Aleksandar Ljubić*, Vesna Piperski, Emilija Đurić, Aleksa Begovic, Marina Sikiraš, Andjela Perovic, Jovana Vukovic and Džihan Abazović

Biological therapies in the prevention of maternal mortality

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Abstract: Although the maternal mortality rate has decreased and significant improvements have been made in maternal care, maternal death remains one of the substantial problems of our society. The leading causes of maternal death are postpartum hemorrhage, the most important cause of death in developing countries, and preeclampsia and venous thromboembolism, which are more prevalent in developed countries. To treat these conditions, a variety of therapeutic approaches, including pharmacologic agents and surgical techniques, have been adopted. However, a certain number of pregnant women do not respond to any of these options. That is the main reason for developing new therapeutic approaches. Biological medications are isolated from natural sources or produced by biotechnology methods. Heparin is already successfully used in the therapy of deep venous thrombosis and pulmonary embolism. Blood derivatives, used in an autologous or allogenic manner, have proven to be efficacious in achieving hemostasis in postpartum hemorrhage. Mesenchymal stem cells, alpha-1-microglobulin, and antithrombin exhibit promising results in the treatment of preeclampsia in experimental models. However, it is essential to evaluate these novel approaches' efficacy and safety profile throughout clinical trials before they can become a standard part of patient care.

***Corresponding author: Aleksandar Ljubić**, Biocell Hospital, Belgrade, Serbia; Special Gynecology Hospital with Maternity Ward Jevremova, Belgrade, Serbia; and Libertas International University, Dubrovnik, Croatia, E-mail: aleksljubicpriv@gmail.com
Tatjana Bozanovic, Clinic of Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia; and School of Medicine, University of Belgrade, Belgrade, Serbia
Vesna Piperski, Aleksa Begovic, Marina Sikiraš, Andjela Perovic, Jovana Vukovic and Džihan Abazović, Biocell Hospital, Belgrade, Serbia
Emilija Đurić, Biocell Hospital, Belgrade, Serbia; and School of Medicine, University of Belgrade, Belgrade, Serbia

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Introduction

Maternal death, as defined by the World Health Organization (WHO), is the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from unintentional or incidental causes [1]. Although significant improvement in maternal care and survival has been made and maternal mortality rates have dramatically decreased, an estimated 295.000 maternal deaths occurred worldwide in 2017 [2]. However, when analyzing maternal mortality rates across different parts of the world, a considerable discrepancy between developed and developing countries may still be observed [3, 4]. For example, the estimated maternal mortality rate in Sub-Saharan Africa for 2017 was 542 per 100,000 live births compared to 9.2 per 100,000 in the United Kingdom in 2015–17 [2].

The leading causes of maternal death may be classified into direct and indirect causes. Direct causes are related to the pregnancy and include postpartum hemorrhage, preeclampsia, deep venous thrombosis with consequent pulmonary embolism, and amniotic fluid embolism [5, 6]. Indirect causes are pre-existing health conditions like heart disease, obesity, diabetes mellitus, and hyperlipidemia, which may pose a significant risk to pregnancy outcomes [5, 6].

Considering the seriousness of this problem, many therapeutic approaches concerning the specific cause of maternal death have been adopted. These include applying pharmacological agents, such as uterotonics, for achieving hemostasis in postpartum hemorrhage, antihypertensive medications in the treatment of preeclampsia, and different surgical procedures. However, many pregnant women and women in the postpartum period do not respond to these therapies, which is a rationale for developing new treatment options, such as biological therapeutics.

As defined by the United States Food and Drug Administration (FDA), biological therapeutics include various products such as vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. They can be composed of carbohydrates, proteins, nucleic acids or combinations, or living entities such as cells and tissues. Biological therapeutics are isolated from various natural sources – human, animal, or microorganism – and may be produced by biotechnology methods and other innovative technologies [7].

In this short review, we give a concise summary of biological therapeutics that can be used to treat or prevent conditions causing maternal mortality. After briefly outlining the leading direct causes of maternal death, we describe biological medications that are already in use or in the development process to be applied in the treatment of this serious global problem.

