Introduction

Active management of third stage of labor for protection against postpartum hemorrhage.

Postpartum hemorrhage is defined as blood loss of at least 500ml after vaginal delivery and 1000 ml after cesarean section and/or the need for blood transfusion within 24 h of delivery ***(Leduc et al., 2010).***

It occur in 5%of all deliveries ***(Carroli et al., 2008)*** and represent the most important cause of maternal morbidity and mortality world wide ***(Homer et al., 2009).***

The risk of postpartum hemorrhage is much higher for women undergoing cesarean section ***(Murphy et al., 2008)*** uterine atony is the first cause of post partum hemorrhage followed by genital tract injury and retained placenta necessitating manual removal.

Risk factors for post-partum hemorrhage, such as grand multiparty, multiple pregnancy, polyhydramnios, fetal macrosomia, uterine myomas, placenta previa, prolonged labor, chorioamnionitis, and previous post partum hemorrhage have remained relatively constant ***(Leduc et al., 2010).***

Active management of third stage of labor involves interventions to assist in expulsion of the placenta with the intention to prevent or decrease blood loss. Interventions include use of uterotonics, clamping of the umbilical cord, and controlled traction of the cord. Use of uterotonic agents to enhance natural uterine contraction and retraction following C.S and in the third stage of labor for vaginal delivery ***(Adegbola et al., 2009)***.

Oxytocin is the most widely used uterotonic agent ***(Macleod et al., 2008)***, but it has only a half-life of 4-10 minutes and must be administered as a continuous IV infusion to achieve sustained uterotonic activity ***(Rath et al., 2009)***.

Recent interest has focused on the prophylactic use of the oxytocin receptor agonist carbetocin ***(Nga et al., 2007).***

Carbetocin is a long-acting synthetic analogue of oxytocin with uterotonic activity resulting from its binding to oxytocin receptors on the myometrial cells ***(Norstrom et al., 1990)***, and it is currently approved 23 countries for prevention of uterine atony and excessive bleeding following cesarean delivery in spinal or epidural anesthesia ***(Rath et al., 2009)***.

It can be administered as a single dose injection either intravenously or intramuscularly. Intravenously administered carbetocin has a half-life of 40 minutes, around 4 – 10 times longer than that reported for oxytocin ***(Engstron et al., 1998)***.

Adverse events reported by at least 10% of women who received prophylactic intravenous carbetocin following caesarean delivery were headache, tremor, hypotension, flushing, nausea, abdominal pain, itching and feeling of warmth ***(Rath et al., 2009).***

Uncommon or sporadic adverse events were tachycardia, sweating, dizziness, chest pain, vomiting metallic taste ***(Rath et al., 2009)***.

Hemorrhage and hypertensive disorders are the greatest contributers to maternal death in developing countries, accounting for more than 30% of direct causes**.** In developed countries both pathologies, together with embolism, are the main reasons for women death during pregnancy. Considering that in 2005 there were 536 000 maternal deaths worldwide (99% in developing countries) any potential for improvement in management of these two disorders should be investigated ***(Leduc et al., 2010)***.

For some years, pharmacological options for the prevention of postpartum hemorrhage have been explored,

among them is the oxytocin agonist, carbetocin. Carbetocin is a long-acting synthetic oxytocin analogue (1-deamino-1 monocarba-[2--methyltyrosine]-oxytocin), with a half life of 40 minutes ***(Carroli et al., 2012)*** Within two minutes of intravenous administration, it has the capacity to generate tetanic uterine contractions that last for six minutes. These tetanic contractions are followed by more rhythmic ones for approximately one hour ***(Oladapo et al., 2009).***

In patients with severe pre-eclampsia there is an increased risk of postpartum hemorrhage. But the hemodynamic changes associated with severe pre-eclampsia make the management of any kind of bleeding particularly troublesome ***(Osvaldo et al., 2011)***.

