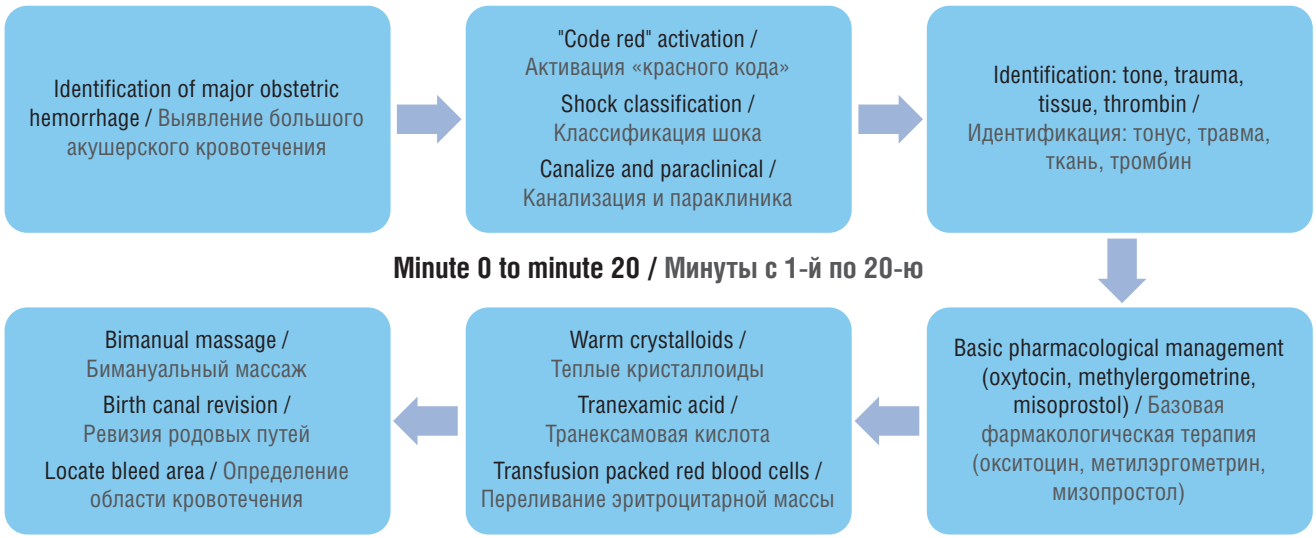

Figure 1. Postpartum bleeding management algorithms minute 0 to minute 20.

Note: *initial management algorithm for major obstetric hemorrhage during the first 20 minutes. It includes early identification, "code red" activation, shock classification, etiological assessment, basic pharmacological treatment, hemodynamic resuscitation with warm crystalloids and tranexamic acid, red blood cell transfusion, and birth canal examination. The intervention is conducted in a stepwise and time-sensitive manner.*

Рисунок 1. Алгоритм ведения послеродового кровотечения с 1-й по 20-ю минуту.

Примечание: *алгоритм начального ведения при большом акушерском кровотечении в течение первых 20 минут включает раннюю диагностику, активацию «красного кода», классификацию шока, этиологическую оценку, базовую фармакологическую терапию, гемодинамическую реанимацию теплыми кристаллоидами и транексамовой кислотой, переливание эритроцитарной массы и осмотр родовых путей. Вмешательство проводится поэтапно и с учетом временных периодов.*

