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Modern ideas about the predictions of postpartum hemorrhage

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ABSTRACT

Postpartum hemorrhage is currently a pressing problem. Its increasing incidence over time is observed not only in developing countries but also in countries with high levels of income and resources that significantly contribute to the development and functioning of the health system, which is the cause of scientific debate worldwide. The risk factors of postpartum hemorrhage include low hemoglobin level before birth, older maternal age, first birth, prolonged duration of the first and second stages of labor, high birth weight of the newborn, abnormal placentation, surgical vaginal birth, cesarean section, episiotomy, and placental defects.

This review outlines the main risk factors of postpartum hemorrhage, displays new data on the relationship between types of assisted reproductive technologies and postpartum hemorrhage, and discusses prospects for research regarding the problem. A link between assisted reproductive technologies and postpartum hemorrhage elucidates the increase in the incidence of postpartum hemorrhage in developed countries. It is crucial to further research on obstetric risks following the use of assisted reproductive technologies and identify additional risk categories for complications to provide quality medical care and reduce maternal and perinatal losses.

Keywords: postpartum hemorrhage; obstetrics; postpartum complications; risk factors for postpartum hemorrhage; postpartum hemorrhage prevention.

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Современные представления о предикциях послеродовых кровотечений

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АННОТАЦИЯ

Послеродовые кровотечения являются актуальной проблемой, имеющей тенденцию к росту, которая отмечается не только в развивающихся странах, но и в странах с высоким уровнем дохода и ресурсов. К факторам риска относят низкий уровень гемоглобина до родов, более старший возраст матери, первые роды, затяжную продолжительность 1-го и 2-го периодов родов, высокую массу тела новорождённого при рождении, аномалии плацентации, хирургические вагинальные роды, кесарево сечение, эпизиотомию, дефект последа.

В обзоре кратко излагаются основные факторы риска послеродовых кровотечений, новые данные о связи вспомогательных репродуктивных технологий с послеродовыми кровотечениями, обсуждаются перспективы исследования проблемы.

Установление связи вспомогательных репродуктивных технологий с послеродовыми кровотечениями объясняет увеличение числа последних в развитых странах. Необходимо продолжать исследования относительно акушерских рисков после вспомогательных репродуктивных технологий и выяснять дополнительные категории риска осложнений для оказания качественной медицинской помощи и снижения материнских и перинатальных потерь.

Ключевые слова: послеродовое кровотечение; акушерство; послеродовые осложнения; факторы риска послеродовых кровотечений; профилактика послеродовых кровотечений.

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目前对产后出血易感性的看法

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摘要

产后出血是一个日益严重的问题，不仅在发展中国家，而且在高收入和高资源国家也是如此。风险因素包括产前血红蛋白水平低、高龄产妇、初产妇、第一次分娩和第二次分娩时间持续过长、新生儿出生体重过高、胎盘异常、手术阴道分娩、剖腹产、外阴切开术和产后缺陷。

这篇综述总结了产后出血的主要风险因素、辅助生殖技术与产后出血相关性的新数据，并讨论了这一问题的研究前景。

辅助生殖技术与产后出血的关联解释了发达国家产后出血增加的原因。需要进一步研究辅助生殖技术后的产科风险，并确定更多的并发症风险类别，以提供高质量的护理，减少孕产妇和围产期损失。

关键词： 产后出血；产科；产后并发症；产后出血的危险因素；产后出血的预防。

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INTRODUCTION

Postpartum hemorrhage (PPH) is defined as the loss of at least 500 mL of blood during vaginal delivery, at least 1,000 mL of blood during cesarean delivery, or any clinically significant amount of blood loss resulting in hemodynamic instability within 42 days (6 weeks) after delivery. This definition is suggested by Russian clinical guidelines [1]. PPH complicates 3%–10% of births and contributes to nearly 20% of maternal deaths worldwide [2], approximately 30% of all maternal deaths in developing countries, and 13% of maternal deaths in developed countries [3]. In Russia, hemorrhage during pregnancy, delivery, and postpartum is one of the leading causes of maternal mortality (approximately 17%).

The incidence of PPH tends to increase over time not only in developing countries, but also in high-income and high-resource countries that contribute significant amounts to develop and operate healthcare systems (USA, Canada, Australia, UK). The reasons for the observed increase are still debated by most researchers [4–6].

The majority of maternal deaths from PPH are thought to be preventable; in 60%–80% of cases, poor quality medical care was provided [7–9].

