Introduction

Maternal mortality is a catastrophe which affects not only the woman but also her family and the community at large. An estimated ٥١٥ ٠٠٠ women die yearly as a result of pregnancy related complication and about ٩٨٪ of these deaths occur in developing countries (**WHO, ٢٠٠١).**

The world Health Organization (WHO) estimated that ٥٢٩,٠٠٠ women died from obestetric causes in the year ٢٠٠٠ **(WHO**, **٢٠٠٤).** In Egypt a maternal mortality rate in (٢٠٠٥) was ٦٥ maternal deaths per ١٠٠,٠٠٠ live birth and this equal to ٣٤٩ maternal deaths due to direct obstetric causes **(Central Agency for Public Mobilization and Statistics, ٢٠٠٧).**

Hemorrhage remains in the top five causes of maternal death in the UK and other countries, both developed and developing **(UK /Department of Health, ١٩٩٨).** In the developing world at least one woman dies in childbirth every minute, of whom ١٥-٢٥٪ die from PPH **(Baskett, ٢٠٠٠).**

There are an estimated ١٤ million cases of pregnancy related hemorrhage every year worldwide, and at least ١٢٨٠٠٠ of these women bleed to death, especially within ٤ hours of birth, from uterine atony due to poor management of the third stage of labor **(WHO, ١٩٩٨; Thornburg et al., ٢٠٠٠).**

There is simply not enough time to seek treatment for PPH. The only way to help women is through preventive measures **(Langenbach, ٢٠٠٦).**

Postpartum haemorrhage is potentially life threatening and is a signifcant contributor to maternal mortality and morbidity worldwide **(McCormick, et al., ٢٠٠٢).**

Postpartum hemorrhage was defined as blood loss of greater than ٥٠٠ ml after giving birth vaginally or as blood loss greater than ١٠٠٠ ml after cesarean section; however the quantity of blood loss doesnot always accurately define the pathology, since for certain individuals a loss of as much as ٥٠٠ ml after vaginal birth is considered within normal limit **(El-Refaey and Rodeck, ٢٠٠٣).**

Postpartum hemorrhage would be better defined as the peripartum fall in haemoglobin (or haematocrit) level of at least ١٠٪ as suggested by the **(American College of Obstetricians and Gynecologists, ١٩٨٩).**

The clinical significance of the diagnosis of postpartum haemorrhage is still open to question. the frequency of postpartum haemorrhage have been high: ٥٪ to ١٦٪ with no treatment and ٢,٥٪ to ١٤,٨٪ with active treatment **(McDonald, et al., ١٩٩٣).**

Postpartum hemorrhage remains an important cause of maternal mortality in developing countries, though the mortality rate has dramatically decreased in Western countries during the twentieth century. This change has coincided with the introduction of oxytocic drugs in the management of the third stage of labour **(Dudley, ١٩٣٥),** though other factors may

also have contributed to this improvement (e.g. improved nutritional status and socio-economic standards, and the availability of blood transfusion services).

Nonetheless, postpartum hemorrhage is still associated with substantial maternal morbidity mainly due to anemia and infections.Meta-analysis of controlled trials has shown the frequency of postpartum hemorrhage to be reduced by ٤٠٪ when routine oxytocic treatment is used **(Prendiville et al., ١٩٨٨)**.

Combs et al. (١٩٩١) identified many factors associated with significant risk for postpartum hemorrhage. Prolonged third stage of labour had the strongest association with postpartum hemorrhage. The third stage of labour commences after delivery of the infant and ends with delivery of the placenta and the membrane, and thus is an event related to the process of labour **(Beazley, ١٩٩٦).**

Despite the many strategies employed for active management of the third stage of labor, there has not been a significant consistent reduction in the postpartum haemorrhage rates reported in industrialized countries in recent times **(McDonald, ٢٠٠٧).**

Various prophylactic strategies have been used to prevent this potential life threatening emergency, the active management of third stage of labour, particularly the prophylactic use of uterotonic agents can significantly decrease the incidence of

postpartum hemorrhage compared with that of expectant management **(Elbourne et al., ٢٠٠٣, McDonald et al., ٢٠٠٤).**

An ideal uterotonic agent should promote prompt, strong and sustained uterine contractions without any significant adverse effects **(Leung et al., ٢٠٠٦).**

A synthetic prostaglandin E١ analogue – misoprostol – is only approved for prevention and treatment of NSAID-associated peptic ulcers. However, it has been extensively studied and widely used for obstetric and gynecological indications, such as prevention and treatment of postpartum hemorrhage ***(Mousa, Alfirevic. 2003).***

Aim of the Work

The aim of the work is to evaluate the effectiveness of the rectally administered PGE١ synthetic analouge (misoprostol) in a new suppository form compared to standard ecbolic therapy in the prevention of postpartum hemorrhage.

