A Comparative Study Of Rectal Misoprostol Versus Intravenous Oxytocin In Reducing Intra And Postoperative Bleeding During Elective Cesarean Section

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ABSTRACT

Background and Objectives :

To Compare the efficacy and safety of 400mcg misoprostol per rectum preoperatively versus intravenous oxytocin in reducing intra operative and post operative bleeding in elective caesarean section.

Methods :

The following study included 300 women who was admitted in Department of obstetrics and gynaecology, _____ as elective cases for cesarean section .Detailed history of all the patients were taken according to the performa and complete examination and all necessary investigations were done. After having met all the inclusion and exclusion criteria and obtaining written consent.

The study will include two groups.Group (A) MISOPROSTOL Group-150: women taken up for cesarean section were given preoperatively tablet misoprostol 400 microgram per rectal after spinal anesthesia before painting and draping was done. Group (B) –OXYTOCIN Group -150: women were given intravenous inj. oxytocin 10 IU in 500ml RL after extraction of baby in cesarean section.

Results :

The age varied from ≤20 years to >25 years. Most common age group was 21-25 years constituted total 185 (61.7%) patients. The mean age of Misoprostol and Oxytocin group was 22.88 and 22.92 years respectively. In the present study we observed the number of multiparous women were higher than primiparous women. Multipaous and primiparous women were 54.7% and 45.3% respectively in Misoprostol group; 64% and 36% in Oxytocin group. The commonest side effect of Misoprostol in the study subjects was shivering accounts for 22% (33) patients

followed by fever constituted for 6% (9) patients. In Oxytocin group nausea and vomiting was observed as side effects constituted 8% patients each. While analyzing for side effects we found a highly significant difference in two groups.

Conclusion :

The above results indicate that in the context of active management of 3rd stage of labour, Misoprostol has comparable effectiveness to oxytocin (10 IU IV in 500 ml RL) in the prevention of early postpartum haemorrhage. However, misoprostol was associated with higher incidence of shivering and pyrexia but no other serious adverse effects occurred. Hence, rectal misoprostol can be safely used in low risk caesarean deliveries as an alternative to 10 IU oxytocin in AMTSL. It should be included as an alternative in delivery protocols and also added to the list of essential drugs for affordable access. In future it may be an important and effective option for the management of third stage labour particularly in women where oxytocin is contraindicated.

Key words : Postpartum hemorrhage; Misoprostol; oxytocin

LIST OF ABBREVATIONS USED

µg	:	Microgram
AD	:	After delivery
AOM	:	Age of menarche
ARM	:	Artificial Rupture of Membranes
B.P.	:	Blood Pressure
B.W.	:	Birth weight
BD	:	Before Delivery
BMPMC	:	B M Patil Medical College Vijayapur
C/O	:	Complains of
CNS	:	Central Nervous System
CVS	:	Cardio Vascular System
CS	:	Caeserean section
DBP	:	Diastolic blood pressure
DM	:	Diabetes Mellitus
DOA	:	Date of admission
DOD	:	Date of discharge
EDD	:	Expected Date of Delivery
FHS	:	Fetal Heart Sound
G	:	Gravida
H/O	:	History of
Hb	:	Haemoglobin
Hrs	:	Hours
HTN	:	Hypertension
I.M.	:	Intramuscular
L	:	Live
LMP	:	Last Menstrual Period

mg	:	Milligram
Mins	:	Minutes
ml	:	Milliliter
NS	:	Not significant
P	:	Para
P/A	:	Per Abdomen
PPH	:	Postpartum haemorrhage
PR	:	Pulse rate
PR	:	Pulse Rate
PV	:	Per Vagina
RHD	:	Rheumatic Heart Disease
RR	:	Respiratory Rate
RS	:	Respiratory System
S	:	Significant
SBP	:	Systolic blood pressure
I.V.	:	Intravenous