In preeclampsia the hemodynamic and vascular adaptation to pregnancy is disturbed. Of the few studies available on early hemodynamic changes in pregnancy one longitudinal study showed that women who subsequently develop PE have an increased cardiac output throughout pregnancy ***(Easterling et al., 1990)***. Late hemodynamic changes in preeclampsia are characterized by increased blood pressure, reduced plasma volume, increased peripheral vascular resistance and vasoconstriction ***(Visser et al., 1991).***

There are many pharmacological options for the management of postpartum hemorrhage, oxytocin being the first line of treatment. There is as yet no evidence about the safety and efficacy of using carbetocin, an oxytocin agonist, in patients with severe preeclampsia ***(Osvaldo et al., 2011).***

Objective

Comparison between carbetocin and oxytocin in the management of the third stage of labor in patients with severe preeclampsia.

Rational of the Study

In patients with severe preeclampsia carbetocin may be better than oxytocin in the management of the third stage of labor.

Research Question

In patients with severe preeclampsia, is carbetocin better than oxytocin in the management of the third stage of labor?

Outcome Measures

1. The primary outcome of the study the was occurrence of postpartum hemorrhage.
2. The secondary outcome of the study were:
   - Difference in hematocrit and hemoglobin estimated before and after delivery by 48 hours.
   - Hemodynamic status, A.B.P., pulse rate.
   - The total amount of infused intra venous fluids.
   - The need for blood transfusion.

Chapter (1)

Third Stage of Labor

INTRODUCTION

Postpartum hemorrhage (PPH) is the leading cause of maternal death worldwide, with an estimated mortality rate of 140 000 per year, or one maternal death every 4 minutes ***(AbouZahr, 2003).*** Postpartum hemorrhage (PPH) occurs in 5% of all deliveries and is responsible for a major part of maternal mortality ***(Subtil et al., 2004 and Reynders et al., 2006).*** The majority of these deaths occur within 4 hours of delivery, which indicates that they are a consequence of the third stage of labor. Nonfatal postpartum hemorrhage results in further interventions, iron deficiency anemia, pituitary infarction (Sheehan's syndrome) with associated poor lactation, exposure to blood products, coagulopathy, and organ damage with associated hypotension and shock ***(Ramanathan and Arulkumaran, 2006).***

Since all parturient women are at risk for postpartum hemorrhage, care providers need to possess the knowledge and skills to practice active management of the third stage of labor to prevent postpartum hemorrhage and to recognize, assess, and treat excessive blood loss.

A review of the data resulted in a joint statement in 2004 by the International Confederation of Midwives and

International Federation of Gynecologists and Obstetricians endorsing the need for all deliveries to be attended by a caregiver trained in active management of third stage of labor, which should include routine use of uterotonics, controlled cord traction, and uterine massage ***(Dean et al., 2009).***

DEFINITION OF THIRD STAGE OF LABOR

The third stage of labor is the time from the birth of the baby to the expulsion of the placenta and membranes. Once the baby is born, the uterus continues to contract and reduce in size. There is a lack of full understanding of the physiology of the third stage of labor, but recent work using ultrasonography has demonstrated that the process of placental separation has three distinct phases ***(Herman, 2002).*** The first, or latent phase, consists of strong uterine contractions, which lead to thickening of the uterine muscle, thus causing a shearing force to occur between the elastic uterine wall and the more rigid placenta ***(Herman, 2002).*** Continued contractions lead to gradual separation of the placenta, commencing at one of the poles (most commonly the lower) and spreading slowly during the contraction or detachment phase until full separation occurs. This is followed by delivery of the placenta in the expulsion phase**.** Muscle fibers surrounding the maternal vessels contract to prevent excessive bleeding and the mother's coagulation system is activated temporarily ***(Herman, 2002).***