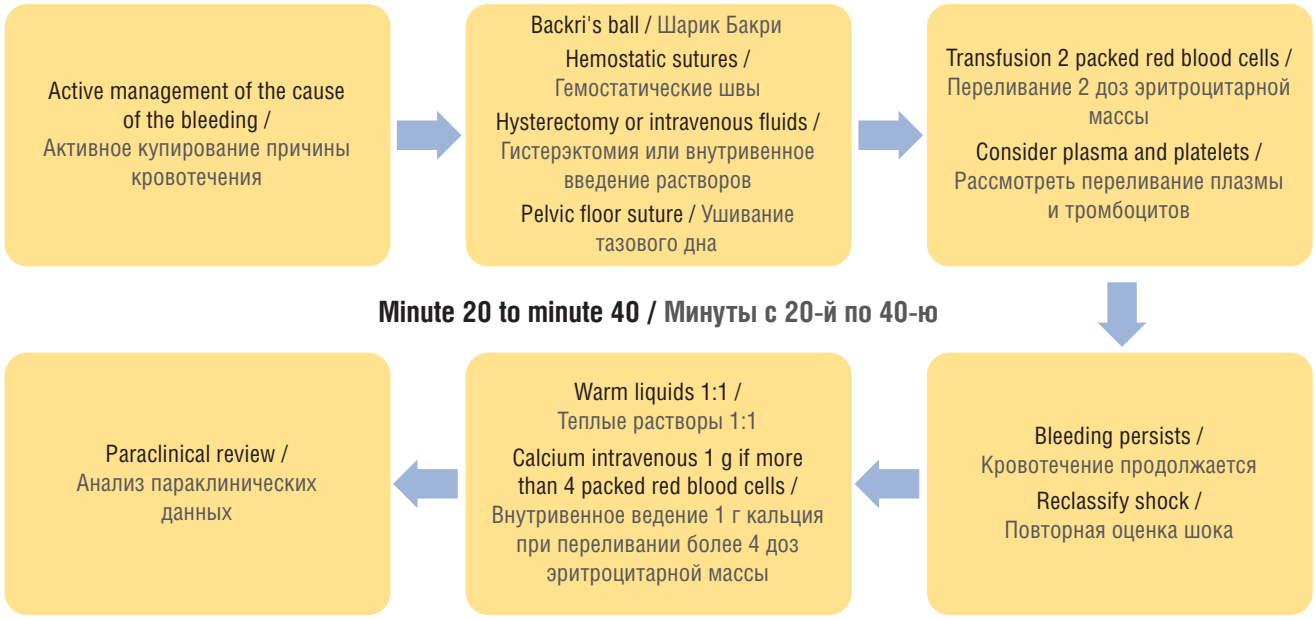

Figure 2. Postpartum bleeding management algorithms minute 20 to minute 40.

Note: *stepwise algorithm for the management of postpartum hemorrhage between minutes 20 and 40. This stage involves escalation of care with active control of the bleeding source through surgical or mechanical interventions (e.g., Bakri balloon, hemostatic sutures, hysterectomy, pelvic floor repair), transfusion of blood components (including red blood cells, plasma, and platelets), and reassessment of clinical status. Warm fluid resuscitation at a 1:1 ratio is recommended, with intravenous calcium supplementation if more than four units of packed red blood cells are administered. Management remains stepwise and time-sensitive, guided by hemodynamic response and paraclinical review.*

Рисунок 2. Алгоритм ведения послеродового кровотечения с 20-й по 40-ю минуту.

Примечание: *поэтапный алгоритм лечения послеродового кровотечения с 20-й по 40-ю минуту включает усиление медицинской помощи с активным контролем источника кровотечения посредством хирургических или механических вмешательств (например, баллон Бакри, гемостатические швы, гистерэктомия, восстановление тазового дна), переливание компонентов крови (включая эритроциты, плазму и тромбоциты) и повторную оценку клинического состояния. Рекомендуются теплые инфузионные растворы в соотношении 1:1, а также внутривенное введение кальция в случае переливания более 4 доз эритроцитарной массы. Лечение остается поэтапным и времязависимым с учетом гемодинамического ответа и параклинического обследования.*

