بسم الله الرحمن الرحيم

قالوا
سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

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Heba Mahmoud Abd El Hakam

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List of Abbreviations

ACOG	:	American college of obstetricians and gynecologists.
AR	:	Absolute Risk
ARR	:	Absolute Risk Reduction.
ASUMH	:	Ain Shams University Maternity Hospital.
AUC	:	Area Under Curve.
BJOC	:	British journal of obstetrician and gynecologists
BMI	:	Body Mass Index.
CBC	:	Complete Blood Count.
CEMACH	:	Confidential Enquiry into Maternal and Child Health
C.I.	:	Confidence Interval
DIC	:	Disseminated Intravascular Coagulopathy
Hb%	:	Hemoglobin
ICD	:	International Classification of Disease.
ICER	:	Incremental Cost-Effectiveness Ratio
JNMC	:	Jawaharlal Nehru Medical College
NICHD	:	National Institute of Child Health and Human Development
NNT	:	Number Needed to Treat
MD	:	Mean difference

List of Abbreviations (Cont.)

MRI	:	Magnetic Resonance Imaging
P.C.V	:	Packed Cell Volume
PPH	:	Postpartum Hemorrhage.
RCOG	:	Royal College of Obstetrics and Gynecology
RR	:	Relative Risk
SD	:	Standard Deviation.
UIC	:	University of Illinois Chicago.
UMKC	:	University of Missouri-Kansas City
WHO	:	World Health Organization

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Introduction

Postpartum hemorrhage (P.P.H.) is defined as loss of 500 ml or more of blood from the genital tract within 24 hours of the birth of a baby ***(Mousa and Alfirevic, 2007)***.Severe PPH was defined as 1000 ml or more in the third stage of labour ***(Begley, 2010)***,but pre-existing health status like severe anemia or cardiac disease can make the effect of lesser blood loss life-threatening ***(Lalonde et al., 2006).***PPH diagnosis is based on International Classification of Disease (ICD) codes recorded in Perinatal Database (ICD-9 and ICD-10). Subtypes of PPH identified with ICD-9 and ICD-10 diagnostic codes included: 1) PPH due to retained placenta, 2) PPH due to uterine atony (occurring within 24 hours following delivery), 3) delayed and secondary PPH (occurring after the first 24 hours following delivery) and 4) PPH due to coagulation defects ***(Knight et al., 2009).***

A study conducted by the International PPH Collaborative Group reports an increasing trend in coded PPH between 1991 and 2006 not only in low income countries, but also in Canada, New South Wales and the USA, as a possible result of increased maternal age at childbirth, increased rate of caesarean delivery, increased rate of induction of labor and higher number of multiple pregnancies ***(Knight et al., 2009).***

Postpartum hemorrhage is potentially life threatening and a leading cause of maternal death worldwide ***(Li et al., 1996; McCormick et al., 2002; Lewis et al., 2007)*** *which is responsible for about one quarter of all maternal deaths worldwide****(Carroli et al.,2008).***Maternal mortality rates are much lower among developed countries, but hemorrhage remains one of the top causes of maternal deaths over the years ***(Cantwell, 2011).***

Non fatal PPH can result in further interventions, severe anemia, need of blood transfusion, Sheehan's syndrome (pituitary infarction), coagulopathy and organ damage due to hypotension and shock.

Uterine atony encounters for four-fifth of postpartum hemorrhage cases **(*Bouwmeester et al., 2005; WHO, 2000)***. Active management of the third stage of labour using uterotonics during the vaginal delivery or caesarean section has successfully declined occurrence of uterine atony induced PPH***(Chong et al., 2004*****; *Begley et al., 2010*).**

The practical guidelines on PPH of the Society of Obstetricians and Gynecologists of Canada (SOGC) suggest that the active management of the third stage of labour reduces the risk of PPH compared with the expectant management and should be offered and recommended to all women. Active management of the third stage of labour has three components - use of a uterotonic agent, early cord clamping and controlled cord traction. The administration of uterotonic drugs widely prevents the PPH, significantly decreases the incidence of PPH and therefore it is the main point of active management. Oxytocin (10 IU), administered intra-muscularly, is the preferred medication for the prevention of PPH in low-risk vaginal and caesarean deliveries. Intravenous infusion of oxytocin (20 to 40 IU in 1000 mL, 150 mL/hour) is an acceptable alternative for the active management. Prophylactic administration of oxytocin reduces rates of postpartum hemorrhage by 40 percent ***(Nordstrom et al., 1997*****).** Care providers should administer this medication after delivery of the anterior shoulder. Oxytocin has a half-life of 4-10 minutes (***Chard et al., 1970*****).**

Although the oxytocin is the most widely accepted uterotonic agent, however other drugs are available, but which agent is ideal for prophylactic use is far to be clearly stated ***(Leduc et al., 2009).***

