Sublingual versus oral misoprostol in preventing primary atonic post partum hemorrhage

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Summary

Postpartum hemorrhage is a major cause of morbidity and mortality both in developed and in developing countries [**Villar et al 2002**]. It is estimated that, worldwide, 140,000 women die of postpartum hemorrhage each year (one every 4 min) [**ACOG 2006**]. About 99% of these occur in developing countries in women who rarely receive prophylaxis because they deliver outside of a hospital setting [**Derman et al 2006**].

Post partum hemorrhage is defined as blood loss of More than 500 ml in the first 24 hours after normal vaginal delivery [**WHO 2003**].

Misoprostol was first reported by El-Refaey for use in the management of third stage of labor [**EL-Refaey et al 1996**].

In a systematic review that include 37 studies showed that the use of misoprostol was effective for reducing the amount of blood loss postpartum and in decreasing severe postpartum hemorrhage [**Gulmezoglu et al 2008**].

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Misoprostol is a prostaglandin E1 analogue that is not only has a strong uterotonic activity, but unlike other prostaglandins, it is inexpensive and is stable at room temperature. These two properties have attracted great interest in the drug as an affordable method for preventing and treating postpartum hemorrhage in both low and middle income countries **[WHO2009].**

However, the use of misoprostol has been associated with some side effects, as it significantly increases the postpartum shivering and fever **[shobhana et al 2009]**. In this regard, it was noticed that fever may reach above 40 degrees Celsius and may be

associated with altered consciousness with the use of 800 micrograms or more misoprostol [**WHO2009]**.

The sublingual route was identified as having the Greatest potential for treatment of primary post-partum haemorrhage because of its rapid uptake, long-lasting duration of effect, and greatest bioavailability compared with other routes of misoprostol administration [**Tang et al 2007**].

A recent study about pharmacological, physiological, and clinical evidence surrounding the use of misoprostol for the treatment of primary postpartum hemorrhage, found that the oral route of administration is the fastest but also the one associated with the shortest duration of action, The rectal route has slow uptake but prolonged duration of action and the buccal and sublingual route has rapid onset and prolonged duration of action with the greatest bioavailability [**Justus Hofmyer et al 2009**].

Moreover, another meta-analysis have shown that no evidence that 600 micrograms is more effective than 400 micrograms for preventing blood loss >500 ml[**Hofmyer et al 2009]** .Contrary to another study that had shown that the administration of sublingual misoprostol of 600 micrograms was more effective than the use of 400 micrograms of misoprostol for active management of third stage of labor[**Singh et al 2009**].

Chapter (1)

MANAGEMENT OF THE THIRD STAGE OF LABOR

Anatomy and Adaptation of the Uterus to Pregnancy:

(1) Hypertrophy and dilatation:

In the non-pregnant woman, the uterus is an almost solid structure weighting about 70 grams with a cavity of 10 milliliter or less. During pregnancy, the uterus is transformed into a relatively thin walled muscular organ of sufficient capacity to accommodate fetus, placenta and amniotic fluid. The average total volume of the contents of the uterus at term about five liters but may be 20 L or more, so that by the end of pregnancy the uterus has achieved a 500 to 1000 times greater capacity than in the non-pregnant state. There's a corresponding increase in uterine weight, and the body of the uterus at term weighs approximately 1100 g ***(Cunningham et al., 2001).***

During pregnancy, uterine enlargement involves stretching and marked hypertrophy of existing muscle cells, whereas the appearance of new muscle cells is limited. The myometrial smooth muscle cell is surrounded by an irregular array of collagen fibrils. The force of contraction is transmitted from the contractile proteins of the muscle cell to the surrounding connective tissue through the reticulum of collagen ***(Cunningham et al., 1997).***