There is always some blood loss during the third stage of labor as the placenta separates and is delivered, but what might be considered a normal amount of loss is the subject of debate ***(Mousa, 2007).*** Nevertheless, some women can suffer from considerable blood loss during or after the third stage of labor. This can be a primary hemorrhage (within the first 24 hours) or a secondary hemorrhage (between 24 hours and six weeks) ***(McDonald, 2008).*** Postpartum hemorrhage (PPH) is commonly defined as a blood loss in excess of 500 mL ***(WHO, 2006),*** with severe hemorrhage being a loss of 1000 mL or more and very severe hemorrhage being a loss of 2500 mL or more ***(Penney, 2005)***. However, the impact of blood loss at birth on an individual woman can vary considerably and will depend not only on the volume of blood lost, but also on her general state of health, the speed of the loss, her hemoglobin (Hb) levels at the time and her coagulation system. It is well documented that blood loss is consistently under- or over-estimated by clinicians; although many centers do try to measure and record blood loss accurately ***(Razvi, 2008)***.

In well-nourished women, some consider that, in general, there is little impact from a blood loss of 500 mL, this being equivalent to a routine blood donation ***(Burnley, 2006),*** but in women in low-income countries who may be poorly nourished and anemic, this loss can cause considerable morbidity or mortality. It has been estimated that at least 25% of maternal deaths in a number of

countries are due to hemorrhage - mostly due to postpartum hemorrhage (PPH) ***(Khan, 2006).*** The vast majority of these happen in the developing world, and postpartum hemorrhage (PPH) is the leading cause of maternal mortality in sub-Saharan Africa ***(Lazarus, 2005).*** However, a study in Mexico reported that while the leading cause of maternal death was hemorrhage, two-thirds of bleeding-related deaths resulted from placental abruption, placenta accreta, placenta previa, and peripartum hysterectomy, rather than uterine atony. Significant morbidity does occur, though, from major bleeding due to uterine atony (poor contraction of the muscles in the uterus), which is far more common than the other causes of bleeding listed above ***(Romero-Gutierrez, 2007).***

There are two distinct approaches to the clinical management of the third stage of labor: expectant and active management ***(Maughan, 2006)***. However, a third approach is sometimes used that consists of a combination of components of both expectant and active management: this has been referred to as ’mixed management’ or the ’piecemeal approach’ Expectant, active and mixed management approaches, and comparisons of different types of active management, have been the subject of a number of critical reviews ***(McDonald, 2007 and Soltani, 2008).***

CLINICAL MANAGEMENT OF THIRD STAGE OF LABOR

(a) Expectant management of the third stage of labor:

Expectant management is also known as conservative or physiological management and is popular in some northern European countries**.** It is also practiced on occasion in midwife-led units and in home births in the United Kingdom and Ireland ***(Fry 2007; Kanikosmay, 2007 and Blackburn, 2008),*** and is the usual practice in domiciliary care in some parts of the developing world. The main principle of expectant management is a ’hands off ’ approach, where signs of placental separation are awaited and the placenta is delivered spontaneously or with the aid of gravity, maternal pushing or, sometimes, nipple stimulation ***(Inch, 1985; Prendiville, 1989),*** hence:

1. A prophylactic uterotonic agent is not administered;

2. Ideally the umbilical cord is neither clamped nor cut until the placenta has been delivered but, as a minimum, caregivers have waited until cord pulsation has ceased.

3. The placenta is delivered spontaneously with the aid of gravity and sometimes by maternal effort ***(Rogers, 1998).*** There can be variations within expectant management. For example, some caregivers will wait for the placenta to be delivered before clamping and cutting the cord whilst others, for convenience, just wait until

pulsation has finished. Breastfeeding or other means of stimulating the physiological release of oxytocin, such as nipple stimulation, is sometimes also used ***(Bullough, 1989)*** but is not an essential component of expectant management.

(b) Active management of the third stage of labour:

In active management of the third stage of labor, the clinician intervenes by using the following package of interventions ***(Prendiville, 1989):***

1. The routine administration of a prophylactic uterotonic drug just before, with, or immediately after, the birth of the baby.