Suppositories are solid preparations which may contain one or more active pharmaceutical ingredient(s) intended for rectal application. They are normally used for local action or systemic absorption of the active ingredient(s).They usually melt, soften, or dissolve at body temperature.

Physiological Overview

Physiology of uterine contraction:

The myometrium is considered one of the unitary smooth muscle. The term "unitary" is confusing because it does not mean single muscle fiber. Instead, it means a whole mass of hundreds to thousands of smooth muscle fibers that contact together as a single unit. The fibers usually are aggregated into sheets or bundles, and their cell membranes are adherent to one another at multiple points so that force generated in one muscle fiber can be transmitted to the next. In addition, the cell membranes are joined by many gap junctions through which ions can flow freely from one cell to the next so that action potentials or simple ion flow can travel from one fiber to the next and cause the muscle fibers to contract together. This type of smooth muscle also is known as syncytial smooth muscle because of its syncytial interconnections among fibers **(Guyton and Hall, ٢٠٠١).**

It is shown that the myometrial cells are electrically coupled, such that electrical stimulation of one cell is followed by stimulation of adjacent smooth muscle cells. This results in a wave of contraction as in peristalsis. Moreover, this wave of electrical activity, and hence contraction, may be initiated by a pacemaker cell (i.e., a smooth muscle cell that exhibits a spontaneous depolarization) **(Ganong, ٢٠٠٣, Berne et al., ٢٠٠٤ and Baker, ٢٠٠٦).**

Regulation of myometrial contraction and relaxation:

The regulation of myometrial cell contraction versus relaxation can be divided temporally into acute and chronic mechanisms. Acutely, the interaction of myosin and actin is essential to muscle contraction. Myosin is comprised of multiple light and heavy chains and is arranged in thick myofilaments. The interaction of myosin and actin, which causes activation of adenosine triphosphatase, adenosine triphosphate 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. Calcium binds to calmodulin, a calcium-binding regulatory protein, which in turn binds to and activates myosin light chain kinase. In this manner, agents that act on myometrial smooth muscle cells to cause an increase in the intracellular cytosolic concentration of calcium ($Ca^{٢+}$) promote contraction. The increase in ($Ca^{٢+}$) is often transient, but contractions can be prolonged through the inhibition of myosin phosphatase activity by Rho kinase, which is activated in a receptor-dependent fashion. Conditions that cause a decrease in ($Ca^{٢+}$) favor relaxation. Ordinarily, agents that cause an increase in the intracellular concentration of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP) promote uterine relaxation. It is believed that cAMP and cGMP act to cause a decrease in $Ca^{٢+}$, although the exact mechanism(s) is not defined **(Cunningham et al., ٢٠٠٥).**

Myometrial cell contractions also can be greatly influenced by the chronic action of hormones on the contractile status of the cell. This influence can occur through the effects that mediate the transcription of key genes that depress or enhance the contractility of the cell. Considerable data indicate that uterine activity is influenced through the regulation of the so-called contraction-associated proteins (CAPs). These proteins include channels associated with smooth muscle excitation and contraction, gap junction components, and uterotonic stimulatory or inhibitory receptors **(Cunningham et al., ٢٠٠٥).**

The increase in the local concentration of prostaglandins increases myometrial cell $Ca^{٢+}$ levels, and triggers uterine contractions. A drop in the ratio of intrauterine progesterone levels to estrogen levels appears to be largely responsible for augmenting local prostaglandin levels and thereby abolishing uterine quiescence. At term, the increased activity of the enzyme ١٧β, ٢٠∝-hydroxysteroid dehydrogenase in the uterine tissue lowers the progesterone/estrogen ratio. This single enzyme reduces the ketone group at position ٢٠ of the steroid nucleus, thereby inactivating progesterone, and generates estradiol from estrone by reducing the ketone at position ١٧, thereby augmenting the estrogen effect. The fetal amnion and chorion also contribute prostaglandins **(Berne et al., ٢٠٠٤).**

