

Open Access Article

IMPROVING THE PREVENTION OF POSTPARTUM HEMORRHAGE IN WOMEN WITH MULTIPLE PREGNANCIES

Shodieva Khurshida

PhD, Senior Lecturer of the Department of Obstetrics and Gynecology No. 2 of the TMA.

Pakhomova Janna

DSc, Professor of the Department of Obstetrics and Gynecology No. 2 of the TMA.

Kamolakhon Davranbekovna

Assistant, Department of Physiatics, Tashkent Institute for Post-Graduate Medical Education.

Nazarova Dilrabo Erkinovna

Senior Lecturer, Candidate of Medical Sciences, Department of Obstetrics and Gynecology No. 2 of the TMA.

ABSTRACT

This research evaluates the clinical efficacy and tolerability of carbetocin for the prevention of PPH in women with multifetal gestation. The study was carried out from 2019 to 2020. 89 patients with multiple pregnancies who were delivered by cesarean section were examined. All patients were divided into two groups – 1st group received the drug carbetocin, the other group received the drug oxytocin. The volume of blood loss in group 1 was 478.3 ± 14.3 ml, in group 2 - 583.3 ± 24.3 ml. PPH in a volume of 500 ml or more was observed in 21% of women of the 1st group and in 48% of women of the 2nd group. More than 800 ml of blood loss occurred in group 2 (8.7%). The postpartum period was without complications in 95.3% of the women in group 1 and 84.7% in group 2. Such complications as uterine subinvolution, hematometra, and metoendometritis occurred in group 2 women. In conclusion, carbetocin, a long-acting synthetic analog of oxytocin, is the best alternative to traditional oxytocin in preventing PPH in women with multiple pregnancies.

Keywords: multiple pregnancy, prevention of postpartum hemorrhage, uterotonics, carbetocin, oxytocin.

抽象的

本研究评估了卡贝缩宫素预防多胎妊娠妇女 PPH 的临床疗效和耐受性。该研究于 2019 年至 2020 年进行，对 89 名剖宫产的多胎妊娠患者进行了检查。所有患者分为两组——第一组接受药物卡贝缩宫素，另一组接受药物催产素。第1组失血量为 478.3 ± 14.3 毫升，第2组失血量为 583.3 ± 24.3 毫升。在第一组 21% 的女性和第二组 48% 的女性中观察到 500 毫升或更多体积的 PPH。第 2 组失血超过 800 毫升 (8.7%)。第1组95.3%的产妇产后无并发症，第2组产后

Received: August 12, 2021 / Revised: September 08, 2021 / Accepted: September 30, 2021 / Published: October 10, 2021

About the authors : Shodieva Khurshida

Corresponding author- Email:

84.7%。第2组产妇出现子宫复旧、血肿、子宫内膜炎等并发症。总之，卡贝缩宫素是一种长效合成催产素类似物，是预防多胎妊娠女性产后出血的传统催产素的最佳替代品。

关键词：多胎妊娠，预防产后出血，宫缩剂，卡贝缩宫素，催产素。

INTRODUCTION

The percentage of obstetric and perinatal complications is high in multiple pregnancies compared with singletons. According to some authors, the incidence of multiple pregnancies ranges from 0.7% to 2.5% of all pregnancies [1]. The course of pregnancy is often complicated by hypertensive syndrome, abnormal fetal position, premature rupture of amniotic fluid, premature birth, placental insufficiency leading to hypoxia and fetal growth restriction syndrome. Labor with multiple fetuses may be accompanied by birth force abnormalities, fetal hypoxia and asphyxia, and bleeding both in labor and the postpartum period [2,3,4].

The relevance of the problem of hemorrhage in obstetrics is beyond doubt. In the structure of maternal morbidity and mortality, obstetric hemorrhage steadily maintains a leading position, belongs to a threatening condition complicating 3-5% of deliveries, and contributes to anemia, anterior pituitary ischemia, coagulopathy, myocardial ischemia, postpartum depression [5,6,7]. The intensity of blood flow in the uterus during pregnancy is 700-800 ml per minute, so if the mechanisms of hemostasis are disturbed, bleeding becomes profuse. One of the causes of obstetric bleeding, leading to maternal morbidity and mortality, is postpartum bleeding caused by impaired uterine contraction (tone), retention of placental parts (tissue), rupture of the birth canal, uterus (trauma) and coagulation disorders (thrombin) [8,9]. Lethal outcomes due to PPH are observed more often in the early postpartum period and,

according to statistics, about 79% of such bleeding is caused by uterine atony [2,10].