The incidence of PPH has been steadily increasing [10–12], mainly due to increased rates of uterine atony and placental abnormalities, operative vaginal deliveries, and cesarean sections with subsequent increase in primary blood loss, and in cases of cesarean sections, the incidence of PPH in subsequent pregnancies is increased [13–19].

Risk factors for PPH after vaginal delivery

A study by Italian physicians Biguzzi et al. [20], conducted in 2007–2009 and including the birth histories of 6,011 women, found that after vaginal delivery, 24.0% of women had a blood loss of more than 500 mL and 4.8% had a blood loss of more than 1,000 mL. The confirmed risk factors for postpartum hemorrhage include first pregnancy, episiotomy, placental defects and placenta adhaerens, and high birth weight. This study also found that the odds ratio for PPH was 0.86 (95% CI 0.78, 0.90) for each 1 g/dL increase in antenatal hemoglobin. As a result, low antenatal hemoglobin was identified as a new potentially modifiable risk factor for PPH [20].

In Egypt, a large study (more than 2,500 postpartum women) was conducted to identify key predictors of PPH (blood loss greater than 500 mL). Using multivariate analysis, the authors found that antenatal hemoglobin, history of previous PPH, increased labor intensity, and prolonged labor were significantly associated with PPH. The probability model showed that even in women with three or more risk factors, PPH could be predicted in only 10% of cases. In contrast to the study mentioned above, the incidence of PPH in 2,510 singleton vaginal deliveries was 3.71%. This study showed that most demographic and antenatal risk factors were weakly associated with PPH. Exceptions included a history of PPH, low hemoglobin, and lack of antenatal care. In addition, the predictive value of antenatal and intrapartum risk factors for PPH is low, although in women with four or more identified risk factors, the predictive value was greater than 30%. It was also found that active management of the third stage of labor significantly (8-fold) reduced the incidence of PPH, including the use of uterotonics, uterine massage, early cord clamping, and cord traction [21].

The aim of this retrospective study in Spain was to develop and validate a prognostic model to assess the risk of PPH in women undergoing vaginal delivery. Binary logistic regression and multivariate analysis were used to assess the risk of PPH, and the main risk factors for PPH after vaginal delivery were found to be older maternal age, primiparity, prolonged first and second stages of labor, high birth weight, and low maternal hemoglobin before delivery [22].

Most studies were retrospective, so some important predictors may not have been assessed. However, the vast majority of known risk factors for PPH can be assessed retrospectively, so this is not considered an issue.

PPH risk scales

Based on retrospective studies, global scales have been developed to predict PPH. The Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) created a hemorrhage-risk prediction tool that classifies women as low-, medium-, or high-risk for hemorrhage, to be implemented upon admission to labor and delivery, pre-birth, and immediately postpartum [23, 24]. Studies suggest that the AWHONN tool is easily implemented, with moderate sensitivity for identifying women who are at risk for severe PPH [25, 26]. This risk assessment framework is used and cited by the American College of Obstetricians and Gynecologists (ACOG) Safe Motherhood Initiative, and is implemented at a national level.

According to this framework, a low-risk group includes women with an unoperated uterus, fewer than four previous vaginal deliveries, no known bleeding disorders, no history of PPH, and a current singleton pregnancy. The moderate-risk group for PPH includes pregnant and postpartum women with a history of uterine surgery, more than four vaginal deliveries, large uterine fibroids, a history of PPH (at least once), morbid obesity (body mass index greater than 35), chorioamnionitis in the current pregnancy, polyhydramnios, fetal death, fetal weight greater than 4 kg, and a family history of PPH in a first-degree relative. A high-risk group for PPH includes women with active uterine hemorrhage, suspected placenta adhaerens or placenta increta, placenta previa or low-lying placenta, known coagulopathy, hematocrit less than 30, a history of two or more PPH episodes, platelet count less than 100,000/mL.

A large retrospective study of the effectiveness of the proposed PPH risk assessment tool showed that this postpartum complication occurred in 2.2% of low-risk patients, 8.0% of moderate-risk, and 11.9% of high-risk

patients [27]. The authors concluded that the AWHONN's Postpartum Hemorrhage Risk Assessment tool not only identifies patients at highest risk for obstetric hemorrhage, but can also be used as a screening tool for risk of bleeding disorders. Women classified as high risk for obstetric bleeding using the AWHONN's Postpartum Hemorrhage Risk Assessment tool were six times more likely to experience bleeding complications than women classified as low risk. One of the limitations of this scale is that low positive predictive values indicate a high rate of false positives.