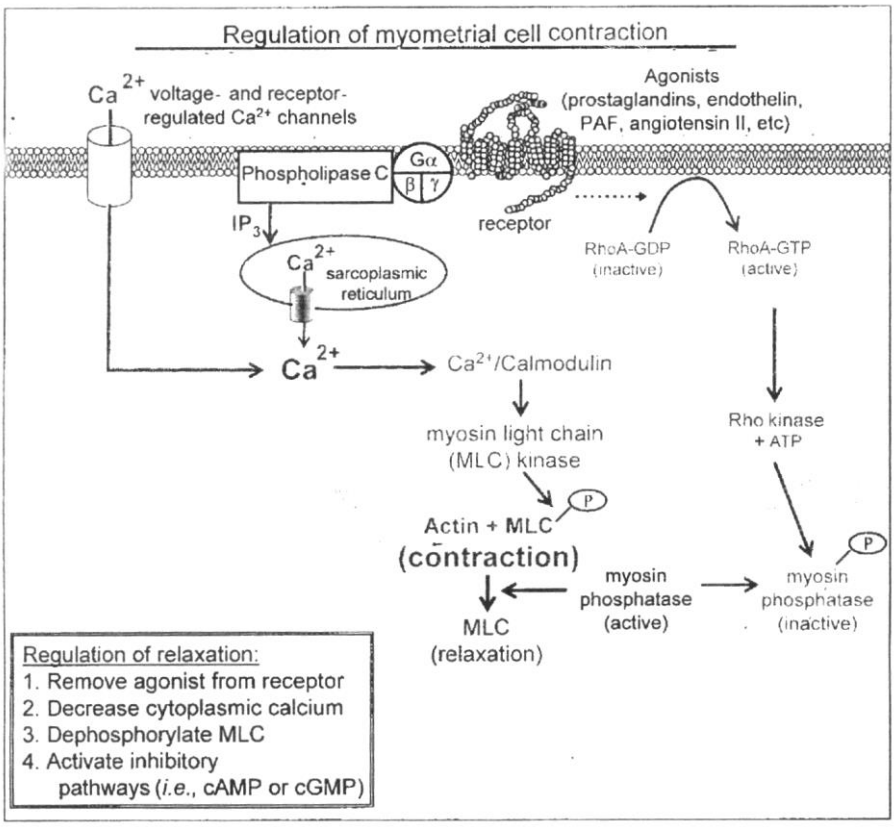

Figure (١): Regulation of myometrial smooth muscle cell contraction and relaxation. There are numerous agonists that bind cell surface receptors and activate phospho-lipase G and its production of inositol ١,٤,٥-trisphosphate (IPs). IPs will bind receptors on the sarcoplasmic reticulum and cause release of calcium ($Ca^{٢+}$) into the cytoplasm. $Ca^{٢+}$ can also be increased through voltage or receptor activated channels. $Ca^{٢+}$ will activate calmodulin, leading to increased activity of myosin, light chain kinase (MLC kinase) and phosphorylation of myosin light chain (MLC). Phosphorylated MLC interacts with actin, activating adenosine triphosphatase and, through the hydrolysis of adenosine triphosphate (ATP), generates the force needed for contraction. Contraction can be sustained by activation of the guanosine triphosphate (GTP) binding protein, RhoA, and Rho kinase, which will inhibit myosin phosphatase **(Cunningham et al., ٢٠٠٥).**

Another major stimulator of myomerial contractions is oxytocin. Although the concentration of oxytocin in maternal plasma does not increase consistently just before labour, the

frequency of oxytocin pulses. Furthermore, myometrial oxytocin receptor content rises dramatically at term, as does the local synthesis of oxytocin by the decidua and the fetal membranes. Oxytocin may therefore reinforce labour contractions, and it probably maximizes the contractions immediately after delivery, and thereby minimizes maternal blood loss **(Berne et al., ٢٠٠٤).**

Retraction is a major feature of uterine contractility during labour. This is the progressive shortening of the uterine smooth muscle cells in the upper portion of the uterus as labour progresses. After the cells contract, they relax, but they do not return to their original length. The result of this retraction process is the development of the thicker, active, contracting segment in the upper portion of the uterus. At the same time, the lower segment of the uterus becomes thinner and more stretched **(Baker, ٢٠٠٦).**

Anatomy and Adaptation of the Uterus to Pregnancy:

During pregnancy it is estimated that the mass of the uterus increases over ٢٠ times **(Kessel, ١٩٩٨).**

Hypertrophy and dilatation:

The non-pregnant woman, the uterus is an almost solid structure weighing about ٧٠ grams with a cavity of ١٠ 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 ٢٠ L or more, so that by the end of pregnancy the uterus has achieved a ٥٠٠ to ١٠٠٠ 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 ١١٠٠ g **(Cunningham et al., ٢٠٠١).**

Arrangement of the muscle cells:

The uterine musculature during pregnancy is arranged in three strata (١) An external hood-like layer, which arches over the fundus and extends into the various ligaments, (٢) an internal layer, consisting of sphincter like fibers around the orifices of the tubes and the internal os; and (٣) 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., ١٩٩٧).**

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. (١٩٩٢) showed that uterine artery diameter doubled by week ٢١ and concomitant flow velocity was increased eight folds.