Multiple pregnancies are the risk factors for postpartum bleeding, the causes of atonic bleeding. It is the total size of fetuses and placentas, a large amount of amniotic fluid leading to overdistension of the uterine walls and impaired contractility of the myometrium. With impaired uterine contractility due to the large size of the placenta also increases the duration of bleeding from the placental site/placentas due to the fact that the open vessels do not have time to form a clot leading to large blood losses, which requires immediate adequate therapy [11,12]. Another reason for atonic bleeding is the frequency of indications for operative delivery in multiple pregnancies, which significantly increases intraoperative blood loss 3-5 times compared with spontaneous delivery [13,14,15].

Cesarean section is the most frequently performed obstetric operation, and it is a method of delivery aimed at improving the outcome of childbirth for the mother and fetus. The reason for the increase in the frequency of operative delivery is due to the expansion of indications for caesarean section aimed at reducing maternal and perinatal mortality when performed in a timely completion. According to a number of authors, the frequency of cesarean section varies widely, averaging 34-46% of the total number of deliveries [16]. In Uzbekistan, there is over time increase from 9.58% in 1999 to 16.10% in 2019. However, WHO does not recommend to increase the frequency of cesarean section above 15% because it does not affect the reduction of perinatal morbidity and mortality in children

born by C-section compared to those born naturally. The consequence of not always reasonable surgical delivery has led to an increase every year of the number of women of reproductive age with a uterine scar. This further increases the frequency of repeated surgical deliveries as one of the indications for cesarean section. Despite all the advantages of cesarean section, with the increase in its frequency the rates of maternal morbidity and mortality increase, the causes of which are hemorrhage, sepsis, pulmonary embolism, complications during anesthesia. Unfavorable and relatively frequent complications of obstetric uterine surgery include pathological and massive bleeding due to decreased contractile function of myometrium - uterine atony [4,17].

In the fight against atonic bleeding, it is customary to adhere to a strict sequence and staging of interventions using medication, intermediate and surgical methods of stopping bleeding. If it is ineffective, intermediate (mechanical) methods of stopping bleeding are used: bimanual compression, manual examination of the uterine cavity with diagnostic and therapeutic purpose, balloon tamponade. The next stage of treatment is surgical, including conservative (compression sutures, ligation of uterine vessels or internal iliac arteries, embolization of uterine vessels) and radical (hysterectomy) methods of stopping bleeding [10, 18]. We would like to note that the use of effective medications for the prevention and treatment of bleeding will eliminate the need for intermediate and surgical methods, which are additional and traumatic factors that lead to disability in women of childbearing age.

Thus, for obstetricians-gynecologists, when managing women with multiple pregnancies, which are already a risk factor for

bleeding, the question arises about the possibility and methods of preventing postpartum hemorrhage with multiple pregnancies after surgical delivery. Reducing the frequency and volume of bleeding during both spontaneous labor and cesarean section is achieved by using a range of measures, among which uterotonic agents occupy a special place. Uterotonics are currently used with a high level of evidence for the prevention of postpartum atonic bleeding [19,20]. The only effective method of preventing postpartum bleeding is active management of the third period of labor, its main link is the use of uterotonics, among which oxytocin is recognized as the first-line drug.

In order to prevent postpartum bleeding, the use of uterotonics is recommended in 100% of cases with a high level of evidence. Commonly used uterotonic agents include oxytocin, misoprostol, ergometrine. These drugs have their advantages, disadvantages and proven effectiveness for the prevention and treatment of postpartum bleeding. Oxytocin is the drug of the first choice for the prevention of PPH. But because of the short half-life (4-10 minutes), continuous intravenous administration is required to achieve a stable uterotonic effect. The second place in the arsenal of drugs for preventing postpartum bleeding is occupied by drugs containing ergometrine. Despite the long-lasting effect of these drugs, they have a number of side effects that limit their use. The risk of side effects such as arterial hypertension, vascular spasm, tachycardia, nausea, vomiting is much higher with this drug than with oxytocin. In recent years specialists interested in prostaglandins have advantages over traditional uterotonics but have a high frequency of side effects such as shivering, fever, severe hyperthermia [4, 9, 21].