Postpartum hemorrhage

Postpartum hemorrhage (PPH) is defined as a cumulative blood loss greater than or equal to 1,000 mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 h after the birth [8]. The Royal College of Obstetricians and Gynaecologists categorizes PPH as minor (500–1,000 mL) or major (more than 1,000 mL) [9].

PPH is caused by obstetric complications, including uterine atony, placenta previa, genital tract trauma, or placental abruption. More typically, PPH is encountered in women who have had an instrumental delivery, induction of labor, or cesarean section. An increased risk for PPH is found in women with pre-existing bleeding disorders and taking anticoagulant therapy [9].

Postpartum hemorrhage remains one of the most common causes of maternal mortality worldwide. In the United States, PPH has generally ranked among the top three etiologies of maternal death, along with embolism and preeclampsia [10].

Despite the improvements in surgical techniques and the development of diverse pharmaceuticals, the effective management of hemostasis is still one of the main concerns in obstetrics [11]. Managing hemostasis is an ongoing fight, and it demands the use of both traditional and bioregenerative approaches. Combining these two therapy modalities will be beneficial for maternal and fetal well-being.

Since the most common cause of postpartum hemorrhage is uterine atony, uterotonics remain the first-line therapy, particularly oxytocin, which has been used for more than 50 years. Blood loss of more than 1000 mL requires the administration of blood products. Surgical and mechanical measures also have their place in managing this life-threatening condition. All these therapeutic approaches are shown in Table 1.

Biological therapeutics for PPH treatment

Blood derivatives are used in PPH to replace different blood components lost during bleeding. Packed red blood cells, platelets, and fresh frozen plasma are employed for volume replacement, while cryoprecipitate, fibrinogen concentrate, prothrombin complex concentrate, and recombinant human factor VIIa compensate for lost coagulation factors necessary for hemostasis. Topical hemostatic agents comprise another group of biologicals (Table 1).

Cryoprecipitate

Cryoprecipitate is a frozen derivative of blood prepared from blood plasma that contains high fibrinogen and coagulation factors VIII and IX. It is generally used to replenish fibrinogen concentrations in patients with acquired coagulopathy undergoing heart surgery, liver transplantation, trauma, or postpartum hemorrhage. Cryoprecipitate has the advantage of high fibrinogen levels in a low-volume product but carries a risk of infectious disease transmission and needs to be thawed, which are drawbacks of this pooled blood product [12].

Fibrinogen concentrates

Fibrinogen plays a crucial role in achieving and sustaining hemostasis, particularly in patients with acquired fibrinogen deficiency during major bleeding, where early treatment with fibrinogen concentrate seems essential. Pooled human plasma is used to make heat-treated and lyophilized fibrinogen (Factor I) powder [13]. In most cases, it is administered alone, but it can be given together with a cryoprecipitate. Since thawing is unnecessary, it can be administered earlier than cryoprecipitate, and studies show improved outcomes.

A combination of intraoperative thromboelastography (TEG) or rotational thromboelastometry (ROTEM) for monitoring clotting disorders and administration of

Table 1: Different treatment options for postpartum hemorrhage.

Pharmacological	Biological	Surgical	Mechanical
Uterotonics	**Blood products**	– Uterine compression suture	– Bimanual uterine compression
– Oxytocin	– Packed red blood cells	– Uterine artery ligation	– Aortic compression
– Ergot alkaloids	– Platelets	– Selective arterial embolization	– Non-pneumatic antishock garment
– Prostaglandins	– Fresh frozen plasma	– Aortic/iliac artery compression	– Intrauterine balloon tamponade
Antifibrinolytics	– Cryoprecipitate	– Hysterectomy, supracervical	
– Tranexamic acid	– Fibrinogen concentrates	– Hysterectomy, total	
– Aprotinin	– Prothrombin complex concentrate		
	Additional options		
	– Recombinant human factor VIIa		
	– Cell salvage		
	Topical hemostatic agents		
	– Bio-regenerative fibrin		

fibrinogen concentrate could be the best strategy when fast evaluation and treatment are needed. Using ROTEM-guided fibrinogen concentrate administration minimizes the need for blood component therapy in massive obstetric hemorrhage [14].