The clinical guidelines for postpartum hemorrhage [28], developed and approved by the Ministry of Health of Russia, provide a risk scale for PPH. Low risk includes singleton pregnancy, parity less than four, no invasive uterine procedures, and no history of postpartum hemorrhage. Moderate risk of postpartum hemorrhage includes multiple pregnancies, parity more than four, a history of cesarean section or other uterine surgery, the presence of large uterine fibroids, induction of labor or oxytocin induction, and the presence of complications (such as chorioamnionitis). According to these clinical guidelines, a high risk of PPH is observed in patients with placentation abnormalities such as placenta previa, placenta adhaerens or placenta increta, hematocrit less than 30, bleeding during hospitalization, coagulopathy, and a history of postpartum hemorrhage.

It should be noted that the above mentioned PPH Risk Assessment Scale is similar in many ways to the AWHONN Postpartum Hemorrhage Risk Assessment tool. The only difference is that women with a history of PPH in a first-degree relative are not considered at high risk for PPH according to the Russian guidelines. It can be concluded that both PPH risk stratification scales have adequate clinical value and are necessary in the routine practice of an obstetrician-gynecologist.

Effects of assisted reproductive technologies on PPH incidence

Assisted reproductive technologies (ART) are used to treat infertility in which some or all of the stages of conception and early embryo development are performed outside the body, including the use of donor and/or cryopreserved gametes, reproductive organ tissues and embryos, and surrogacy [29].

Infertility (subfertility) is considered an independent risk factor for obstetric complications and adverse perinatal outcomes, even in the absence of ART. However, as infertility rates rise and the use of ART expands, it is important to study obstetric outcomes in women undergoing ART.

The national project Demography ensures development and availability of ART for the population. In the first 9 months of 2022, 62,500 IVF procedures were performed. In 2023, over 89,500 procedures were performed, which is 18% more than in 2022. To date, more than 8 million children have been conceived after ART globally [30, 31], and up to 6% (range between 0.2% and 6.4%) of the European birth cohorts is conceived by ART [32].

Although definitions vary worldwide, ART is generally considered any procedure involving handling of eggs, sperm, or both outside the human body (*in vitro*). ART includes in vitro fertilization with or without intracytoplasmic sperm injection (ICSI), fresh or frozen embryos (by cryopreservation or vitrification and transfer of thawed embryos) and IVF with donor eggs, intrafallopian gamete transfer, and intrafallopian zygote transfer. ART has expanded beyond *in vitro* methods to intrauterine insemination and ovulation induction with gonadotropins or ovarian stimulants [33, 34].

In vitro fertilization (IVF) includes traditional *in vitro* insemination and ICSI [35].

There has been an increasing global use of ICSI; in 2014, with 71.3% of fresh IVF/ICSI cycles performed with ICSI in Europe in 2014, as shown in the latest reports from European Society of Human Reproduction and Embryology (ESHRE) [32]. Among fresh IVF cycles in the US, ICSI use increased from 36.4% in 1996 to 76.2% in 2012, with the largest relative increase in cycles without male factor infertility [36].

In Europe, cryopreservation constituted 27.4% of all cycles in 2014, with the highest rate in Switzerland at 41.1% [30, 34]. Routine freezing of all good-quality embryos and transfer in subsequent cycles has been introduced as a way to reduce ovarian hyperstimulation syndrome and improve reproductive outcomes.

This represents an additional contribution of the healthcare system to increasing fertility rates, and therefore support for ART programs will increase. It is necessary to clearly understand and, where possible, prevent all obstetric risks associated with such pregnancies.

It should also be noted that the prevalence of PPH is increasing worldwide; this trend is observed in developed countries with very high living standards and quality of medical care [34, 36, 37]. These countries also show increased use of ART and increased births resulting from these medical interventions [31, 32].

The link between these two trends was discovered by research team from Japan who studied the birth histories of 2,914 women, including 411 pregnancies achieved with ART. Multivariate logistic regression analysis showed that ART pregnancy is an independent risk factor for PPH. Propensity score-matched analysis for with and without ART showed a 3.39-fold higher incidence of PPH for ART pregnancy in the vaginal delivery group (p <0.001). Only vaginal deliveries were found to have a higher incidence of PPH in ART-assisted pregnancies [30].

PPH in singleton and multiple pregnancies

A large-scale study was conducted in Norway to identify causes of severe PPH (blood loss greater than 1,500 mL or need for blood transfusion). The study population included all cases of severe PPH (1,064 subjects) and a random sample of controls (2,059 subjects). It was concluded that ART was

associated with an increased risk of severe PPH (odds ratio (OR)=2.92; 95% confidence interval (CI): 2.18, 3.92; p <0.001). After adjustment for confounding factors and interactions, an increased risk was observed in both the multiple pregnancy group (OR=7.00; 95% CI: 2.70, 18.12; p <0.001) and the singleton pregnancy group (OR=1.58; 95% CI: 1.12, 2.24; p=0.010) [38].