Immediately after the placenta has separated from the wall of the uterus, the interlocking muscle fibers of the uterus contract. This occludes the blood vessels that were supplying the placenta and reduces blood loss. If the placenta has been attached to the lower uterine segment, the relative lack of muscle in this part of the uterus makes the hemostatic mechanism less efficient, and postpartum hemorrhage can occur **(Baker, ٢٠٠٦).**

Separation of the placenta occurs because of the reduction of volume of the uterus due to uterine contraction and the retraction (shortening) of the lattice-like arrangement of the myometrial muscle fibres **(Baker, ٢٠٠٦).**

The average diameter of the placental attachment is ١٨ cm, in the immediate postpartum uterus the average diameter of the site of placental attachment measures ٩ cm **(Gabbe et al., ٢٠٠٢).**

The Third Stage of Labor

Labor is the physiologic process by which a fetus is expelled from the uterus to the outside world. Labor is defined as an increase in myometrial activity (**Nathanielsz et al., ١٩٩٧**), resulting in effacement and dilatation of the uterine cervix. In normal labor, there appears to be a time dependent relationship between the biochemical connective tissue changes in the cervix, which usually precede uterine contractions and cervical dilatation **(Duff et al., ١٩٨٤).**

Stages of labor:

First stage:

The first stage of labor refers to the interval between the onset of labor and full cervical dilatation. It has been subdivided by **Friedman (١٩٥٥).** The latent phase is defined as the period between the onset of labor and a point at which a change in the slope of the rate of cervical dilatation is noted. The active phase is associated with a greater rate of cervical dilatation and usually begins at around ٢ to ٣ cm dilatation **(Peisner and Rose., ١٩٨٦).**

Second stage:

The second stage of labor is the interval between full cervical dilatation (١٠ cm) and delivery of the infant. The nulliparous patient is recommended to push for a maximum of ٢ hours without regional anesthesia (or ٣ hours with regional

anesthesia). The multiparous patient is recommended to push for a maximum of ١ hour without regional anesthesia (or ٢ hours with regional anesthesia) **(American College of Obstetricians and Gynecologists ACOG., ١٩٩٤).**

The third stage:

The thid stage of labor begins immediately after delivery of the fetus and involves the separation and expulsion of the placenta and membranes **(Cunningham et al., ٢٠٠٥).**

This normally takes between ٥ and ١٠ minutes. If longer than ٣٠ minutes, it should be regarded as prolonged.

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Management of the third stage:

The third stage of labor is perhaps the most dangerous part of labor for the mother, the main being postpartum hemorrhage **(McDonald et al., ١٩٩٣).**

Several complications encountered in the third stage of labour may lead to maternal morbidity. PPH may cause anemia or lead to poor iron reserve, ultimately contributing to anemia which may cause weakness and fatigue **(AbouZahr, ١٩٩٨)**.

Hospitalization may be prolonged, and the establishment of breast feeding may be affected. A blood transfusion may

ameliorate the anemia and shorten the hospital stay, but it carries risks of transfusion reaction and infection. Access to safe blood is not universal, and PPH can sometimes strain the resources of the best blood bank. Severe PPH, retained placenta, and uterine inversion may require emergency anesthetic services. Any exploration or instrumentation of the uterus increases the risk of sepsis **(AbouZahr, ١٩٩٨).**

In ١٩٨٨, Prendiville et al., showed that a policy of active management of the third stage was justified, but routine drug administration without specific indication is being challenged. In women at low risk of postpartum hemorrhage, recent studies have suggested that active pharmacological management does not reduce blood loss when compared with physiological management, and that routine use of oxytocic drugs benefits only seven women per ١٠٠ **(Thilaganathan et al., ١٩٩٣).**

Active management is superior to expectant management to decrease the risk of PPH **(McDonald, ٢٠٠٧).**

Expectant management of the third stage of labor:

Expectant management of the third stage of labor involves allowing the placenta to deliver spontaneously or aided by gravity or nipple stimulation **(Prendiville et al., ٢٠٠٠)**.

Nipple stimulation involves putting the infant to the breast or by nipple massage. Umbilical cord drainage, manual