Despite the use of uterotonics-oxytocin, ergometrine and prostaglandins in obstetrics, the problem of postpartum hemorrhage (PPH) has not lost its relevance, which gives reason to search for new methods of prevention and treatment of bleeding. This circumstance served as the reason for developing new uterotonics with powerful uterotonic and minimal side effects, such as “carbetocin”, to prevent PPH [2, 22].

The drug carbetocin belongs to the group of long-acting synthetic analogs of oxytocin, recommended for single administration. Like oxytocin, carbetocin binds to oxytocin receptors in the uterine muscles and promotes an increase in uterine tone by regular contraction of smooth muscles in the uterine muscles for 40-60 minutes, which proves its superiority over oxytocin by 5-10 times [17,23].

The use of a single dose of carbetocin (100 mcg / 1 ml) to ensure adequate uterine contractions to prevent uterine atony and excessive bleeding is sufficient and can be compared to continuous administration of oxytocin over several hours to achieve uterine tone. Carbetocin is recommended to be administered once intravenously only after the birth of the fetus/fetuses. The drug is contraindicated during pregnancy, in the first and second stages of labor, because the uterotonic effect after one injection lasts several hours [24,25].

Carbetocin is currently used in 24 countries to prevent uterine atony and heavy bleeding after caesarean section. This prescription is supported by the results of published controlled clinical trials. After a single intravenous injection of 100 µg of carbetocin, the intraoperative blood loss level has been shown to decrease as effectively

as after a 16-hour administration of oxytocin [9, 26, 27].

The data of a number of studies were analyzed, including the results of the Cochrane systematic review (2012 - 11 randomized trials), a double-blind, randomized study (2011 - Austrian specialists) and a prospective randomized multicenter comparative study of the Russian Federation (led by V.E. Radzinsky), which assessed the efficacy and tolerability carbetocin with other uterotonic drugs (oxytocin, methylergometrine, misoprostol) in the prevention of postpartum bleeding after vaginal and surgical delivery. Studies have shown that the drug carbetocin reduces blood loss and the need for other methods of stopping bleeding [2, 13, 17, 21]. Despite the large number of comparative studies investigating carbetocin and oxytocin's effectiveness for the prevention of postpartum hemorrhage, no similar study has been carried out in Uzbekistan. Therefore, Uzbekistan's registration and appearance of uterotonic carbetocin (Pabal, Ferring production) cause great interest among obstetricians, gynaecologists, and anesthesiologists resuscitators and healthcare organizers.

MATERIAL AND METHODS

This study was carried in 2019 to 2020 in women with multiple pregnancies, delivered to the multidisciplinary clinic of the Tashkent Medical Academy and to the City Maternity Complex No. 6.

Medication of the study drug.

To attain the objective, we have examined 89 patients with twins and divided them into two groups. The main group - group 1 (43) of patients received the drug carbetocin solution for intravenously 100 µg/1 ml, group 2 (46) - the

comparison group oxytocin 5 IU/1 ml intravenously. Both drugs were administered to patients with twins who indicated operative delivery immediately after extraction of the second fetus in the third period of labor (before the separation of the placenta) once intravenously slowly over one minute.

Randomization.

Selected and informed consenting women with multiple pregnancies were randomized by simple randomization. Distribution into groups was carried out on the basis of sealed envelopes, after the patient was enrolled in the study and assigned a serial number, the envelope corresponding to this number was opened and the treatment enclosed in this envelope was prescribed.

Inclusion criteria.

Inclusion criteria were women with multiple pregnancies aged 27.8 ± 0.8 years who were delivered by cesarean section at 35.5 ± 0.4 weeks.

Exclusion criteria.

The exclusion criteria were the patient's lack of informed written consent to participate in the clinical trial, age less than 18 years, pregnancy, labor in the first and second periods, premature detachment of normally situated placenta, patients with planned hysterectomy, and the patient's need for drugs inadmissible in the study (hepatic, renal, and CVD pathology in decompensation, severe hypertension, epilepsy).

Evaluation parameters.

The main parameters evaluated were uterine tone, volume of blood loss, the need for additional uterotonic drugs, and in the

postpartum period, control of uterine involution. Monitoring was based on hemodynamic parameters (BP, Ps, temperature), hemoglobin level, erythrocytes and other blood parameters (hematocrit, fibrinogen, PTI, APPT) before and after drug administration. Tolerability and side effects were followed up.