Prothrombin complex concentrate

Prothrombin complex concentrate (PCC) is a human-derived virus-inactivated pooled plasma product. It combines blood clotting factors II, VII, IX, and X with Protein C and Protein S and has been used as an alternative to fresh frozen plasma. The advantages of PCC are decreased risk of volume overload, no need for thawing and determining blood group type, and reduced possibility of transfusion-associated acute lung injury and hypersensitivity reactions. High prices and a greater risk of thrombosis are disadvantages of this therapeutic. PCC can be used to rapidly reverse the effects of warfarin treatment or vitamin K deficit in patients with severe bleeding signs or needing urgent surgical procedures [15].

Recombinant factor VIIa

Recombinant human activated factor VII (rFVIIa), made by recombinant technology, was developed to promote hemostasis in hemophilic patients. Later, its use expanded to patients with intractable postpartum hemorrhage caused by atony, placenta accreta, or uterus rupture [16].

The results of retrospective clinical studies in women with massive postpartum hemorrhage demonstrated that administration of rFVIIa effectively stopped or decreased bleeding and reduced the need for arterial embolization, ligation of arteries, or hysterectomy in some patients [17]. However, it may increase the risk of thrombotic events, and the medicine is costly, which is also one of its drawbacks [17].

Cell salvage

Cell salvage is an autotransfusion technique used for minimizing allogeneic transfusion in major blood loss surgeries. Historically, cell salvage has been considered contraindicated in maternal hemorrhage due to the risk of contaminating the collected blood with amniotic fluid. Recently acquired data show that this risk is unfounded, and many medical societies now recommend autotransfusion during maternal hemorrhage [18].

Topical hemostatic agents

Topical hemostatic agents (HA) are synthetic or biological adhesives or sealants with hemostatic properties. Studies in various surgical specialties have demonstrated that hemostasis can be achieved effectively with topical HA, with decreased blood loss, reduced operative times, and minimized perioperative transfusion. HA could be used in surgery as an alternative to diathermy to avoid thermal damage, devascularization, and necrosis of the tissue caused by diathermy [19]. There is some concern about the blood-borne disease while using biological sealants because they are made from pooled human donor plasma. On the other hand, synthetic products can cause significant foreign body reactions. In addition, these products necessitate the use of high-dose exogenous thrombin derived from bovine or human sources [19].

Bio-regenerative fibrin (BRF)

Our research group developed an autologous fibrin sealant, bio-regenerative fibrin (BRF), by multiple filtrations of patients' blood. This procedure separates plasma and concentrates all proteins, particularly fibrinogen. BRF is an autologous product, so it does not induce immunologic rejection, can be safely and quickly made in the operating theater, and helps reduce the need for allogeneic blood transfusions in cardiac surgery. These properties also make it a candidate for future use in PPH [20].

Preeclampsia (PE)

Preeclampsia is a disorder defined by elevated blood pressure and proteinuria, which occurs in pregnant women without a history of hypertension and can cause maternal and fetal death. One in ten women has high blood pressure during the gestational period, and 2–8% of pregnancies are complicated by preeclampsia [21]. PE is considered severe when the diastolic blood pressure is higher than 110 mmHg. The main complication of preeclampsia is HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome occurring in 10–20% of preeclamptic women [22]. PE and eclampsia are responsible for 10–15% of all direct maternal fatalities [23, 24].

The exact etiology of PE has not yet been identified. PE is a two-stage illness, according to the most widely accepted concept [25]. The impairment of the spiral arteries during placental formation is the first step in reducing uteroplacental perfusion, which leads to placental damage. Circulating toxic substances released from the placenta, such as syncytiotrophoblast microvesicles, free fetal DNA, cytokines, and antiangiogenic factors, pass the blood-placenta barrier and enter the maternal circulation, triggering an inflammatory reaction and endothelial injury [26]. As a result, general organ damage occurs, leading to PE after the 20th week of gestation.