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INTRODUCTION

Deliveries by caesarean section (CS) is one of the most widely performed obstetric activities everywhere throughout the world[1]. By and by it opens ladies to the danger of abdominal procedure, damage to the pelvic structures, may leads to requirement for blood transfusion[1]. During end of pregnancy blood supply of uterus is 500-750 ml/min.[2]

Due to huge blood supply there is bood loss of approximately 1000ml during CS[3].Many factors would be implicated to affect intra-operative blood loss during CS e.g. maternal causes; weight, parity, previous CS, foetal causes; multiple gestation, polyhydramnious, malpresentation, technical causes; operative time, type of incision, placental separation technique, placental position and the type of anaesthesia. Consequently, judicious estimation of operative blood loss during CS is very much significant for abating peri-operative morbidity and mortality and refraining need and risks of unwanted blood transfusion[4].

Intra-operative estimation of blood loss for CS is both poorly reproducible and typically an under-estimate[5].Therefore comparison of surgical blood loss is a challenging exercise and it varies from one institution to another.

There are diverse projects that had been endeavour to evaluate intra-operative blood loss[6]. Most conventional practice of assessing blood loss by operative staff is through perception in spite of being claimed to be notorious by some investigators[7]. Not only anesthesiologist but also obstetricians follows visual estimation of blood loss[8].

PPH is sorted as essential on the off chance that it happens within 24 hours of conveyance and auxiliary if inordinate blood loss happens at 24 hours or progressively after the conveyance. Most cases are primary PPH and the time from starting to death is shorter than other major obstetric entanglements. Death from PPH has been seen because of two important factors. The first one is due to low level of haemoglobin that affects the survival rate of women from PPH.[9] according to World Health Organization (WHO) " anemia in pregnancy as Hb level <11 g/dl anemia in developing countries" has been noted more than 50%[10]. Risk of low Hb and PPH has a very good correlation and need of emergency hysterectomy as well [11]. Anemia can be recognized during pregnancy however early recognition and management are not continually encouraging in spots where constrained access to quality antenatal consideration and is additionally included by dietary lacks and simultaneous co-morbidities influencing iron assimilation [12,13.] The second factor that has been viewed as contributing factors to death rates from PPH has more switches for impact, as it identifies with accessibility to an emergency clinic and facilities for management of Post partum haemorrhage, including blood donation centres and prepared staffs to analyze and treat PPH. In the mean time the management of PPH may additionally confounded by deferred diagnosis[9.]

The most well-known reason for Postpartum haemorrhage is atonicity of uterus which is in charge of roughly 70% of primary PPH. With the expanding occurrence of caesarean section, PPH may turn out to be increasingly basic since the normal blood loss while caesarean area is double that of during vaginal conveyance.[14.] Despite the fact that the utilization of intravenous oxytocin, which is pushed either bolus or an imbuement, as a first-line management to avoid uterine atonicity and lessen blood loss during caesarean section, In 10–42% of ladies extra utero-tonics are

needed those who are receiving only oxytocin such as ergot alkaloids and prostaglandins[15,16.] Now and then, oxytocin may not be an ideal drug for avoidance of PPH in patients with pre-eclampsia, prolonged labor or cardiac disease, since it can cause tachycardia and hypotension ,or water retention[17,18.] as it likewise has negative inotropic, antiplatelet and antidiuretic effects[17.] Oxytocin has both light and heat sensitive properties, and requires refrigerator for storage, which restrains its utilization in developing nations and in rural settings.

Misoprostol is a prostaglandin E1 (PGE1) analogue, it is not only strong utero-tonic through selectively binding E–series prostanoid receptors (Ep2/Ep3)[19.]but it is relatively inexpensive and stable at room temperature unlike other prostaglandins. It has different routes of administration that makes it ease of use[20.] This favours a big advantage to use in PPH where all facilities are not available. However different studies showed inconsistent reports regarding oxytocin and misoprost. Several randomised trials has shown the efficacy of reducing blood loss by use of misoprostol[21-23] . Through multicentre randomised trial demonstrated by WHO showed that 10 international units (IU) of oxytocin either through intramuscular or intravenous route was found to be superior to 600 μg of per rectal misoprostol in active management of the third stage of labour[24]. Some time due to side effects of misoprostol such as shivering ,pyrexia and nausea vomiting limit its use[27].The use of oxytocin has been preferred by WHO in the prevention of PPH during the third stage of labour as compared to misoprostol through orally, sublingually or rectally[28.]