2. Early cord clamping and cutting* (i.e. prior to, alongside, or immediately after administration of an oxytocic, which is before cord pulsation ceases); and

3. Controlled cord traction to deliver the placenta. * Current WHO recommendations ***(WHO, 2006)*** are to delay cord clamping, although the National Institute for Health and Clinical Excellence (NICE) still supports early cord clamping ***(NICE, 2007).***

Table (1): Advantages and Disadvantages of AMTSL and EMTSL ***(Ganges et al., 2007).***

	Expetant management of third stage of labor (EMTSL)	**Active management of third stage of labor (AMTSL)**
Advantages	Does not interfere with normal labor process	Decreases length of third stage.
	Does not require special drugs/supplies.	Decrease likelihood of prolonged third stage.
	May be appropriate when immediate care is needed for the baby (such as resuscitation) and no trained assistant is available.	Decreases average blood loss.
		Decreases the number of PPH cases.
	May not require a birth attendant with injection skills	Decreases need for blood transfusion
Disadvantages	Length of third stage is longer compared to AMTSL	Requires uterotonic and items needed for injection/injection safety
	Blood loss is greater compared To AMTSL	
	Increased risk of PPH	Requires a birth attendant with giving experience and injection skills

These interventions are implemented routinely and prophylactically in an attempt to reduce the blood loss associated with the third stage of labor and to reduce the risk of PPH. There are many possible variations with this package of interventions:

1. There are different uterotonic drugs that can be used, e.g. oxytocin (intravenous (IV) or intramuscular (IM)); syntometrine (IM); ergometrine (IV or IM); misoprostol (IM) ***(Cotter, 2001; Gülmezoglu, 2007; Liabsuetrakul, 2007; McDonald, 2007b and Su, 2007).*** There is also debate over the route of administration and dosage of the drugs used. However, recent guidelines from WHO, FIGO, ICM and NICE all recommend the use of 10 IU oxytocin IM ***(WHO, 2006 and NICE, 2007).*** Misoprostol is potentially the most important uterotonic for use in some low-income countries because it is stable at ambient temperatures and is inexpensive ***(Parsons, 2007)***. However, it does have adverse side effects ***(Mousa, 2007)*** such as shivering, nausea and headaches, and it has been shown to be less effective than other agents ***(Gülmezoglu, 2007).***

2. There are differing timings for giving the prophylactic uterotonic drug, e.g. with the crowning of the baby's head; with the birth of the anterior shoulder; immediately after the birth of the baby; after the birth of the baby but before the placenta is delivered ***(Harris, 2004)*** and after the placenta is delivered ***(Winter, 2007).*** The timing of

administration of uterotonic drugs is the subject of another Cochrane review ***(Soltani, 2006).***

3. There can be variation in the time when the cord is clamped and cut; this can be immediately the baby is born; within a set time after the birth, e.g. within 30 seconds, or a minute; or anytime before umbilical cord pulsation ceases ***(Rabe, 2004; Van Rheenan, 2007 and McDonald, 2008).***

4. There are also different timings for the initiation of controlled cord traction, such as waiting for signs of placental separation or not ***(McDonald, 2003).***

5. There can also be a delay in using the whole package of active management until after cord pulsation ceases, which has been described as 'delayed active management' ***(Gyte, 2006).***

6. Some guidelines add uterine massage to the active management package although there is little evidence to support this ***(Abdel-Aleem, 2010).*** Placental cord drainage is sometimes used with active management of the third stage. This involves releasing the clamp on the maternal end of the umbilical cord to allow the blood from the placental side to drain, thus reducing the size of the placenta and thereby hoping to help separation and reduce the chance of a retained placenta ***(Soltani, 2005).***

Some of these variations in the components of active management of the third stage of labor may no longer be