Previous studies have shown that one of the prominent contributors to the etiology and pathogenesis of PE is extracellular fetal hemoglobin (HbF), which causes oxidative stress by producing reactive oxygen species (ROS). They damage the blood-placenta barrier and allow extracellular HbF to leak into the maternal bloodstream [27]. As a result, extracellular HbF concentrations in maternal plasma increase in the first three months of pregnancy in women who eventually develop PE. Elevated concentrations of HbF in plasma in the later stages of the third trimester correlated with maternal blood pressure [28].

PE pathogenesis cannot be entirely reversed or stopped, and it is more challenging to treat than to prevent. The current preeclampsia treatment options focus on diagnosing the disease, assessing its severity, initiating antihypertensive therapy, and eventually deciding on delivery time [29]. Labor induction is the only proven treatment for PE and HELLP syndrome, resulting in preterm birth and low birth weight [24].

Potential biological therapeutics for PE

Due to the inability of standard therapy to cope with severe preeclampsia and HELLP syndrome, biotherapeutics have emerged as a potential treatment approach. Biological drugs investigated for this indication are anticoagulant antithrombin (AT), free radical scavenger alpha-1-microglobulin (A1M), and mesenchymal stem cells (MSCs) because of their regenerative potential [30, 31].

Antithrombin

The primary enzyme in thrombosis and hemostasis is thrombin. Thrombin formation on the injured endothelium's surface induces coagulation and the secretion of vasoactive agents, which cause vasoconstriction. In individuals with preeclampsia/eclampsia, vasoconstriction may be accompanied by a hypercoagulable condition triggered by thrombin production.

Antithrombin (AT) is a principal inhibitor of coagulation that forms irreversible complexes with numerous clotting factors. A reduction of the AT level indicates increased thrombin binding due to increased thrombin production, contributing to the development of PE. AT concentrations appear to be linked to maternal and fetal morbidity in PE [32].

Antithrombin effects have been studied in women with PE and animal models of PE [33–35]. A clinical study evaluating AT treatment of severely preeclamptic women in the 3rd trimester of pregnancy found significant improvement of the gestosis index (hypertension, proteinuria, edema) and estimated fetal weight gain in AT group, as well as prolongation of gestation and a significant decrease in the number of infants with low birth weight. AT treatment was effective and safe and improved perinatal outcomes [33]. In addition, a clinical study comparing AT administration with heparin in preeclamptic women with intrauterine growth retardation revealed that

the AT group had considerably lower systolic blood pressure and higher fetal weight gain than the heparin group [34]. In a rodent model of PE, high-dose AT induced a substantial reduction in blood pressure and proteinuria compared to the control or low-dose groups [35]. All these results suggest that AT could be valuable biomedicine for treating PE.

Alpha-1-microglobulin (A1M)

Alpha-1-microglobulin (A1M) is a small globular circulating protein involved in neutralizing the detrimental effects of extracellular hemoglobin (Hb) and ROS, acting as a part of the heme scavenger system [36]. Elevated oxidative stress and Hb/heme upregulate cellular A1M expression. Earlier studies have found increased plasma concentration of A1M in pregnant preeclamptic women, which agrees with elevated concentrations of oxidant agents, Hb, and heme in this condition [37].

The effects of A1M administration were studied in experiments using mice, rabbits, and sheep. To induce preeclamptic-like symptoms, researchers used various techniques, including transgene animals, HbF infusions, and fasting. In a transgenic mice model of PE, human recombinant A1M significantly reduced hypertension and proteinuria during gestation and diminished cellular damage in both placenta and kidneys [38]. Positive effects of A1M have also been demonstrated in the preeclamptic rabbit model, where proteinuria was significantly lowered in animals treated with A1M [39]. Also, in an ex vivo study, treatment with A1M inhibited the Hb leakage, morphological damage, and gene up-regulation caused by Hb-perfusion [40]. These results suggest that A1M could have beneficial effects in treating PE.

