

Comparing the Efficacy of Carbetocin during an Elective Cesarean Section in Preventing Postpartum Hemorrhage in Obese versus Non-Obese Women

Shaimaa Mostafa Elshemy^{*1}, Nadine Alaa Sherif¹, Sherif Sameh Zaki¹,

Asmaa Ahmed Mohammed Alashwah²

¹Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Egypt

²Department of Obstetrics and Gynecology, Faculty of Medicine, Mansoura University, Egypt

Corresponding Author Name: Shaimaa Mostafa Elshemy, **Email:** sh.elshemy@gmail.com,

Mobile: +20 122 063 2263, **ORCID:** 0000-0002-7470-2692

ABSTRACT

Background: One of the most frequent preventable causes of maternal death is still obstetric hemorrhage. The World Health Organization advises using carbetocin to avoid post-partum hemorrhage in all pregnancies, especially in situations when oxytocin is not available.

Objective: This study aimed to assess how well carbetocin worked in obese full-term pregnant women to improve uterine contraction and reduce blood loss.

Subjects and methods: Between July 2023 and October 2023, 150 pregnant women who were admitted for an elective cesarean section at term, were included in this prospective randomized controlled clinical study. Two equal groups of pregnant women were formed: 75 women in the study group had a body mass index (BMI) of at least 30 kg/m² and 75 women in the control group had a BMI of less than 30 kg/m². Following cord clamping, each woman received a one-minute intravenous bolus of 100 mcg carbetocin as the research medication. Estimation of blood loss was done by measuring the volume of blood of intraoperatively utilized blood-soaked towels and comparing preoperative and 24-hour post-delivery hemoglobin and hematocrit values.

Results: Among the groups being studied, no statistically significant difference was found with respect to hemoglobin level, hematocrit level, uterine tone, mean weighted blood loss, or estimated blood loss at birth. Neither the requirement for blood transfusions nor the adverse effects of the medication varied significantly between the groups under study. No cases indicated that more uterotonic medications were required.

Conclusion: Obesity does not appear to have an impact on carbetocin's ability to prevent PPH.

Keywords: Postpartum hemorrhage, Carbetocin, Obesity

INTRODUCTION

Postpartum hemorrhage (PPH) is currently characterized as "blood loss greater than or equal to 1000 ml or blood loss associated with signs or symptoms of hypovolemia", according to the American College of Obstetricians and Gynecologists (ACOG)⁽¹⁾.

It is advised to use uterotonic medications to lessen blood loss and the possibility of PPH during cesarean delivery⁽²⁾.

There are several preventative uterotonic medications, including as carbetocin, oxytocin, and oxytocin/ergometrine. Synthetic carbetocin is an analogue of oxytocin with a half-life of 85–100 min as opposed to 3–4 min for oxytocin, which has a longer duration of action⁽³⁾.

Obese and morbidly obese women's decreased uterine contractility has been suggested as the primary reason of obstetric hemorrhage in recent clinical and translational investigations. It was discovered that pregnant women who were obese did not differ in their rates of PPH and those who were not, but obese women with PPH required higher dosages of uterotonic medications, such as carbetocin, than non-obese women⁽⁴⁾.

This study's goal was to ascertain whether obese women would require higher carbetocin dosages in order to prevent PPH or not.

SUBJECTS AND METHODS

Between July 2023 and October 2023, 150 women scheduled for elective cesarean sections at Cairo University's Kasr Al Ainy Hospital, Department of Obstetrics and Gynecology, were recruited for this prospective randomized controlled experiment.

Clinical trial registration: **NCT06217354**.

Study population:

A total of 150 pregnant women at term admitted for elective C.S. were recruited into two groups:

- **Group 1 (study group):** 75 Parturient with BMI equal or more than 30 kg/m² (weight in kg/height in m²).
- **Group 2 (control group):** 75 Parturients with BMI < 30 kg/m².