Due to lack of proper study regarding efficacy and effectiveness of misoprostol during caesarean section , it has been documented that misoprostol is equally safe and effective in third stage of labor to control excessive blood loss, there is no a systematic and comprehensive summary has been published regarding the

pertinent evidence[29-33]. We therefore performed a meta-analysis to compare the efficacy and safety of rectal misoprostol with those of oxytocin in during and after caesarean section to see intra and post-operative blood loss.

OBJECTIVE OF THE STUDY

To Compare the efficacy and safety of 400mcg misoprostol per rectal preoperatively before skin incision, within one minute of spinal anaesthesia versus intravenous oxytocin 10U in 500ml RL after extraction of baby in reducing intra operative and post-operative bleeding in elective caesarean section.

NEED OF THE STUDY

Caesarean section is the most major surgical procedure performed on women worldwide and its rates are continuously rising both developed and developing countries. Based on world health statistic 2016, MMR(Maternal Mortality Rate) of India is 174/100,000live birth versus 12/100,000 in developed countries. Thus 99% of maternal death occur in developing countries with more of than half these death occur in Sub-Saharan Africa and all most in south Asia, within countries maternal deaths being most among low income group and rural areas as compared to high income group and urban area.

Though the third stage of labour constitutes short span of time, it is the phase of maximum mortality and morbidity.

Mean amount of blood loss is 500ml during vaginal delivery and 1000ml during in caesarean section. Bleeding can be reduced by 60% using active management of 3rd stage of labour.

There are different utero-tonic agents, like Oxytocin, Methyl-ergometrine and 15 methyl PGF2 etc. These agent are given by injection which require sterile needle and syringes, special storage conditions, not stable at room temperature, given parenterally and expensive.

Now a days, Misoprostol has become an important drug in obstetric practice and had many advantages like longest shelf life, does not required refrigeration, has less side effect.

In contrast to misoprostol, at high doses, Oxytocin has some limitation like it is not a safe drug for use in severe pre-eclamsia, heart disease, it has negative ionotropic, antiplatelet and anti-diuretic effect.

Recent studies have estimated that the prevalence of postpartum haemorrhage after CS ranges from 0.6% to 6.4%(median 3%) although frequency depends upon the criteria used to define the condition and methods to estimate blood loss.

MISOPROTOL,a prostaglandin E1 analogue with strong utero-tonic properties has been suggested as an alternative to injectable utero-tonic in preventing postpartum haemorrhage following vaginal and CS.

For this study,Misoprostol though rectal route is chosen because of practical advantages of rectal use namely ease of administration,patient compliance,less gastro-intestinal symptoms.

The mean Tmax after rectal misoprostol administration is 40minutes.This is thought to be beneficial when Misoprostol is given prior to surgery as by the end of CS the maximum effect will be obtained.

This study will assess the safety and efficacy of preoperative per rectal misoprostol versus 10U oxytocin in 500ml RL intravenous for elective CS to reduce intraoperative and pots operative bleeding.

REVIEW OF LITERATURE

PHYSIOLOGY OF THIRD STAGE OF LABOUR

Definition:

The third stage of labour is defined as the interval from the complete extraction of fetus to the complete expulsion of the placenta and membranes, and firm contraction and retraction of the uterus subsequently.[34]

The third stage of labour commences with the delivery of the infant and ends with the delivery of the placenta[35]. The normal case can become abnormal within a minute and successful delivery can turn swiftly to a disaster if neglected[36].