Mesenchymal stem cells (MSCs)

MSCs are adult stem cells that can self-renew and differentiate into many cell lineages. In animal models of cardiac disorder, lung injury, and hypertension, human MSCs isolated from bone marrow, placenta, and umbilical cord have exhibited anti-inflammatory, immunoregulatory, and healing properties.

The beneficial effects of human umbilical cord-derived MSCs were documented in an endotoxin-induced rat model of PE. The blood pressure, levels of urine proteins, the number of leukocytes, and the proinflammatory cytokines TNF-α and IL-1β were significantly lower in the treated group [41]. In another study in the Th1-induced PE mice model, MSCs isolated from decidua significantly decreased both clinical and histopathological manifestations of PE's severity and protected the fetoplacental development via the suppression of TNF-α expression [42]. In one ex vivo study, the administration of placenta-derived MSC conditioned medium decreased pro-inflammatory cytokines and anti-angiogenic agents, specific to preeclamptic placentae, such as macrophage-migration inhibitory factor, tumor necrosis factor, interleukin 6, and anti-angiogenic soluble fms-like tyrosine kinase-1 mRNA in PE villous explants [43]. All these results mark MSC-based therapy as a potential treatment option for PE.

Venous thromboembolism (VTE)

Venous thromboembolism is a term that unifies two related diseases – deep venous thrombosis (DVT) and pulmonary embolism. In most cases, DVT precipitates pulmonary embolic events, although they may occur independently of DVT [44]. As stated by multiple epidemiological reports, thrombosis and thromboembolism represent the leading direct cause of maternal death across developed countries [45].

Pregnancy is a physiologically hypercoagulable state, and the risk for thromboembolic events increases up to 5 times in otherwise healthy women, with a prevalence of approximately 1 per 1,000 pregnant women [46]. Levels of fibrin and thrombin, as well as factors VII, VIII, and X, all increase during gestation, with a simultaneous decrease of fibrinolytic activity and anticoagulant proteins C and S. In addition, the gravid uterus causes the obstruction of venous blood flow and blood vessel damage is inevitable during delivery [47]. Pulmonary embolism is the most significant complication of DVT and the leading cause of mortality. The incidence of thrombosis is similar throughout all three trimesters and 4–6 weeks after delivery. The additional risk factors for VTE comprise previous thromboembolic events, antiphospholipid syndrome, hereditary or acquired thrombophilia, and delivery via cesarean section [47].

Biological therapeutics for venous thromboembolism

Unfractionated heparin (UFH)

UFH was the drug of choice in the prophylaxis and treatment of VTE for more than 50 years until the introduction of

low molecular weight heparin (LMWH) in the 1980s. UFH is a heterogeneous mixture of sulfated polysaccharides with a mean molecular weight of approximately 15.000 Da, produced from porcine intestines. The primary anticoagulant mechanism of action is the inactivation of thrombin and activated factor X (FXa) by potentiating the effect of antithrombin III and restriction of fibrin formation and thrombin-dependent platelet aggregation [48]. UFH does not cross the placenta, so it is believed safe for the fetus. However, it can produce significant side effects in mothers, such as allergic reactions, heparin-induced thrombocytopenia, and osteoporosis. UFH has some unfavorable pharmacokinetic properties, such as a short half-life, and requires frequent monitoring of activated partial thromboplastin time [49].

Low molecular-weight heparin (LMWH)

LMWH has a lower molecular weight than UFH, and it is more active against FXa than against thrombin. LMWH replaced UFH during the last decades because of its more favorable pharmacokinetic profile, with a longer half-life and better bioavailability. Also, monitoring during therapy is not required. Like UFH, LMWH does not cross the placenta, so it is considered safe for the fetus and the mother as it does not induce thrombocytopenia and osteoporosis [49]. The safety profile of LMWH has been confirmed in several clinical studies [50, 51]. The most serious complication of LMWH administration is bleeding, especially during labor and peripartum. Therefore, it is necessary to stop its application at least 12 h before planned delivery [52].