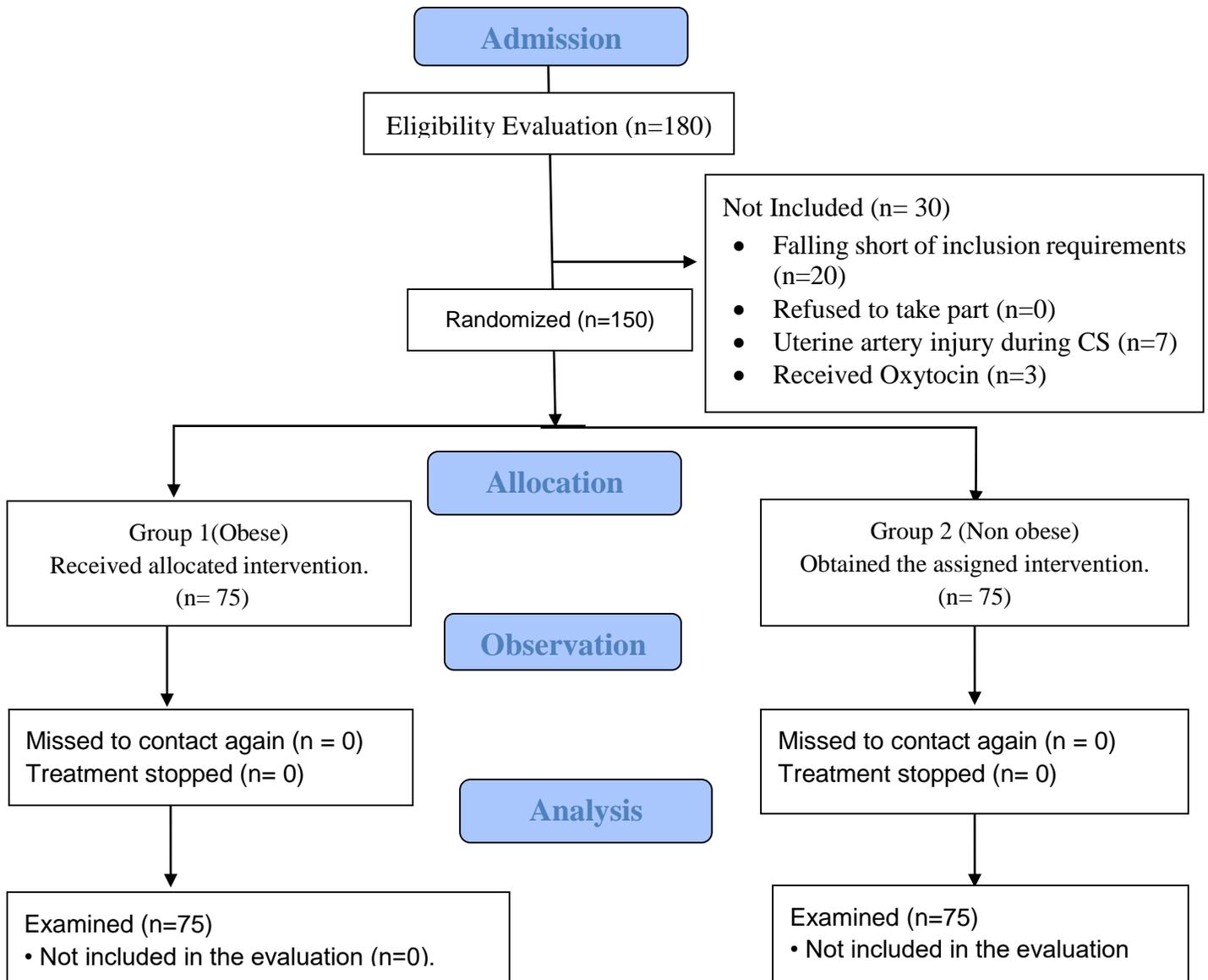


Figure (1): Consort flow chart showing study design.

Following cord clamping, all women were given the study drug in the form of an intravenous bolus of 100 mcg carbetocin (Pabal VR, Ferring AG, Baar, Switzerland) over a minute only after the baby was delivered, ideally before placental separation.