RESULTS AND DISCUSSION

Analysis showed that during the study period, twin births accounted for 2.7% and triplet births 0.1% of the total number of births in 2019-2020. Of the 89 surveyed women with twins, pregnancy occurred spontaneously in 59 (66.3%) due to ovulation stimulation - in 19 (21.3%), after the use of assisted reproductive technologies (IVF) in 11 (12.3%). The placentation type corresponded to monochorionic-biamniotic type in 53.9%, bichorionic-biamniotic type in 32.6%, and monochorionic-monoamniotic type in 13.5%. Of these, 32 (36%) were primary pregnant, 57 (64%) were re-pregnant, and 42 (47.2%) were primiparous women with multiple pregnancies.

Of the gynecological diseases in the anamnesis, the women examined by us had inflammatory diseases of the pelvic organs, endometriosis, uterine fibroids, PCOS and surgical interventions in connection with ovarian cystic formations. Overall, complicated gynecological history, which was the cause of infertility, occurred in 36% (32) of the patients. Spontaneous miscarriage (11), missed miscarriage (10), premature birth (6), uterine scarring after cesarean section (14) had a history of repeated pregnancies.

The course of pregnancy in patients with multiple pregnancies was most often complicated by vomiting of pregnant women of varying severity (34.8%), the threatened

miscarriage in the first half (37%) and in the second half (41.5%), polyhydramnios (24.7%), chorioamnionitis (13.4%), hypertensive disorders (27%). Of the hypertensive disorders, chronic arterial hypertension was found in 3, gestational hypertension in 11, mild preeclampsia in 6, severe preeclampsia in 4 women with MP.

Of the extragenital diseases, the most frequent ones were anemia of varying severity in 48.3%, varicose veins of the lower extremities in 13.4%, and infections of the urogenital tract in 31.4%. Acute respiratory infections complicated pregnancy in 40.5% of pregnant women at different gestational periods, which required inpatient treatment.

The mode of delivery in multiple pregnancies remains another controversial issue in modern obstetrics and perinatology. Our study included women with multiple pregnancies delivered by cesarean section as planned and in an emergency procedure in group 1, 46.5% and 53.4%, respectively, and in group 2, 41.3% and 54.3%. The term of delivery was 36.2 ± 0.41 weeks in group 1, 35.7 ± 0.37 weeks in group 2. The most frequent indications for surgical delivery were: pelvic or trunk position of the first fetus (34.8%), uterine scar (19.1%), placental insufficiency with blood flow disorders (12.3%), pregnancies against the background of ART

(12.3%), premature detachment of the normally located placenta (4.5%), premature rupture of amniotic fluid in the absence of biological readiness for delivery (4.5%), weak labor (5.6%), and history of obstetrics and gynecology (6.7%).

During operative delivery in group 1, after the removal of the second fetus, the drug carbetocin 100 µg/1 ml was administered slowly intravenously in the third stage of labor and 88.4% of women in labor at the time of the first traction without difficulty, the placenta with all membranes and lobules was separated and excreted. A tetanic contraction of the uterus was observed in 1-2 min from the moment of administration. After separation of the placenta, the uterus contracted/reduced by half. With the drug oxytocin administration, contraction of the uterus was noted after 3-5 minutes. The placenta's separation and isolation were carried out with the second or third traction for the umbilical cord. The need for additional use of uterotonics in women in labor with multiple pregnancies in the group using carbetocin in the early postpartum was 6.9%. Whereas in the second group, given the short half-life, continuous intravenous administration of oxytocin was required until a stable uterotonic effect was achieved in 69.5% of women in the postoperative period.

Table 1

Evaluation of the effectiveness of carbetocin for the prevention of PPH in women with multiple pregnancies

Parameters		Group 1 (n=43)	Group 2 (n=46)
Blood loss (ml)	during the operation	478,3±14,3	583,3±24,3***
	in the early postoperative period	79,4±2,28	107,5±2,28
Onset of uterotonic effect (minutes)		1,1±0,04	4,4±0,15***
Uterine tone (%)	Good	95,4	26,2

	Average	4,6	69,5
	Poor	0	4,3
Need for additional uterotonics(%)		6,9	69,5

Note: *-significantly compared with the indicators of group 1 (**- $P < 0.01$; ***- $P < 0.001$)

Blood loss volume in the 1st group was $478,3 \pm 14,3$ ml, receiving carbetocin to prevent PPH, and $583,3 \pm 24,3$ ml in the 2nd group, receiving oxytocin. PPH of 500 ml or more was observed in 21% of 1st group women and 48% of 2nd group women. More than 800 ml of blood loss occurred in the group using oxytocin (8.7%), resulting in the need for hemotransfusion in the

postpartum period (Table 1). Additional interventions ligation of two or three main vessels was performed in group 1 in 4.6% and in group 2 in 24%. B-Lynch suturing (6.5%) and hysterectomy (4.3%) were performed in group 2 because of the uterotonic therapy's ineffectiveness.