PPH and transfer of cryopreserved twin embryos

Another study was conducted to evaluate incidence of PPH after twin pregnancies in ART cycles. The incidence of PPH was higher in twin pregnancies (5.3%) compared to the controls (4.0%). The highest incidence was observed among women in the frozen-thawed group (13.8%) which differed significantly compared with the controls (p=0.024). A significant difference was also observed in the mean decrease of postpartum hemoglobin levels between these two groups (2.13 g/dL versus 1.3 g/dL respectively, p=0.002). Blood transfusion was nearly 2.5 times more common in the frozen-thawed group (3.4%) compared to the control group (1.3%) [39].

The study demonstrated that frozen embryo transfer ART-conceived twin pregnancies are associated with a markedly increased rate of PPH compared to spontaneously conceived twins.

Comparison of PPH manifestations in IVF and IVF with ICSI

Researchers from Japan stated that the aim of the study was to evaluate the risk of maternal and perinatal complications and adverse pregnancy and birth outcomes in children conceived using ART compared with those conceived naturally. A large study (over 90,000 subjects) showed that compared to women who conceived naturally, those who conceived by ovulation induction without IVF had a higher risk of placenta previa, placenta adhaerens, placenta increta, and gestational hypertension, while those who conceived by IVF with ICSI had a higher risk of placental abruption, placenta previa, placenta adhaerens, and placenta increta. Women who conceived by ART had a higher risk of blood transfusion and intensive care unit admission (for both isolated ovulation stimulation and IVF cycles with ICSI), even after controlling for potential complications. Newborns conceived through the ART had a higher risk of being born prematurely [32].

Effect of three-day or five-day embryo transfer on incidence of PPH

Blastocyst transfer (day 5–6) is thought to improve the selection of the most viable embryos compared to cleavage-stage transfer (day 2–3) [40], increasing pregnancy and live birth rates per transfer and potentially resulting in a greater number of healthier infants. However, systematic reviews and meta-analyses show similar total live birth rates for blastocyst-stage and cleavage-stage transfers, including fresh and subsequent frozen embryo transfers from single oocyte retrieval [41]. However, by improving embryo selection, blastocyst culture may facilitate planned single embryo transfer and thus reduce incidence of multiple deliveries. However, it should be noted that a recent large population study found an increased incidence of placenta previa and placental abruption after blastocyst transfer [42]. In a systematic review [43] and meta-analysis of 38 studies, the incidence of monozygotic twins after blastocyst transfer ranged from 0% to 13.3%, with a 2-fold increased risk compared with cleavage-stage transfer [44]. The authors suggest that the key mechanisms of the increased risk may include characteristics of culture media and the young age of a mother, in addition to prolonged culture time [45]. Blastocyst transfer has also been associated with a higher fetal male-to-female ratio and monozygotic twinning [46, 47].

Therefore, the results confirm an increased risk of severe PPH in women who have conceived using ART. In addition, the high risk of severe PPH in twin or triplet pregnancies is an additional argument for single embryo transfer.

PPH and endometriosis

A study [48] evaluated pregnancy outcomes in women with endometriosis after ART. It was concluded that women with or without endometriosis have similar reproductive outcomes, but women with endometriosis who conceive by ART are at high risk for PPH, ectopic pregnancy, placenta previa, and twin conception.

Prevention of PPH

PPH is the major cause of maternal mortality and morbidity across the world, responsible for more than 25% of deaths annually. It is therefore necessary to prevent PPH in carefully selected and improved risk groups and to be prepared to provide medical care in the early and late postpartum period.

The clinical guidelines for postpartum hemorrhage [28], approved by the Ministry of Health of the Russian Federation in 2021, state that the primary measure for antenatal prevention of PPH is to obtain a detailed obstetric and gynecologic history and complaints to assess the risk factors. Planning for delivery management in patients at high risk for PPH is recommended in level II and III hospitals with the involvement of a multidisciplinary team when appropriate.

During labor, at least a 16 G venous catheter should be inserted in a high-risk patient, and the umbilical cord should be clamped no earlier than the first minute after delivery if the infant is in satisfactory condition and there is no doubt about the integrity of the umbilical cord [48, 49]. PPH can also be prevented by intramuscular/intravenous use of oxytocin at 10/5 IU immediately after delivery.