Follow up after surgery of all patients by:

Level of consciousness, vital indicators (blood pressure, pulse, temperature, and respiratory rate), urine production, and, if any, drain output, tone of the uterus, bleeding from the vagina, transfusion of blood, if necessary, if there were any pharmacological side effects, problems for the mother during childbirth (if any), before and 24 hours after surgery, the CBC was measured.

- Following the administration of carbetocin, the obstetrician evaluated the uterine tone at two and five minutes, rating it as satisfactory (firm) or unsatisfactory (not firm) on a scale of 0 to 10 (10 being the pinnacle of firmness), and at their discretion after that.

- Blood loss was estimated by:
The formula to calculate the estimated loss of blood (EBL) is: estimated blood volume (EBV) X Preoperative hematocrit (preop Hct) - postoperative hematocrit (postop Hct) / preoperative hematocrit (preop Hct).
- The hematocrit value was evaluated 24 hours after birth as well as right before.
- Blood amount was obtained from towels that were completely submerged in blood.
- Measurements of hemoglobin were made both before and 24 hours after surgery.

Inclusion criteria:

Every woman between the ages of 19 and 39 who underwent an elective CS delivery, had a pregnancy with single fetus and a gestational age of a minimum of 37 weeks.

Exclusion criteria:

Emergency CS, maternal diseases as epilepsy, severe cardiovascular disease, kidney or liver disease, coagulopathies, and maternal comorbidities. uterine malformations, such as didelphys, septum, and myoma. Fetal malformation, excessive distention of the uterus (such as in polyhydramnios, twins, as well as macrosomia of the fetus), known hypersensitivity to either oxytocin or carbetocin, damage to the uterus or uterine artery during cesarean section.

Outcome measurement:

The primary outcome was estimated blood loss following carbetocin injection in full-term pregnant patients undergoing elective cesarean surgery. Uterine contractility, the percentage of women who received extra uterotonics following the injection of one

carbetocin dosage, blood product transfusions, and non-pharmacological methods for treating PPH were among **the secondary outcomes.**

Ethical Consideration:

The Helsinki Declaration and the ethical guidelines for human subjects' research established by the World Health Organization were followed in the conduct of the study. The Faculty of Medicine at Cairo University's Research Ethics Committee gave its ethical approval to this study (IRB: MD-69-2023). After receiving a comprehensive clarification of the goal and potential benefits of the research, all prospective participants completed informed written consent forms.

Sample size estimation:

Based on a prior study about PPH management, the sample size was determined. It was discovered that obese women had a higher likelihood of receiving a uterotonic drug (95.7 vs. 89.8%, $p = 0.007$). The likelihood of receiving extra oxytocin, misoprostol, methyl ergonovine, and carboprost 5 was the same for both groups⁽⁵⁾. Consequently, it was determined that in order to detect a difference at an α level and an 80% power, 150 women would be required in the sample. Based on these numbers, a minimum sample size of 75 cases was obtained for each group.

Using MedCalc© version 13, a computer-generated randomization sheet was used for the randomization process.

Statistical analysis and data interpretation:

Data analysis was performed by SPSS software, version 25 (SPSS Inc., PASW statistics for windows version 25. Chicago: SPSS Inc.). Qualitative data were described using number and percent. Quantitative data were described using mean \pm Standard deviation for normally distributed data after testing normality using Kolmogorov-Smirnov test. Significance of the obtained results was judged at the (≤ 0.05) level.

- Chi-Square, Fisher exact test were used to compare qualitative data between groups as appropriate.
- Student t test was used to compare 2 independent groups for normally distributed data.
- Paired t test was used to compare 2 paired readings for normally distributed data.
- **Two-sided p-value < 0.05** was considered statistically significant.
 - P value > 0.05 insignificant.
 - P < 0.05 significant.
 - P < 0.01 highly significant.

RESULTS

The difference between the control group and the study group was statistically insignificant regarding age. But there was a statistically significant higher weight and body mass index, EBV among cases than control group. (Table 1).

Table (1): Comparison of age, body mass index and estimated blood volume (EBV) between studied groups.