Obstetric tradition has set somewhat arbitrary limits on third-stage duration.The average duration of third-stage in singleton vaginal deliveries is found to be 6 minutes[37].The third-stage usually lasts between 5 and 15 minutes, but any period upto 1 hour may be considered to be abnormal limits[38].The average duration is reduced to 5 minutes from 15 minutes with active management of labour[39].In about 3% of such women, the duration of third stage was more than 30 minutes with an increasing incidence of complications[37].

Physiology of Third Stage of Labour:

The physiology of third-stage of labour is a continuation of the processes and forces that work during the earlier stages of labour.[38]

The phenomenon of the third stage of labour includes:

1. The characteristic uterine contraction
2. The separation of the placenta

3. The expulsion of the placenta
4. The control of haemorrhage and
5. The permanent contraction and retraction of the uterus

The factors involved in the third stage of labour are[35]

1. Stage of placental separation
2. Placental descent
3. Expulsion of the placenta

Placental Separation:

Contraction and retraction of the uterine muscle brings out the separation of the placenta. There is no appreciable diminution of the surface area of the placental attachment during the first stage. While in the second stage, there is slight but progressive diminution of the area following successive retraction which attains a peak immediately following the birth of the baby[39].

The contraction and retraction of the uterine muscle, thickens the wall and reduces the capacity of the upper uterine segment, while the lower segment is thrown into folds.

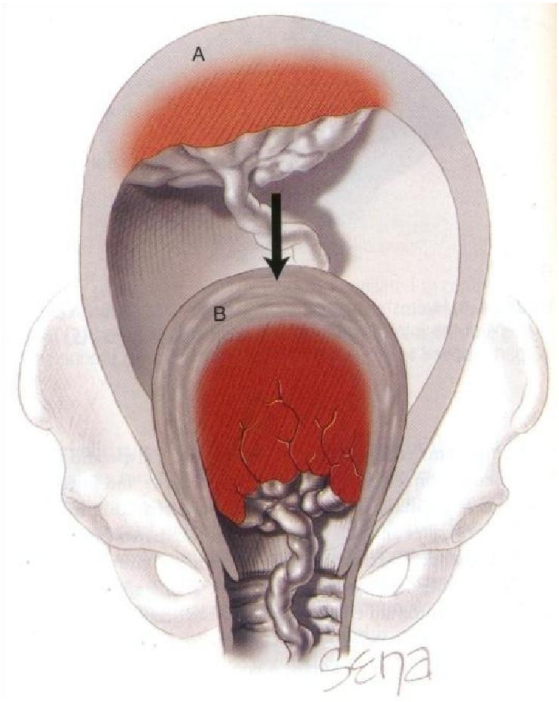
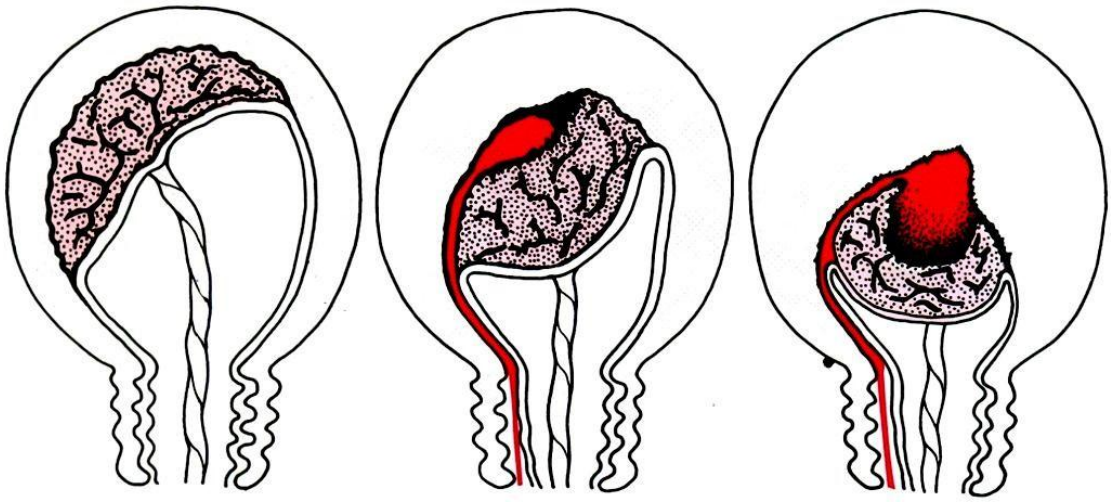