Although numerous studies have confirmed the significance of LMWH in treating acute VTE in pregnancy, recognizing women at high risk for developing VTE is still tricky, and there are no straightforward answers to this question. The American College of Obstetricians and Gynecologists Guidelines define pregnant women with previous spontaneous thromboembolic events and/or thrombophilia as candidates for prophylactic LMWH therapy, although with inconsistent evidence [53]. For example, a Cochrane review comparing the results of 29 clinical trials (from 1975 to 2016) did not find any significant difference between pregnancy outcomes in women at high risk treated with heparin vs. placebo [54]. Positive effects of LMWH application, such as the lower incidence of pregnancy loss, were also observed. However, these results should be interpreted cautiously because of study heterogeneity and different designs [54].

LMWH is a part of the standard treatment of VTE during pregnancy, based on practice and experience. However, extensive randomized clinical trials including more patients, need to be conducted to obtain relevant data about LMWH efficacy and safety and develop optimal prevention strategies.

Conclusions

Research in the field of biological therapeutics attracts more and more scientists worldwide. The utilization of MSCs, A1M, or BRF in the management of conditions that cause maternal death in everyday gynecologic and obstetric practice is still a long way off due to a lack of relevant studies and ethical, regulatory, and other concerns. It is necessary to conduct more clinical trials and provide rigorous evidence of the safety and effectiveness of these innovative treatment approaches to implement them in standard measures of patient care.

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References

1. World Health Organization. The WHO application of ICD-10 to deaths during pregnancy, childbirth, and the puerperium: IDC – MM. World Health Organization; 2012. Available from: https://apps.who.int/iris/handle/10665/70929 [Accessed 18 Jan 2022].
2. Estimates by WHO, UNICEF, UNFPA, World Bank Group, and the United Nations Population Division. Trends in maternal mortality 2000 to 2017. World Health Organization; 2019. Available from: https://apps.who.int/iris/handle/10665/327595 [Accessed 18 Jan 2022].
3. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Global Health 2014;2:323–33.
4. Kurjak A, Stanojevic M, Sen C, Chervenak F. Maternal mortality: tragedy for developing countries and shame for developed world. Donald Sch J Ultrasound Obstet Gynecol 2020;14:17–27.
5. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet 2006;367:1066–74.
6. van den Akker T, Bloemenkamp KWM, van Roosmalen J, Knight M. Netherlands audit Committee maternal mortality and morbidity; UK confidential enquiry into maternal deaths. Classification of