	Group 1 (Obese) n=75	Group 2 (Control) n=75	Test of significance
Age years	29.28±4.53	28.04±4.58	t=1.67 p=0.098
Weight (kg)	94.84±7.53	76.04±4.45	t=18.61 p<0.001*
Height (cm)	164.13±3.41	164.83±5.07	t=0.983 p=0.327
BMI (Kg/m²)	35.23±2.70	27.95±0.91	t=22.11 p<0.001*
EBV (ml)	6639.52±515.82	5320.40±315.09	t=18.9 p<0.001*

t: Student t test, Parameters are described as mean ±SD, *: Significant, Kg:kilograms,cm:centimeter,m²:meter square,ml:millimeter.

The control group and the study group had similar mean gestational age at birth. Also, in terms of parity and previous prior C-section, there was a lack of statistical significance between both groups (Table 2).

Table (2): Obstetric history of the studied groups.

	Group 1 (Obese) n=75	Group 2 (Control) n=75	Test of significance
Gestational age at delivery (weeks)	38.56±1.35	38.84±1.03	t=1.34 p=0.155
Parity			
Nulli para	8(10.7)	17(22.7)	χ ² =4.32 p=0.115
Para 1	33(44.0)	32(42.7)	
≥2	34(45.3)	26(34.7)	
Median (min-max)	1(0-3)	1(0-3)	
Prior CS			
None	8(10.7)	17(22.7)	χ ² =3.93 p=0.140
1	38(50.7)	34(45.3)	
≥2	29(38.7)	24(32.0)	
Median (min-max)	1(0-3)	1(0-3)	

t: Student t test, χ²: Chi-Square test, Parameters are described as mean ±SD, median (range), or number (percent).

Regarding preoperative and postoperative hemoglobin levels, statistically speaking, there was no difference between the groups under investigation. Although each group's hemoglobin level decreased statistically significantly after surgery compared to before (Table 3).

Table (3): Hemoglobin and hematocrit level changes between pre- and postoperative and between different studied groups.

		Group 1 (Obese) n=75	Group 2 (Control) n=75	Test of significance (Student t test)
Hemoglobin (gm/dl)	Pre-operative	10.77±0.69	10.66±0.66	t=0.949 p=0.344
	24 h Post-operative	9.49±0.71	9.36±0.68	t=1.17 p=0.244
Paired t test		t=40.48 p<0.001*	t=48.66 p<0.001*	
% of change		11.9%	12.2%	p=0.952
Hematocrit (%)	Preoperative	31.78±1.69	31.31±1.42	t=1.82 p=0.07
	24 h Post-operative	27.43±1.57	26.98±1.75	t=1.65 p=0.101
Paired t test		t=53.96 p<0.001*	t=24.23 p<0.001*	
% of change		13.7%	13.8%	p=0.915

t: Student t test, Parameters are described as mean ±SD, *: Significant

This table (4) demonstrates that a non-statistically significant difference was detected between weighted blood loss and estimated blood loss between group 1 and group 2 (Table 4).

Table (4): Comparison of weighted and estimated blood loss between studied groups.

	Group 1 (Obese) n=75	Group 2 (Control) n=75	Test of significance (Student t test)
Weighted blood loss (gm)	768.33±88.94	744.0±88.5	t=1.68 p=0.095
Estimated blood loss (ml)	843.13±138.65	812.57±90.03	t=1.60 p=0.112

t: Student t test, Parameters are described as mean ±SD

When uterine tone was measured two and five minutes after surgery; statistically speaking, there was no

difference between the groups under investigation. Nonetheless, there was a statistically significant increase in uterine tone after surgery compared to preoperative in each group individually. The percentage of uterine tone change was higher in the obese group in contrast to the control group, however the difference was statistically insignificant (Table 5).

Table (5): Comparison of the study groups' uterine tone before and after surgery.

		Group 1 (Obese) n=75	Group 2 (Control) n=75	Test of significance
Uterine tone	At 2 minutes	7.93±0.70	8.08±0.59	t=1.38 p=0.168
	At 5 minutes	8.40±0.52	8.48±0.50	t=0.958 p=0.340
paired t test		t=5.91 p<0.001*	t=5.84 p<0.001*	
% of change		5.92%	4.95%	p=0.794

t: Student t test, Parameters are described as mean ±SD, *: Significant

Regarding the requirement for blood transfusions; statistically speaking, there was no difference between the groups under investigation (Table 6).