Fig.1 Diminution in size of the placental site after the birth of the infant

Mechanism of Separation:

The surface area at the placental site is reduced to about its half by marked contraction. It cannot keep pace with the diminution resulting in its buckling as the placenta is inelastic. The placenta itself becomes squeezed and the blood in the intervillous spaces is forced back into the spongy layer of the decidua. Retraction of the oblique muscle fibers, exerts pressure on the blood vessels so that blood does not drain back into the maternal system[40]. As a result the vessels become tense and congested, and with the next contraction, the vessels burst and 30 to 60 ml of blood seeps between the thin septa of the spongy layer and the placental surface, stripping the placenta from its attachments. The placenta is then forced out of the upper segment into the lower segment, and finally into the vagina[40].



A B C

Fig 2. The mechanism of placental separation

A. Uterine wall partially retracted but not sufficient to cause placental separation.

B. Further contraction and retraction thicken uterine wall, reduces placental site and aid placental separation.

C. Complete separation and formation of the retroplacental clot.

Note: The thin lower segment has collapsed like a concertina following the birth of the baby.

Separation of the Membranes:

The membranes which are attached loosely in the active part are thrown into multiple folds. Those attached to the lower segment are separated during its stretching. The separation is facilitated partly by uterine contraction and mostly by weight of the placenta as it descends down[41].

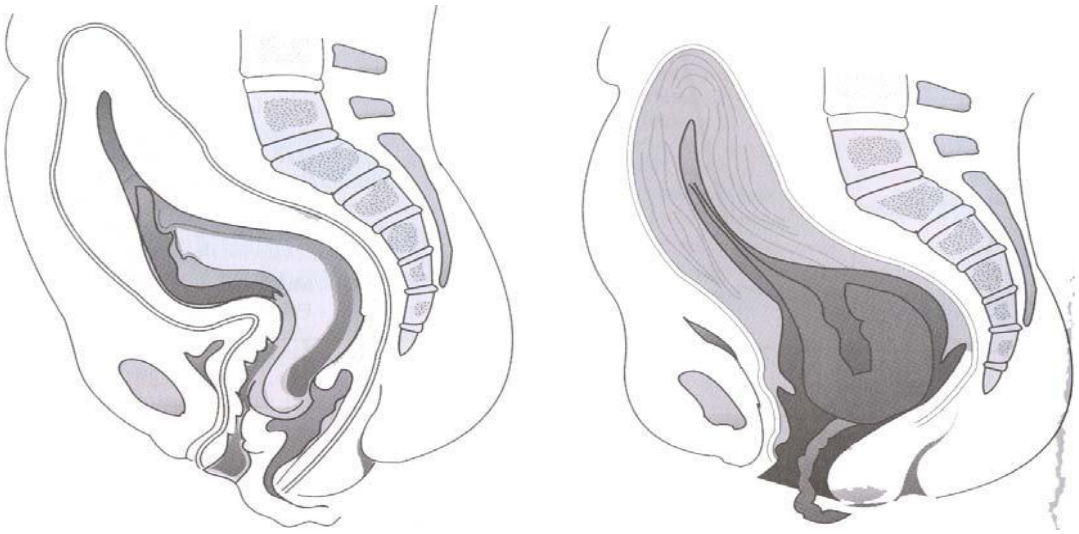
Expulsion of placenta:

After complete separation of the placenta, it is forced down into the flabby lower segment or upper part of the vagina by effective contraction and retraction of the uterus. It is expelled out by either voluntary contractions of abdominal muscle (bearing down efforts) or by manipulative procedure[41].