Table 2

Monitoring of uterine involution after using carbetocin in the postpartum period according to ultrasound examination

Days	Length (cm)		Width (cm)		Anteroposterior dimension	
	1 st group	2 nd group	1 st group	2 nd group	1 st group	2 nd group
3	$12,8 \pm 0,18$	$15,7 \pm 0,26$	$10,9 \pm 0,15$	$12,9 \pm 0,3$	$8,8 \pm 0,1$	$10,6 \pm 0,21$
5	$10,5 \pm 0,17$	$13,3 \pm 0,27$	$8,6 \pm 0,16$	$8,8 \pm 0,19$	$6,7 \pm 0,1$	$7,2 \pm 0,14$

Hemodynamic control of BP, Ps, was carried out before and after 15 min and 2 hours of drug administration. In women of the first group, after administration of the drug carbetocin, after 15 minutes, a slight increase was observed in blood pressure and moderate tachycardia. Changes in hemodynamic indices had no adverse effect on the labourer's well-being, and there were no indications for the use of other drugs to correct them.

Blood analysis with the counting of form cells, hematocrit and coagulation indices was carried out to evaluate the effect of carbetocin and oxytocin drugs on various parts of hemostasis over time. No effect of uterotonics on hemostasiogram indexes was revealed. A decrease of haemoglobin level connected with

blood loss was observed in the women of the 2nd group, and it was the reason for hemotransfusion (8.7%).

An echographic examination was carried out to evaluate the rate and course of uterine involution over time on the 3rd and 5th days. On the basis of the ultrasound examination, we found that the mean uterine length, width, and anteroposterior dimension were significantly lower on the 3rd and 5th days in the women in group 1 who received carbetocin to prevent PPH as compared to the comparison group (Table 2).

The postpartum period was without complications in 95.3% of the women in group 1 and 84.7% in group 2. Such complications as uterine sub-involution, hematometra, and metoendometritis occurred in group 2 women and they were associated with impaired uterine

contractility in the postpartum period. Analysis of the length of stay in the postpartum ward showed significant differences between group 1 and group 2 patients; the average bed-day in group 1 was 4.2 ± 0.08 days, and 5.1 ± 0.16 days in group 2.

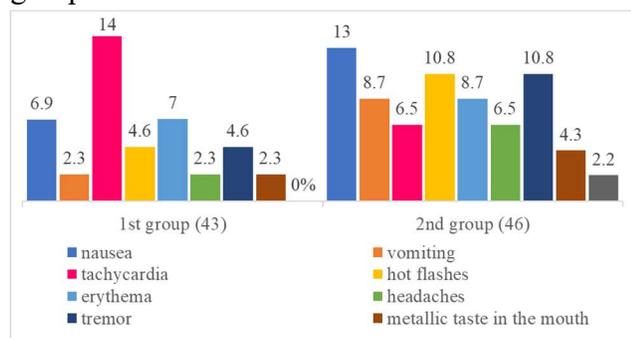


Figure 1. Assessment of adverse events during carbetocin administration in women with multiple pregnancies (%)

The frequency of side effects of the studied drugs showed that in the group where oxytocin was used, such phenomena as nausea, vomiting, tremor, headache, itching was 26%, which is 2.8 times more than in the group where carbetocin was used. The incidence of other adverse reactions was comparable between the groups. Yet, tachycardia was more common in the carbetocin group. Both groups had a similar adverse event profile with no signs of unexpected adverse events.

CONCLUSION

Thus, complications during pregnancy and childbirth in women with multiple pregnancies lead to a high operative delivery rate. And postpartum complications associated with uterine overdistention and cesarean section increase the risk of atonic bleeding several times more than in singleton pregnancy. International recommendations for the use of uterotonics in women with a high risk of uterine atony during

cesarean section vary, but most of them give a unique recommendation for the prevention of bleeding [12,20,21].