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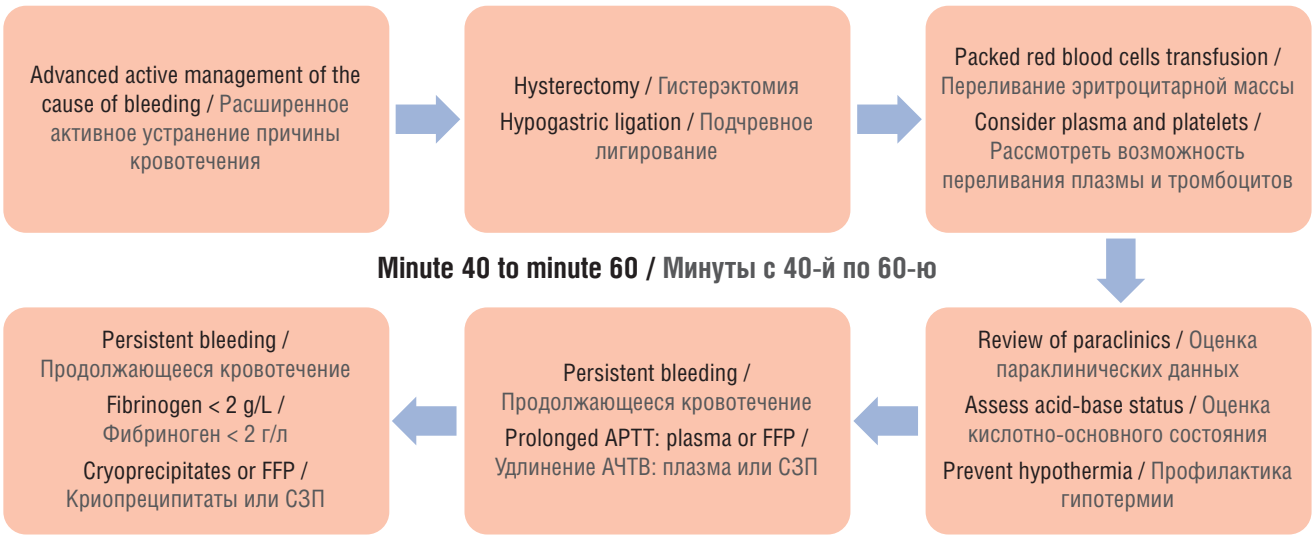

Figure 3. Postpartum bleeding management algorithms minute 40 to minute 60.

Note: *stepwise algorithm for the management of postpartum hemorrhage between minutes 40 and 60. This stage includes advanced active management of bleeding, such as hysterectomy and hypogastric artery ligation, along with transfusion of packed red blood cells, plasma, and platelets. Persistent bleeding is addressed with targeted correction of coagulopathies: low fibrinogen levels (< 2 g/L) are treated with cryoprecipitates or fresh frozen plasma (FFP), and prolonged partial thromboplastin time (PTT) is managed with plasma or FFP. Clinical reassessment includes review of paraclinical tests, acid-base balance evaluation, and prevention of hypothermia.*

Рисунок 3. Алгоритмы ведения послеродового кровотечения с 40-й по 60-ю минуту.

Примечание: *пошаговый алгоритм лечения послеродового кровотечения на 40-60 минутах включает расширенную активную остановку кровотечения посредством гистерэктомии и перевязки гипогастральной артерии, а также переливание эритроцитарной массы, плазмы и тромбоцитов. При продолжающемся кровотечении проводится целенаправленная коррекция коагулопатий: низкий уровень фибриногена (< 2 г/л) купируют криопреципитатами или свежезамороженной плазмой (СЗП), а удлиненное активированное частичное тромбопластиновое время (АЧТВ) – применением плазмы или СЗП. Повторная клиническая оценка включает анализ параклинических тестов, оценку кислотно-основного баланса и профилактику гипотермии.*