Accompanying the increase in size of the uterine muscle cells during pregnancy, there's an accumulation of fibrous tissue, particularly in the external muscle layer, together with a considerable increase in elastic tissue. The network that is formed adds materially to the strength of the uterine wall. Concomitantly, there's a great increase in size and number of blood

vessels and lymphatics. The veins that drain the placental site are transformed into large uterine sinuses, and there's hypertrophy of the nerves examplified by the increase in size of the frankenhauser cervical ganglion ***(Russel et al., 1978).***

(2) Arrangement of the Muscle Cells:

Uterine musculature during pregnancy is arranged in three strata (1) an external hood-like layer, which arches over the fundus and extends into the various ligaments, (2) an internal layer, consisting of sphincter like fibers around the orifices of the tubes and the internal os; and (3) lying between these two, a dense network of muscle fibers perforated in all directions by blood vessels. The main portion of the uterine wall is formed by the middle layer, which consists of an interlacing network of muscle fibers between which extend the blood vessels. Each cell in this layer had a double curve, so that the interlacing of any two gives approximately the form of the figure eight. As a result of this arrangement, when the cells contract after delivery they consitrict the penetrating blood vessels and thus act as ligatures ***(Cunningham et al., 1997).***

(3) Control of Uteroplacental Blood Flow:

The increase in maternal-placental blood flow principally occurs by means of vasodilatation, whereas fetal-placental blood flow is increased by a continuing increase in placental vessels. ***Palmer et al. (1992)*** showed that uterine artery diameter doubled by week 21 and concomitant flow velocity was increased eight folds.

Using measurements of uterine resistance index, ***Juaniaux et al. (1994)*** found that both estradiol and progesterone contributed to the downstream fall in resistance to blood flow with advancing gestational age.

Biochemistry of smooth muscle contraction:

The basis of uterine contraction is the interaction between actin and myosin in myometrial smooth muscle. Myosin is comprised of multiple light and heavy chains and is laid down in thick myofilaments.

The interaction of myosin and actin, which causes activation of adenosine tri phosphatase (ATPase), ATP hydrolysis, and force generation, is affected by enzymatic phosphorylation of the light chain of myosin. This phosphorylation reaction is catalyzed by the enzyme myosin light chain kinase, which is activated by calcium ***(Stull et al., 1998).***

Moreover, calcium sensitization occurs via activation of Rho kinase, a calcium-independent pathway that promotes contractility by inhibiting myosin phosphates and probably by phosphorylating myosin on the same site as through Calcium-calmodulin (a calcium binding regulatory protein)-dependent myosin light chain kinase (MLCK) ***(Lopez, 2003).***

In the human myometrium, one of the most important signaling pathways is the adenylate cyclase-cyclic adenosine mono phosphate (CAMP) system, which can be activated by the corticotrophin releasing hormone (CRH) receptor ***(Grammatopoulos and Willhouse, 1999).***

Before term, the uterus undergoes activation and stimulation. Activation occurs in response to uterotropins, including estrogen, and is characterized by increased expression of a series of contraction-associated proteins (including myometrial receptors for prostaglandins and oxytocin), activation of certain ion channels, and an increase in connexin 43 (a key component of gap junctions). An increase in gap junctions between adjacent myometrial cells leads to electrical synchrony within the myometrium and allows effective coordination ***(Norwitz et al., 1999).***

Management of the Third Stage of Labor:

The third stage of labor begins immediately after delivery of the fetus and ends with the delivery of the placenta and fetal membranes so the third stage of labor is the stage of separation and expulsion of the placenta ***(Cunningham et al., 2001).***

Oxytocin is as effective as ergometrine at reducing the incidence of postpartum hemorrhage, but without the undesirable side effects of nausea, vomiting, and elevated blood pressure associated with ergometrine ***(Orji et al., 2007).***

Intraumbilical vein injection of oxytocin reduces the rate of placentas remaining undelivered beyond 15 minutes and subsequent blood loss. It shortens the third stage of labor ***(Ghulmiyyah et al., 2007).***

The duration of the third stage of labor:

Combs and Larros (1991) studied 12.275 singleton vaginal deliveries and reported the median duration of the third stage to be 6 minutes however 3.3% of patient duration of the third stage was more than 30 minutes also hemorrhage increased with third stage duration of 30 minutes or longer.