Table (6): A comparison of the complications among the groups under study.

	Group 1 (Obese) n=75(%)	Group 2 (Control) n=75(%)	Test of significance
Additional methergine	0	0	P=1.0
Surgical intervention	0	0	P=1.0
Need blood transfusion	3(4.0)	1(1.3)	FET,P=0.367

FET: Fisher's exact test, Parameters are described as number (percent).

This table (7) shows that, in terms of the occurrence of pharmacological side effects, the tested groups did not differ in a way that was statistically significant.

Table (7): Comparison of drug side effects between studied groups.

Drug side effect	Group 1 (Obese) n=75(%)	Group 2 (Control) n=75(%)	Test of significance
Facial flushing	6(8.0)	7(9.3)	$\chi^2=0.084$ p=0.772
Headache	9(12.0)	11(14.7)	$\chi^2=0.231$ p=0.631
Fever	0	0	
Shivering	3(4.0)	2(2.7)	FET,p=1.0
Diarrhea	0	0	p=1.0

χ^2 : Chi-Square test, FET: Fisher's exact test, Parameters are described as number (percent).

DISCUSSION

Obesity has been linked in several studies to higher incidence of obstetric problems, including postpartum hemorrhage^(6,7). One of the most frequent reasons why mothers can still be saved from death is still obstetric hemorrhage^(8,9).

One important treatment for uterine atony, the main factor contributing to obstetric hemorrhage, is the use of uterotonic drugs. Obese and morbidly obese women may have less uterine contractility, according to clinical research⁽¹⁰⁾. The World Health Organization advises using carbetocin to prevent PPH in all pregnancies, especially in situations where the availability or quality of oxytocin is questionable⁽¹¹⁾.

The purpose of this study was to evaluate how well carbetocin worked in obese full-term pregnant women to improve uterine contraction and reduce blood loss.

Regarding parity, previous C.S., mean gestational age, hemoglobin level, hematocrit level, uterine tone, mean weighted blood loss, and estimated blood loss at birth, in this study, there were no discernible differences between the groups that were investigated. Additionally, none of the groups under study had any appreciable differences in the **need for blood transfusions** or **adverse medication reactions**. There were no cases where **further uterotonic medication** or **surgical intervention** was required, and there were no maternal fatalities.

Similar findings were made by Attilakoset *al.*, who showed that postnatal fundal height or uterine tone did not differ significantly from the mean hemoglobin fall following the procedure as when postpartum haemorrhage occur due to uterine atony the uterine fundal level will be higher than normal⁽¹²⁾.

The postoperative decline in hematocrit and hemoglobin, on the other hand, did not differ. This could be because these measurements were only documented when they were measured as part of routine treatment, not prior to labor. As a result, measurements in certain patients may have skewed the results⁽¹³⁾.

With reference to our findings, which revealed not a single statistically significant variation in the mean weighted blood loss and estimated blood loss among the group under investigation, a similar study found no correlation between obesity and an increased chance of post-cesarean section carbetocin failure (i.e., decreased uterine contractility and increased blood loss)⁽¹⁴⁾.

As opposed to our findings; a study indicated that among women with PPH, obese women had a larger

quantitative blood loss than non-obese women⁽⁵⁾. Furthermore, our findings conflict with a study by **Doherty et al.** that discovered a substantial link between obesity and longer operating times, which in turn led to higher blood loss⁽¹⁵⁾.

El Behery et al.'s study, which examined the safety and effectiveness of comparing an IV oxytocin infusion to an IV carbetocin bolus dosage for the prevention of postpartum hemorrhage (PPH) in 180 obese nulliparous women after an emergency caesarean, produced comparable findings with regard to uterine tone. In the oxytocin group, there were more transfusions and more severe PPH (≥ 1000 mL) ($p = 0.03$ and $p = 0.04$, respectively). A total of 71.5% in the oxytocin group and none in the carbetocin group required extra uterotonics ($p < 0.01$)⁽¹⁶⁾.