Active management strategies for the third stage of labor include controlled traction on the umbilical cord to prevent retention of the detached placenta in the uterine cavity (where trained personnel are available) or use of external maneuvers for placental expulsion.

Active management of the third stage of labor includes the use of uterotonics, clamping of the umbilical cord between the first and third minutes after the fetus is born, spontaneous delivery of the placenta, or its removal using external maneuvers within 30 minutes. The placenta can be delivered by controlled traction on the umbilical cord, but this should only be done by trained healthcare personnel. If no trained healthcare personnel is available, it is necessary to wait for signs of placental separation and expel the placenta using external maneuvers. Controlled cord traction reduces the risk of retained placenta and manual placenta removal [28, 50].

In addition, intravenous tranexamic acid (0.5–1.0 g) is recommended in the third stage of labor for women at high risk of PPH [49, 51]. Assessment of uterine tone after delivery is also required [49, 52].

Studies show that carbetocin is more effective than oxytocin in the high-risk group for PPH [53–55]. Misoprostol has no advantages compared with oxytocin and is associated with significantly more side effects [55].

In the PPH risk group, uterine tamponade or combined uterine/vaginal tamponade are recommended [28].

Studies focusing on segmented non-pneumatic compression devices for PPH should be mentioned [56, 57]. These devices are designed as a first aid tool to treat hypovolemic shock and reduce blood loss during obstetric hemorrhage. Segmented non-pneumatic compression consists of connected neoprene segments held together with hook-and-loop fasteners to redirect blood flow from the lower body to the major organs and to increase blood pressure, preload, and cardiac output. In observational studies, segmented non-pneumatic compression showed better outcomes than standard care in reducing maternal mortality (OR = 0.52; 95% CI: 0.36, 0.77), with a slight decrease in the risk of maternal mortality (OR = 0.43; 95% CI: 0.14, 1.33). No differences were observed between segmented non-pneumatic compression and standard treatment with blood products. Therefore, segmental non-pneumatic compression should be considered as a non-invasive option when standard care conditions are optimized. This is especially important when the distance to a bleeding site makes it difficult to provide qualified medical care.

Key measures to reduce the incidence and severity of PPH include as follows:

- Use of improved PPH risk scales based on new global data,
- Assessment of PPH risk factors over time (at the stage of pregnancy management by a local obstetrician-gynecologist, during and after delivery at a maternity hospital),
- Careful patient management (women identified as being at high risk for PPH should be transferred to a level III maternity hospital with appropriate support and a multidisciplinary team capable of preventing organ removal surgery and maternal morbidity and mortality),
- For timely and effective management of PPH, all departments in a maternity hospital should be able to treat emergency patients with massive bleeding, and all personnel should have a clear procedure for managing PPH and receive regular training,
- Annual simulation training to model PPH situations and improve the surgical skills of obstetricians and gynecologists to increase effectiveness of organ-sparing techniques for PPH management,
- Ability to perform emergency blood tests in an emergency room setting,
- All cases of blood loss greater than 1,500 mL should be clinically evaluated and appropriate management decisions should be made,
- Close regulatory monitoring of supply of all necessary agents for PPH prevention and treatment (blood products, tranexamic acid, recombinant activated factor VII, prothrombin complex, uterotonics) to maternity hospitals,
- Use of segmented non-pneumatic compression devices at the stage of patient transport to the place of treatment for comprehensive prevention of hypovolemia and hemorrhagic shock is one of areas of development in obstetric and gynecological care of PPH patients in Russia.

CONCLUSION

PPH is a pressing issue with a trend of increasing incidence. Risk factors include low hemoglobin level before delivery, older maternal age, first delivery, prolonged first and second stages of labor, high birth weight, placental abnormalities, operative vaginal delivery, cesarean section, episiotomy, and placental defects.

The reasons for the increased risk of PPH in patients with ART-assisted pregnancy are not fully understood. However, the available data indicate that these patients are at higher risk for placental abnormalities, which certainly has an impact on the incidence of PPH risk. In addition, in these patients, confirmed infertility may be of both endocrine and infectious origin, thereby increasing the risk of purulent and septic complications and, consequently, PPH. Further research is needed to identify obstetric risks following ART and to ensure quality care and reduce maternal and perinatal loss.

ADDITIONAL INFO

Authors' contribution. A.R. Iskandarova, P.A. Berg, M.N. Makarova, G.H. Murtazina — article writing, analysis of literature data, collection of material; I.I. Musin — development of research design, collection of material; A.G. Yashchuk — development of the research concept, text editing, approval of the final version of the article; E.A. Berg — text editing, material collection. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a substantial

contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work).

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