Pierre et al. (2000) found that cord traction increases the duration of the third stage of labor and reduces blood loss but does not decrease the incidence of manual removal of the placenta.

Bias et al. (2004) found that the most important risk factors of severe postpartum hemorrhage were related to an abnormal third stage of labor; third stage more than or equal 30 minutes and retained placenta.

Recently, a study was published concluded that a third stage longer than 18 minutes is associated with a significant risk of postpartum

hemorrhage. After 30 minutes, the odds of having postpartum hemorrhage are 6 times higher than before 30 minutes ***(Magann and Lanneau, 2005).***

Mechanisms of placental separation:

As the fetus is born, the uterus spontaneously contracts down to diminish its contents and now the uterine fundus lies just below the umbilicus. This sudden diminution in uterine size is accompanied by a decrease in the area of placental implantation site. So the placenta increases in thickness but because of limited placental elasticity it is forced to buckle and the resulting tension causes the weakest layer of the decidua which is the spongy layer or decidua spongiosa to give way and cleavage take place at this site. So the separation of placenta results from disproportion between the unchanged size of the placenta and the reduced size of the underlying implantation site ***(Cunningham et al., 2005).***

Separation of amniochorion:

The greatest decrease in the surface area of the cavity of the uterus immediately causes the fetal membranes and deciduas to be thrown into innumerable folds that increase the thickness of the layer from less than 1 mm to 3-4 mm. The membranes usually remain in situ until separation of placenta is nearly completed then they are peeled off the uterine wall partly by traction by the separated placenta ***(Cunningham et al., 2005).***

Signs of placental separation:

1- The uterus becomes globular and as a rule, firmer. This sign is the earliest to appear.

2- Sudden gush of blood.

3- Elongation of the umbilical cord.

4- The uterus rises in the abdomen because the placenta has separated passing down into the lower uterine segment and vagina where its bulk pushes the uterus upward.

These signs appear within one minute after delivery of the infant and within 5 minutes the placenta is separated so any attempts to pull on the placenta prior to its separation are dangerous so it is important to wait until the appearance of signs of placental separation ***(Cunningham et al., 2005).***

Mechanism of placental expulsion:

There are two methods of expulsion of placenta either Schultze mechanism or Duncan mechanism.

Schultze mechanism:

The central part of placenta starts to separate so the retroplacental hematoma is believed to push the placenta towards the uterine cavity first the central portion and then the rest of the placenta is separated. As the surrounding membranes are still attached to the decidua; the placenta can descend only by dragging the membranes then pull of its periphery. So the sac formed by the membranes is inverted with the glistening amnion over the placental surface presenting at the vulva and the retroplacental hematoma either follows the placenta or found within the inverted sac ***(Cunningham et al., 2005).***

Duncan mechanism:

In this mechanism the separation of placenta start at the periphery and the blood collects between the membranes and the uterine wall and escapes from the vagina. In this circumstance the placenta descends to the vaginal side way with the maternal surface is the first to appear at the vulva ***(Cunningham et al., 2005).***

Methods of placental delivery:

There are two methods for delivery of placenta either:

**** Conservative method:***

After delivery of the fetus put the ulnar border of the left hand on the fundus and wait for signs of placental separation then massage the uterus when the placenta reaches the perineum hold it between hands and roll it to deliver the membranes completely. Suspect for any missing parts of placenta ***(Prendville et al., 1988).***

**** Active method:***

The active method is associated with less bleeding but more liability for retained parts, uterine inversion and rarely retained placenta from contraction ring of the uterus due to abuse of ecbolics ***(Miller et al., 2004).***

Active management of the third stage of labor consists of interventions designed to speed the delivery of the placenta by increasing uterine contractions and to prevent PPH by averting uterine atony.