The 90% effective dose (ED90) of carbetocin in obese women having an elective caesarean section was shown to be almost four times greater than the previously documented ED90 in non-obese women in a double-blind, dose-finding trial. The female participants in the study had a BMI of greater than 40 kg/m²⁽¹⁷⁾.

In terms of blood transfusion requirements, the obese group had a larger need than the non-obese group (4% versus 1.3%, respectively), although this difference was statistically insignificant.

This contradicts the findings by **Polic et al.** Compared to non-obese women, obese women with PPH had a higher risk of experiencing a higher quantitative blood loss. Compared to non-obese women, obese women experienced also more morbidity and required more blood transfusions despite receiving the same level of treatment. Anemia was also more common in non-obese women.⁽⁵⁾

No statistically significant difference was seen between the groups under study in terms of pharmacological side effects. In the obese group, there were 4% shivering, 12% headaches, and 8% face flushes. 9.3% of the control group experienced face flushing, 14.7% had headaches, 2.7% shivered, and there was no fever or diarrhea.

This is consistent with a systematic review and meta-analysis that found flushing, nausea, headaches, and vomiting to be the most frequently reported side effects of carbetocin use against PPH. The meta-analysis comprised 17 RCT studies encompassing 32,702 women. When carbetocin was used in intravenous and cesarean delivery patients to avoid postpartum hemorrhage, the risk of vomiting was reduced. The outcome was supported by evidence of medium to high quality⁽¹⁸⁾.

Clinical research that contrasted the detrimental effects of carbetocin and oxytocin in order to avoid PPH have also examined the side effects of carbetocin. They discovered that following carbetocin, nausea was less common, although there was no statistically significant change⁽¹⁹⁾.

With reference to the fact that no cases indicated a need for further uterotonics or surgery; **Tse et al.** reported that compared with oxytocin, carbetocin can reduce the need for additional uterotonics or procedures in selected high-risk patient groups. Of 1236 women included in the study, 752 received oxytocin first and 484 received carbetocin first. The two groups had comparable blood loss, operating time, rate of postpartum hemorrhage, requirement for additional uterotonics or procedures, need for blood transfusion, and need for hysterectomy. There was a reduction in the requirement for additional uterotonics or procedures, and in the rate of postpartum hemorrhage for women with major placenta praevia or with multiple pregnancies, following receipt of carbetocin first⁽²⁰⁾.

According to another study, one intravenous injection of carbetocin administered during CS considerably reduced the requirement for subsequent uterotonic treatments. Since adverse effects, hematologic values (decrease in hemoglobin levels), and vital signs did not differ significantly between Carbetocin and Oxytocin groups in this regard, Also Carbetocin has the same safety profile as oxytocin⁽²¹⁾.

CONCLUSION AND RECOMMENDATIONS

- Numerous research examining the connection between higher BMI and birth outcomes have found associations between obesity and PPH.
- In this trial, carbetocin controlled uterine tone and prevented PPH in both the non-obese and obese groups equally well.
- More RCTs with bigger sample sizes are needed to show how effective carbetocin is at preventing PPH in obese pregnant women as opposed to non-obese pregnant women, as well as its side effects.
- Further studies comparing the use of oxytocin and carbetocin in overweight women are relevant to determine whether there is a difference in the effectiveness of the two uterotonics based on BMI.

Declaration of conflict interest:

The authors of this article have declared that they have no potential conflicts of interest pertaining to the research, writing, or publication of this article.

Funding: The research was conducted without any financial support to the author(s).