Over the past two decades, several other alternatives have been explored, including the use of prostaglandins such as misoprostol and carboprost. The peak concentration is achieved 30 minutes after sublingual and oral administration, whereas after vaginal administration, it takes 75 minutes ***(Tang et al., 2002*)** and in rectal administration it takes 40-65 minutes ***(Meckstroth et al., 2006)***. It is associated with a high incidence of shivering, fever, and possible risk of severe hyperthermia ***(Chong et al., 1997; Gulmezoglu et al., 2004).***Promising results have been published recently with the use of misoprostol for the prevention of postpartum hemorrhage compared to placebo *(**Chong 2006; Gulmezoglu 2011)***. The recent Cochrane review by Gulmezoglu et al concluded that oral or sublingual misoprostol shows promising results when compared to placebo in reducing blood loss postpartum. However, oral misoprostol is associated with higher risk of severe postpartum hemorrhage and use of additional uterotonics compared to the conventional injectable uterotonics ***(Gulmezoglu, 2011).***

Carbetocin is a long-acting synthetic oxytocin analogue, 1-deamino-1-monocarbo-(2-O-Methyltyrosine)-Oxytocin,
firstly described in 1987. It has a half-life of 40 minutes (around 4-10 times longer than Oxytocin) and uterine contractions occur in less than two minutes after intravenous administration of optimal dosage of 100 µg slowly I.V. or I.M. ***(Sweeney et al., 1990).*** A single dose of Carbetocin has been hypothysed to act as a 16 hours intravenous Oxytocin infusion

regarding the increase in uterine tone and the reduction of the risk of PPH in elective caesarean section ***(Boucher et al., 1998)***

Several data of literature ***(Attilakos et al., 2010 - Boucher et al., 2004)*** suggest that prophylactic administration of Carbetocin may be a good alternative to Oxytocin to prevent post-partum hemorrhage, but which uterotonic agent is ideal for prophylactic use is being debated. Nonetheless, primary prevention of a post-partum hemorrhage begins with the assessment of identifiable risk factors.

The Aim of the Work

The aim of this study is mainly evaluating the efficacy of intravenous carbetocin after elective caesarean section and comparing it to that of oxytocin. **Additionally** this study aims at comparing the efficacy of both drugs in women with risk factors for postpartum hemorrhage and evaluating the cost effectiveness of carbetocin.

Chapter 1

Hemodynamic Adaptation to Pregnancy

Hematologic changes during pregnancy

Over the course of pregnancy plasma volume increases by 10 to 15 percent at 6 to 12 weeks of gestation, expands rapidly until 30 to 34 weeks, after which there is only a modest rise ***(Lund et al., 1967; Bernstein et al., 2001; Whittaker et al., 1993)***. The total gain at term averages 1100 to 1600 mL and results in a plasma volume of 4700 to 5200 mL, 30 to 50 percent above that found in non-pregnant women ***(Lund et al., 1967; Pritchard et al., 1965)***.Red blood cell mass begins to increase at 8 to 10 weeks of gestation and steadily rises by 20 to 30 percent (250 to 450 mL) above non pregnant levels by the end of pregnancy in women taking iron supplements ***(Pritchard et al., 1965; Metcalfe et al., 1988; Ueland et al., 1976)***.

The increased plasma erythropoietin induces the rise in red cell mass, which partially supports the higher metabolic requirement for oxygen during pregnancy ***(Milman et al., 1997)***.Although platelet counts remain in the normal non pregnant range in most women during uncomplicated pregnancies ***(Giles et al., 1981)***.Mean platelet counts of pregnant women may be slightly lower than in healthy non pregnant women ***(Matthews et al., 1990)***.Serial platelet counts during uncomplicated pregnancies may ***(Verdy et al., 1997)*** or may not ***(Ahmed et al., 1993)***decrease, but the mean values in groups of women do not necessarily reflect changes in individual women ***(Minakami et al., 1996)***.

Pregnancy is associated with leukocytosis, primarily related to increased circulation of neutrophils. The neutrophil count begins to increase in the second month of pregnancy and plateaus in the second or third trimester ***(Kuvin et al., 1962)***. In healthy women with normal pregnancies, there is no change in the absolute lymphocyte count and no significant changes in the relative numbers of T and B lymphocytes ***(Kühnert et al., 1998).***

Changes in Systemic Coagulation

Pregnancy is associated with changes in several coagulation factors that result in a 20 percent reduction of prothrombin and the partial thromboplastin times ***(Talbert et al., 1964; Walker et al., 1997).*** Resistance to activated protein C increases in the second and third trimesters ***(Walker et al., 1997)***Protein S decreases ***(Toglia et al., 1996)***Factors I, II, V, VII, VIII, X, and Xll increase ***(Toglia et al., 1996; Hellgren et al., 1981).***Activity of the fibrinolytic inhibitors PAI-1 and PAI-2 increases, although total fibrinolytic activity may not be