Our comparative study of the efficacy and tolerability of carbetocin and oxytocin showed that carbetocin has a more pronounced and prolonged uterotonic effect than oxytocin and greater clinical efficacy for the prevention of bleeding associated with uterine tone disorder. Intraoperatively, it presented a picture of sharp disturbance of microcirculation, the uterus acquired a “marbled” appearance, the usual colouring was restored in 5-6 min, and uterine tone persisted for more than 40-60 min. The drug carbetocin significantly reduced PPH (≥ 500 ml), severe PPH (≥ 1000 ml), and blood transfusion compared with the drug oxytocin. A single intravenous injection of carbetocin $100 \mu\text{g}/1$ ml in stage III of labour reduced the need for uterine massage and the need for additional uterotonic drugs to maintain adequate uterine tone in the postpartum period, especially after cesarean section in women with multiple pregnancies, compared with oxytocin, which requires continuous venous access for an extended period of time. Visual findings and laboratory values prove the powerful uterotonic effect of carbetocin in reducing blood loss (≤ 500 ml) and the associated complications affecting haemoglobin levels before and after delivery.

There was no significant intergroup difference concerning tolerability and unwanted side effects in our study, except for tachycardia, which was observed in women who received carbetocin. However, side effects such as nausea, vomiting, hot flashes, trembling were observed more in the group with oxytocin, which is associated with the continuation of infusion-uterotonic therapy in the postpartum period.

Thus, the capabilities of reducing complications of multiple labor lie in the correct assessment of risk, in the selection of the method of delivery and timely prevention of PPH with the use of effective uterotonic drugs, such as carbetocin. It is the best alternative to traditional oxytocin, which has reliable advantages in preventing PPH in women with multiple pregnancies, a risk factor for bleeding, and one of the main causes of maternal mortality.

CONFLICT OF INTERESTS AND CONTRIBUTION OF AUTHORS

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article and report on the contribution of each author.

SOURCE OF FINANCING

No funding was required for this research.

REFERENCES:

1. Egorova A.T, Ruppel N.I, Maiseenko D.A, Bazina M.I Integrated assessment of the social status, reproductive and somatic anamnesis of pregnant women in induced multiple pregnancy // Russian Bulletin of Obstetrician-Gynecologist. - 2014. - №4. - P.69-73. (InRuss.)
2. Baev O.R. Administration of carbetocin for prevention of postpartum hemorrhage // Obstetrics and Gynecology. - 2013. - №7. - C.101-105. (InRuss.)
3. Egorova A.T, Ruppel N.I, Maiseenko D.A, Bazina M.I Integrated assessment of the social status, reproductive and somatic anamnesis of pregnant women in induced multiple pregnancy // Russian Bulletin of Obstetrician-Gynecologist. - 2014. - №4. - P.69-73. (InRuss.)
4. Elgafor el Sharkwy IA. Carbetocin versus sublingual misoprostol plus oxytocin infusion for prevention of postpartum hemorrhage at cesarean section in patients with risk factors: a randomized, open trail study // Arch Gynecol Obstet. - 2013. - Vol. 288, №6. - P. 1231-1236.
5. Shifman E.M., Kulikov A.V., Protsenko D.N. et al. Anesthesia and intensive care for massive blood loss in obstetrics. Clinical recommendations (treatment protocols) // Issues gynecology, obstetrics and perinatology. - - 2018. - T. 17, №3. - - C. 81-100. (InRuss.)
6. Evensen A., Anderson J.M., Fontaine P. Postpartum Hemorrhage: Prevention and Treatment // Am. Fam. Physician. - 2017. - Vol. 95 (7), №1. - P. 442-449.
7. WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage. — Geneva: World Health Organization. — 2017. — Licence: CC BY-NC-SA 3.0 IGO.
8. Kurtser M.A, Kutakova Yu, Spiridonova E.I, et al. Experience of using carbetocin for the prevention of hypotonic bleeding // Akush. i gin. - 2015. - №7. - P. 38-42. (InRuss.)
9. Bohong Jin, Yongming Du, Fubin Zhang et al. Carbetocin for the prevention of postpartum hemorrhage: a systematic review and meta-analysis of randomized controlled trials // J. Mater. Fetal Neonatal Med. – 2016. – Vol. 29, №3. –P. 400-407.
10. WHO recommendations: Uterotonics for the prevention of postpartum haemorrhage. Geneva: World Health Organization. - 2018. - P. 43
11. Akhmadeev N.R., Fatkulin F.I., Khairullina G.R., Bystritskaya N.Yu. Opportunities to reduce blood loss in time and after multiple births // Kazan Medical Journal. - 2016. - T. 97, №6. - C. 934-938. (InRuss.)