maternal deaths: where does the chain of events start? Lancet 2017;390:922–3.
7. US Food and Drug Administration. What are 'biologics' questions and answers; 2018. Available from: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm [Accessed 18 Jan 2022].
8. Committee on Practice Bulletins-Obstetrics. Practice bulletin No. 183: postpartum hemorrhage. Obstet Gynecol 2017;130:168–86.
9. Mavrides E, Allard S, Chandraharan E, Collins P, Green L, Hunt BJ, et al. Thomson AJ on behalf of the royal College of Obstetricians and Gynaecologists. Prevention and management of postpartum haemorrhage. BJOG 2016;124:106–49.
10. Kaunitz AM, Hughes JM, Grimes DA, Smith JC, Rochat RW, Kafrissen ME. Causes of maternal mortality in the United States. Obstet Gynecol 1985;65:605–12.
11. Allard S, Green L, Hunt BJ. How we manage the haematological aspects of major obstetric haemorrhage. Br J Haematol 2014;164:177–88.
12. Nascimento B, Goodnough LT, Levy JH. Cryoprecipitate therapy. Br J Anaesth 2014;113:922–34.
13. Fenger-Eriksen C, Ingerslev J, Sørensen B. Fibrinogen concentrate–a potential universal hemostatic agent. Expert Opin Biol Ther 2009;9:1325–33.
14. Whiting D, DiNardo JA. TEG and ROTEM: technology and clinical applications. Am J Hematol 2014;89:228–32.
15. Franchini M, Lippi G. Prothrombin complex concentrates: an update. Blood Transfus 2010;8:149–54.
16. Magon N, Babu K. Recombinant factor VIIa in post-partum hemorrhage: a new weapon in obstetrician's armamentarium. N Am J Med Sci 2012;4:157–62.
17. Barillari G, Frigo MG, Casarotto M, Farnia A, Masse B, Wetzi R, et al. Use of recombinant activated factor VII in severe post-partum haemorrhage: data from the Italian Registry: a multicentric observational retrospective study. Thromb Res 2009;124:e41–7.
18. Waters JH, Beck S, Yazer MH. How do I perform cell salvage in obstetrics? Transfusion 2019;59:2199–202.
19. Ito TE, Martin AL, Henderson EF, Gaskins JT, Vaughn VM, Biscette SM, et al. A systematic review of topical hemostatic agent use in minimally invasive gynecologic surgery. JSLS 2018;22:1–12.
20. Micovic S, Everts P, Calija B, Strugarevic E, Grubor N, Boricic M, et al. Novel autologous, high concentrated fibrin as advanced hemostatic agent for coronary surgery. Transfus Apher Sci 2021;60:1–5.
21. Ngwenya S. Severe preeclampsia and eclampsia: incidence, complications, and perinatal outcomes at a low-resource setting. Int J Women's Health 2017;9:353–7.
22. Haram K, Svendsen E, Abildgaard U. The HELLP syndrome: clinical issues and management. A Review. BMC Pregnancy Childbirth 2009;26:8.
23. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol 2009;33:130–7.
24. Wataganara T. Preeclampsia screening: combining all the right markers to predict a wrong disease? Donald Sch J Ultrasound Obstet Gynecol 2016;10:367–71.
25. Young BC, Levine RJ, Karumanchi SA. Pathogenesis of preeclampsia. Annu Rev Pathol: Mech Dis 2010;5:173–92.
26. Lee SM, Romero R, Lee YJ, Park IS, Park CW, Yoon BH. Systemic inflammatory stimulation by microparticles derived from hypoxic trophoblast as a model for inflammatory response in preeclampsia. Am J Obstet Gynecol 2012;207:337.e1–8.
27. Hansson SR, Gram M, Akerstrom B. Fetal hemoglobin in preeclampsia: a new causative factor, a tool for prediction/diagnosis and a potential target for therapy. Curr Opin Obstet Gynecol 2013;25:448–55.
28. Anderson UD, Jälmby M, Faas MM, Hansson SR. The hemoglobin degradation pathway in patients with preeclampsia – fetal hemoglobin, heme, heme oxygenase-1, and hemopexin – potential diagnostic biomarkers? Pregnancy Hypertens 2018;14:273–8.
29. English FA, Kenny LA, McCarthy FP. Risk factors and effective management of preeclampsia. Integr Blood Pressure Control 2015;8:7–12.
30. Grimes S, Bombay K, Lanes A, Walker M, Corsi DJ. Potential biological therapies for severe preeclampsia: a systematic review and meta-analysis. BMC Pregnancy Childbirth 2019;19:163–75.
31. Ljubić A, Abazović D, Draganić VD, Srbinović M, Perović A, Ljubić D, et al. Ultrasound and biologic therapy in reproductive and perinatal medicine. Donald Sch J Ultrasound Obstet Gynecol 2020;14:214–9.
32. Kobayashi T, Terao T, Ikenoue T, Sameshima H, Nakabayashi M, Kajiwara Y, et al. Treatment of severe preeclampsia with antithrombin concentrate: results of a prospective feasibility study. Semin Thromb Hemost 2003;29:645–52.
33. Maki M, Terao T, Ikenoue T, Satoh K, Nakabayashi M, Sagara Y, et al. Antithrombin therapy for severe preeclampsia. Thromb Hemostasis 2000;84:583–90.
34. Nakabayashi M, Asami M, Nakatani A. Efficacy of antithrombin replacement therapy in severe early-onset preeclampsia. Semin Thromb Hemost 1999;25:463–6.
35. Shinyama H, Yamanaga K, Akira T, Uchida T, Yaguchi M, Watanabe M, et al. Antithrombin III prevents blood pressure elevation and proteinuria induced by high salt intake in pregnant stroke-prone spontaneously hypertensive rats. Biol Pharm Bull 1996;19:819–23.
36. Åkerström B, Gram M. A1M, an extravascular tissue cleaning and housekeeping protein. Free Radicals Biol Med 2014;74:274–82.
37. Olsson MG, Centlow M, Rutardóttir S, Stenfors I, Larsson J, Hosseini-Maaf B, et al. Increased levels of cell-free hemoglobin, oxidation markers, and the antioxidative heme scavenger α1-microglobulin in preeclampsia. Free Radicals Biol Med 2010;48:284–91.
38. Erlandsson L, Ducat A, Castille J, Zia I, Kalapotharakos G, Hedström E, et al. Alpha-1 microglobulin as a potential therapeutic candidate for treatment of hypertension and oxidative stress in the STOX1 preeclampsia mouse model. Sci Rep 2019;12:8561.
39. Nääv Å, Erlandsson L, Axelsson J, Larsson I, Johansson M, Wester-Rosenlöf L, et al. A1M ameliorates preeclampsia-like symptoms in placenta and kidney induced by cell-free fetal hemoglobin in rabbit. PLoS One 2015;10:1–16.
40. May K, Rosenlöf L, Olsson MG, Centlow M, Mörgelin M, Larsson I, et al. Perfusion of human placenta with hemoglobin introduces preeclampsia-like injuries that are prevented by α1-microglobulin. Placenta 2011;32:323–32.
41. Fu L, Liu Y, Zhang D, Xie J, Guan H, Shang T. Beneficial effect of human umbilical cord-derived mesenchymal stem cells on an endotoxin-induced rat model of preeclampsia. Exp Ther Med 2015;10:1851–6.