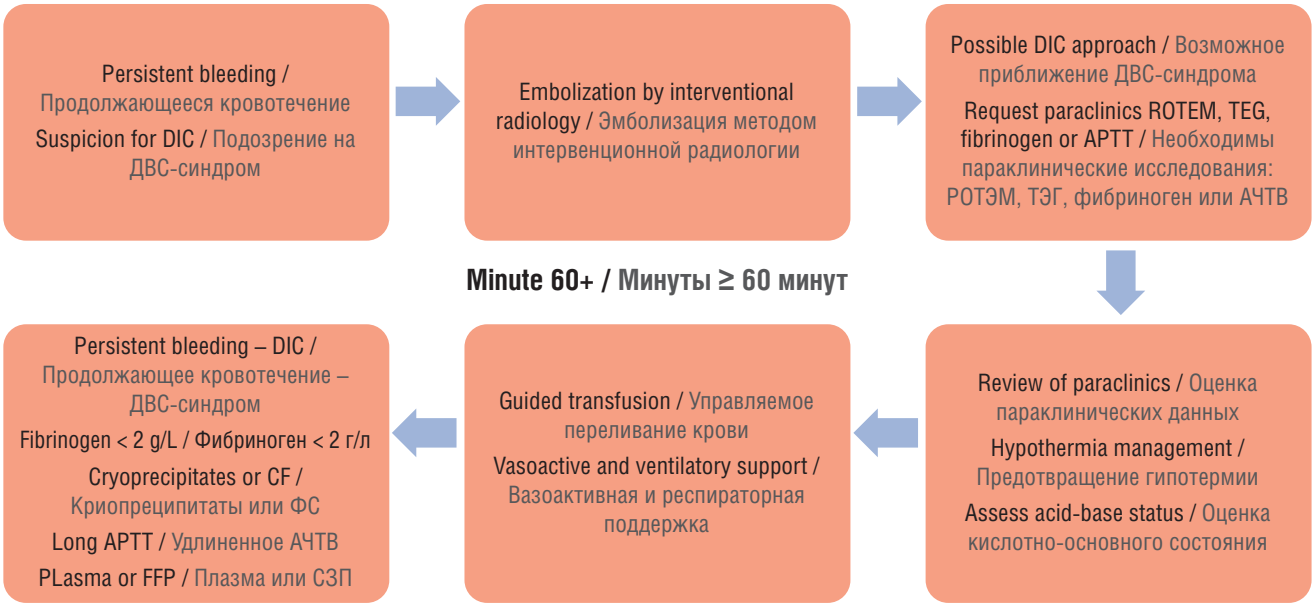

Figure 4. Postpartum bleeding management algorithms minute 60+.

Note: *this phase addresses persistent bleeding with suspicion of disseminated intravascular coagulation (DIC). Initial steps include embolization by interventional radiology and targeted laboratory evaluation (ROTEM, TEG, fibrinogen, or APTT). Management involves guided transfusion, vasoactive agents, and ventilatory support when needed. Persistent DIC with hypofibrinogenemia (< 2 g/L) and prolonged coagulation times is treated with cryoprecipitates or coagulation factors (CF), and plasma or fresh frozen plasma (FFP). Continuous reassessment of paraclinical results, hypothermia, and acid-base balance is essential.*

Рисунок 4. Алгоритм ведения послеродового кровотечения в период ≥ 60 минут.

Примечание: *на данном этапе продолжающееся кровотечение оценивается как возможное диссеминированное внутрисосудистое свертывание (ДВС). Первые этапы включают эмболизацию с помощью интервенционной радиологии и целенаправленное лабораторное обследование – ROTEM, TEG, определение значений фибриногена или активированного частичное тромбопластиновое время (АЧТВ). Лечение включает в себя контролируемое переливание крови, вазоактивные препараты и искусственную вентиляцию легких при необходимости. Персистирующий ДВС-синдром с гипофибриногенемией (< 2 г/л) и удлинением времени свертывания лечится криопреципитатами или факторами свертывания (ФС), а также плазмой или свежезамороженной плазмой (СЗП). Необходим постоянный контроль параклинических данных, гипотермии и кислотно-основного баланса.*

6. The empirical use of fibrinogen concentrate in the early treatment of postpartum hemorrhage is not recommended without verifying hypofibrinogenemia [10].

7. When the use of specific rapid tests is available: Point of Care Testing for fibrinogen measurement (Red Blood Cell Transfusion/ROTEM) are useful or strategies to expedite the speed of laboratory assays [10].

8. The suggested literature-based dose is 3 to 4 g of fibrinogen concentrate when the amount of blood reaches 3–4 L and bleeding continues uncontrolled.

ARTICLE INFORMATION	ИНФОРМАЦИЯ О СТАТЬЕ
Received: 26.01.2024. **Revision received:** 16.04.2024. **Accepted:** 13.07.2025. **Published:** 30.12.2025.	**Поступила:** 26.01.2024. **В доработанном виде:** 16.04.2024. **Принята к печати:** 13.07.2025. **Опубликована:** 30.12.2025.
Author's contribution	**Вклад авторов**
All authors contributed equally to the article.	Все авторы внесли равный вклад в написание и подготовку рукописи.
All authors have read and approved the final version of the manuscript.	Все авторы прочитали и утвердили окончательный вариант рукописи.
Conflict of interests	**Конфликт интересов**
The authors declare no conflict of interests.	Авторы заявляют об отсутствии конфликта интересов.
Funding	**Финансирование**
The authors declare no funding.	Авторы заявляют об отсутствии финансовой поддержки.
Publisher's note	**Комментарий издателя**
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