Placental Expulsion:

There are two methods by which placental expulsion may occur

1. Schultze Method (central separation)
2. Mathew - Duncan Method (marginal separation)



Duncan's Schultze's

Fig 3: The mechanism of expulsion of placenta

1. **Schultze Method:**

It is the commonest method of placental expulsion. Detachment of placenta from its uterine segment starts at the centre resulting in opening up of few uterine sinuses and accumulation of blood behind the placenta (retroplacental haematoma). With increasing contraction, more and more detachment occurs facilitated by weight of the placenta and retroplacental blood until whole of the placenta gets detached[41].

The placenta slips down into the vagina through the hole in the amniotic sac: the fetal surface appears at the vulva with the membranes like an inverted umbrella as they are peeled off the uterine wall. The maternal surface of the placenta is not seen, and any blood clot is inside the inverted sac[42].

2. **MathewDuncan Method:**

The placenta slides down sideways and comes through the vulva with the lateral border first. The maternal surface is seen and the blood escapes[42].

In this type of separation, on account of the contraction of the uterus, the placenta may be folded on itself, so that the long axis of placenta corresponds to the axis of the uterus. The margin that presents at the cervix or vagina is the lower margin, showing a little of the fetal surface[34].

Clinically central separation is much more common than marginal separation. And it is not possible to predict which method of separation is going to happen in a particular case nor does it have any clinical importance.

Mechanism of Control of Bleeding:

The normal volume of blood flow through the placental site is 500-800 ml per minute. At placental separation this has to be arrested within seconds or serious hemorrhage will occur[40]. The interplay of three factors within the normal physiological processes which control bleeding are critical in minimizing blood loss and the serious sequel of maternal morbidity and, or mortality which may result. These are:

1. Living ligature
2. Thrombosis 3.Myotamponade

1. Living Ligature:

The intermediate layer of the myometriurn is formed by interlacing muscle fibres which are of the shape of figure of eight around the blood vessels or in a trellis fashion[8]. The contraction of these fibres, closes the gaps of the trellis and thus occludes the blood vessels.

Retraction of the oblique uterine muscle fibres in the upper uterine segment causes thickening of the fibres. This exerts pressure on the torn vessels, and efficiently clamps them, thereby securing a „ligature" action. For this reason these muscle fibres are known as „living ligatures" and occlusion is brought about by complete retraction.

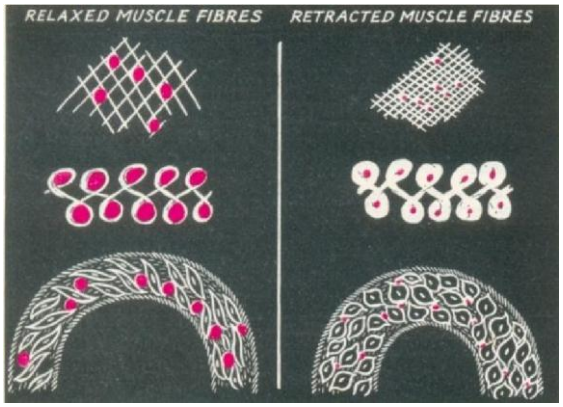


Fig.4: Living ligature

It is the absence of the oblique fibres in the lower uterine segment that explains the greatly increased blood loss that usually accompanies placental separation in placenta previa[40].

2. Thrombosis:

Thrombosis occurs to occlude the torn sinuses, a phenomenon which is facilitated by the hypercoagulable state of pregnancy[41]. There is evidence to suggest that there is a transitory activation of the coagulation and fibrinolytic system, during and immediately following, placental separation[43]. It is also believed that this protective

response is especially active at the placental site so that clot formation in the torn vessels is intensified. Following separation, the placental site is rapidly covered by fibrin mesh utilizing 5-10% of the circulating fibrinogen[40].