42. Liu L, Zhao G, Fan H, Zhao X, Li P, Wang Z, et al. Mesenchymal stem cells ameliorate Th1-induced pre-eclampsia-like symptoms in mice via the suppression of TNF-α expression. PLoS One 2014; 18:e88036.
43. Nuzzo AM, Giuffrida D, Piccoli E, Zenerino C, Barrile R, Todros T, et al. Anti-inflammatory and proangiogenic effects of placental mesenchymal stromal cells conditioned media on preeclamptic placental tissue. Placenta 2014;35:A87.
44. Simpson EL, Lawrenson RA, Nightingale AL, Farmer RD. Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal base. BJOG 2001;108:56–60.
45. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005;143:697–706.
46. Devis P, Knuttinen MG. Deep venous thrombosis in pregnancy: incidence, pathogenesis and endovascular management. Cardiovasc Diagn Ther 2017;7:309–19.
47. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol 2006; 194:1311–5.
48. Gray E, Mulloy B, Barrowcliffe TW. Heparin and low-molecular-weight heparin. Thromb Haemostasis 2008;99:807–18.
49. Bates SM, Greer A, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy – antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:691–736.
50. Jacobson B, Rambiritch V, Paek D, Sayre T, Naidoo P, Shan J, et al. Safety and efficacy of enoxaparin in pregnancy: a systematic review and meta-analysis. Adv Ther 2020;37:27–40.
51. Galambosi PJ, Kaaja RJ, Stefanovic V, Ulander VM. Safety of low-molecular-weight heparin during pregnancy: a retrospective controlled cohort study. Eur J Obstet Gynecol Reprod Biol 2012; 163:154–9.
52. Romualdi E, Dentali F, Rancan E, Squizzato A, Steidl L, Middeldorp S, et al. Anticoagulant therapy for venous thromboembolism during pregnancy: a systematic review and a meta-analysis of the literature. J Thromb Haemostasis 2013;11: 270–81.
53. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin No. 196: thromboembolism in pregnancy. Obstet Gynecol 2018;132:e1–7. Erratum in: Obstet Gynecol. 2018;132:1068.
54. Middleton P, Shepherd E, Gomersall JC. Venous thromboembolism prophylaxis for women at risk during pregnancy and the early postnatal period. Cochrane Database Syst Rev 2021;3:CD001689.