REFERENCES

1. **Menard M, Main E, Currigan S (2014):** Executive summary of the reVITALize initiative: standardizing obstetric data definitions. *Obstet Gynecol.* ,124(1):150–3.
2. **Gallos I, Papadopoulou A, Man R(2018):** Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. *Cochrane Database Syst*

Rev.,12:CD011689

3. **Widmer M, Piaggio G, Nguyen T et al.(2018):** Heat-stable carbetocin versus oxytocin to prevent hemorrhage after vaginal birth. *N Engl J Med.*,379(8):743-752.
4. **Luca A, Carvalho J, Ramachandran Net al.(2020):** The effect of morbid obesity or advanced maternal age on oxytocin-induced myometrial contractions: an in vitro study. *Canad J Anaes.*, 67:836–846
5. **Polic, A, Curry T, Louis J(2022):** The impact of obesity on the management and outcomes of postpartum hemorrhage. *Am J Perinatol.*,39(6):652–657.
6. **Blomberg M (2011):** Maternal obesity and risk of postpartum hemorrhage. *Obstet Gynecol.*, 118(03):561–568.
7. **Sebire N, Jolly M, Harris J et al. (2001):** Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. *International Journal of Obesity and Related Metabolic Disorders. J Int Assoc Study Obesity*,25(08):1175–1182.
8. **Mehta P, Kieltyka L, Bachhuber M et al.(2020):**Racial inequities in preventable pregnancy-related deaths in Louisiana, 2011-2016. *Obstet Gynecol.*,135(02):276–283.
9. **Petersen E, Davis N, Goodman Det al.(2019):** Vital signs: pregnancy-related deaths, United States, 2011-2015, and strategies for prevention, 13 States, 2013-2017. *MMWR Morb Mortal Wkly Rep.*,68(18):423–429.
10. **Higgins C, Martin W, Anderson L et al.(2010):** Maternal obesity and its relationship with spontaneous and oxytocin-induced contractility of human myometrium in vitro. *Reprod Sci.*,17(02):177–185
11. **WHO Recommendations(2018):** Uterotonics for the prevention of postpartum haemorrhage. Geneva. <https://www.who.int/publications/i/item/9789241550420>
12. **Attilakos G, Psaroudakis D, Ash Jet al.(2010):** Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomised trial. *BJOG.*, 117:929-936.
13. **Holleboom C, Van Eyck J, Koenen S et al.(2013):** Carbetocin in comparison with oxytocin in several dosing regimens for the prevention of uterine atony after elective caesarean section in the Netherlands. *Archives of Gynecology and Obstetrics*, 287:1111- 1117.
14. **Degez M, Planchel, Dorion A et al.(2021):** Risk factors for carbetocin failure after a caesarean section: Is obesity one of them? *J.Clin. Med.*, 10: 3767.
15. **Doherty D, Magann E, Chauhan Set al.(2008):** Factors affecting caesarean operative time and the effect of operative time on pregnancy outcomes. *Aust. N. Z. J. Obstet. Gynaecol.*, 48: 286–291.
16. **El Behery M, El Sayed G, El Hameed A et al.(2016):** Carbetocin versus oxytocin for pre-vention of postpartum hemorrhage in obese nulliparous women undergoing emergency cesarean delivery. *J. Matern. Fetal. Neonatal Med.*, 29: 1257–1260.
17. **DrewT, BalkiM, Farined et al.(2019):**Carbetocin at elective caesarean section: A sequential allocation trial to determine the minimum effective dose in obese women. *Anaesthesia*, 75: 331–337.
18. **Ai W, Zeng Y, Ma Y et al.(2021):**Side-effects of carbetocin to prevent postpartum hemorrhage: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res Perspect.*, 9(2):e00745.
19. **Mannaerts D, Van der Veecken L, Coppejans Het al.(2018):**Adverse effects of carbetocin versus oxytocin in the prevention of postpartum haemorrhage after caesarean section: A randomized controlled trial. *J Pregnancy*,1374150.
20. **Tse K, Yu F, Leung K(2020):**Comparison of carbetocin and oxytocin infusions in reducing the requirement for additional uterotonic or procedures in women at increased risk of postpartum haemorrhage after Caesarean section. *Hong Kong Med J.* ,26(5):382-389.
21. **DeBonis M, Torricelli M, Leoni L et al. (2012):** Carbetocin versus oxytocin after caesarean section: similar efficacy but reduced pain perception in women with high risk of postpartum haemorrhage. *J Matern Fetal Neonatal Med.*, 25:732- 735.