12. Danielly S. S., Fernanda G. S., José G. C. Multiple Pregnancy: Epidemiology and Association with Maternal and Perinatal Morbidity. // *Rev Bras GinecolObstet* Vol. - 2018. - Vol. 40, №9. - P. 554–562.
13. Belomestnov S.R., Galina T.V., Zhilin A.V. et al. Results of a multicenter prospective comparative randomized trial of the efficacy and safety of pabal (carbetocin) and oxytocin drugs // *Archives of Obstetrics and Gynecology*. V.F. Snegiryov. -- 2015. - №1. - P. 48-54. (InRuss.)
14. Matthew J Blitz, AnarYukhayev, Sarah L Pachtman, Jenny Reisner et al. Twin Pregnancy and Risk of Postpartum Hemorrhage // *Matern Fetal Neonatal Med.* - 2019. - Mar 5. - P. 1-6.
15. Wenckus DJ, Gao W, Kominiarek MA, Wilkins I. The effects of labor and delivery on maternal and neonatal outcomes in term twins: a retrospective cohort study // *BJOG* – 2014. - Vol 121. – P. 1137–1144.
16. Babloyan A.G, Tsakhilova S.G, Apresyan S.V, Pikhut P.P Clinical significance of the effectiveness and safety of uterotonics for the prevention of obstetric bleeding in pregnant women of high risk // *Effective Pharmacotherapy*. - 2020. - T. 16, № 28. - P. 12–17. (InRuss.)
17. Radzinsky V. E, Galina T. V, Kirbasova N. P Reserves to reduce blood loss during abdominal delivery: results of a randomized multicenter trial: keep the uterus toned // *Status Praesens*. - 2015. - №1. - P.29-36. (InRuss.)
18. Evseeva M.P, Ivanyan A.N, Gustovarova T.A et al. Hypotonic bleeding during cesarean section. efficacy and safety of conservative therapy // *Bulletin of the Smolensk State Medical Academy*. - 2015. - T. 14, № 4. - P. 55-59. (InRuss.)
19. Guseva E.M. Comparative assessment of the effectiveness of methods to prevent bleeding in the postpartum and early postpartum periods // *Bulletin of new medical technologies*. Electronic edition. - 2014. - №1. - P. 3-15. (InRuss.)
20. Lockhart E. Postpartum hemorrhage: a continuing challenge // *Hematology*. -2015. - Vol. 1. - P. 132–137
21. Belotserkovtseva L.D., Kovalenko L.V., Kilicheva I.I., Ivannikov S.E. Prevention of bleeding with carbetocin during abdominal delivery // *Vopros. gynecol.* - 2014. - №4. - P. 24-28. (InRuss.)
22. Amsalem H, Aldrich CJ, Oskamp M, Windrim R, Farine D. Postpartum uterine response to oxytocin and carbetocin. // *J Reprod Med.* - 2014. - №59 (3-4). - P. 167-173.
23. Bruyere M., AitHamou N., Benhamou D. et al. QT interval prolongation following carbetocin in prevention of post-cesarean delivery hemorrhage // *Int. J. Obstet. Anesth.* – 2014. – Vol. 23, №1. – P. 88-89.
24. Demetz J., Clouqueur E., D’Haveloose A. et al. Systematic use of carbetocin during cesarean delivery of multiple pregnancies: a before-and-after study // *Arch. Gynecol. Obstet.* – 2013. – Vol. 287, №5. – P. 875-880.
25. Prevention and management of postpartum haemorrhage. Royal College of Obstetricians and Gynaecologists. – Greentop Guideline 52. – 2016.
26. ShodievaKh.T. Prediction of complications in multiple pregnancy // *Problems of Biology and Medicine*. - 2021. - №1.1 (126). - C.328-330ю(InRuss.)
27. Cordovani D., Balki M., Farine D. et al. Carbetocin at elective Cesarean delivery: a randomized controlled trial to determine the effective dose // *Canfd. J. Anaesth.* – 2012. – Vol. 59, №8. – P. 751-757.