The usual components are:

1. Giving an uterotonic drug within one minute of birth of the newborn.
2. Clamping and cutting the umbilical cord soon after birth.
3. Applying controlled cord traction to the umbilical cord while applying simultaneous counter pressure to the uterus through the abdomen after delivery of the placenta, massaging the fundus of the uterus through the abdomen also can help the uterus contracts to minimize further bleeding. Active management of the third stage of labor is commonly used in the United Kingdom, Australia and several other countries ***(Chong et al., 2004).***

There are two slightly different methods for delivery of the placenta:

***Brandt-Andrews method*:**

It is known also by controlled cord traction. After the fundus is firm, put the left hand on the suprapubic region and push the uterus upward and by the other hand do gentle downward backward traction on the cord simultaneously and when the placenta appears from the vulva it is rolled and examined for any missed parts ***(Wilson and Stillwill, 1996).***

Crede's Method:

The uterus is massaged to contract, the fundus is then squeezed between the thumb and 4 fingers to separate the placenta, then the contracted uterus is pushed downwards and backwards into pelvis to expel the separated placenta, this method should not be used to deliver the placenta as it may lead to the following complications:

1- It may lead to pain and shock.

2- Partial separation of the placenta and postpartum hemorrhage.

3- The supporting ligaments of the uterus may be stretched and lacerated leading to prolapse.

4- Inversion of uterus,if it is compressed while lax***(Cunningham et al., 2005)***

Hemostasis at the placental site:

Near term 600 ml/min of blood flows through the intervillous space. With separation of the placenta, there is also separation of many uterine arteries and veins that carry blood to and from the placenta. Usually, hemostasis in absence of surgical ligation depends on:

* Intrinsic vasospasm and formation of blood clots at the placental implantation site.

* Contraction and retraction of the myometrium to compress the vessels and obliterate their lumens ***(Cunningham et al., 2005).***

In the pregnancy, plasma fibrinogen levels are 300-600 mg/dL with activation of coagulation and these high levels protect against clinically significant hypofibrogenemia and promote clinical coagulation at placental site after delivery ***(Cunningham et al., 2001).***

Use of ecbolics:

Careful consideration should be given to the timing of administration and to the type of oxytocic drug used. It is customary to give intravenous (IV) or intramuscular (IM) ecbolics like oxytocin 10-20 international unit (IU), ergometrine 0.2-0.4 µg, or syntometrine with crowning of the head or at delivery of the anterior shoulder ***(Pritchard et al., 1985).***

In a review for the effect of oxytocin administration as an active management of third stage of labor, they concluded that routine use of oxytocic drugs, like ergometrine and oxytocin in association with management of the third stage reduces the risk of postpartum hemorrhage and the need for administration of the oxytocin later or the need for blood transfusion ***(Prendiville et al., 1988).***

The practice of prophylactic administration of parenteral oxytocics in the active management of the third stage of labor has led to a 30% to 40% reduction in the incidence of postpartum hemorrhage ***(Chong et al., 2001).***

Another study approved that bolus oxytocin of 10 IU is not associated with adverse hemodynamic responses and can safely be administered to

women with intravenous access in the third stage of labor for postpartum hemorrhage prophylaxis ***(Davies et al., 2005).***

In the third stage of labor one definition of active management includes directions to administer an uterotonic with birth of the anterior shoulder of the baby and to clamp the umbilical cord within 30-60 seconds of birth of the baby (which is not always feasible in practice). Delaying clamping of the cord for at least two to three minutes seems not to increase the risk of postpartum hemorrhage. In addition, late cord clamping can be advantageous for the infant by improving iron status which may be of clinical value particularly in infants where access to good nutrition is poor, although delaying clamping increases the risk of jaundice requiring phototherapy ***(McDonald and Middleton, 2008).***