3. Myotamponade:

The presence of vigorous uterine contraction following separation brings the walls into apposition so that further pressure is exerted on the placental site[40].

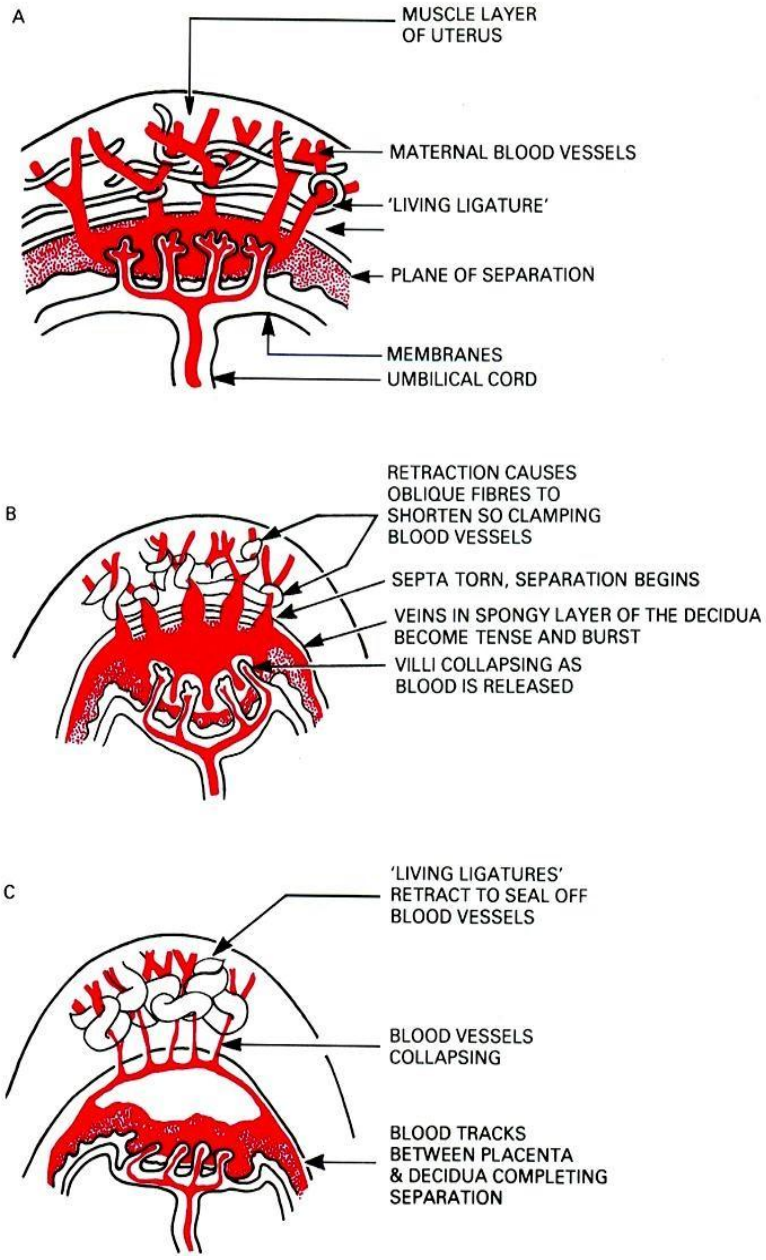


Fig 5. The placental site during separation

A. Uterus and placenta before separation

B. Separation begins

C. Separation complete

Signs of Placental Separation[44]:

Attempts to express the placenta prior to its separation are futile and possibly dangerous; hence it is important that the signs of placental separation be recognized.

- The uterus becomes globular, and as a rule firmer. This sign is the earliest to appear.
- There is often a sudden gush of blood.
- The uterus, rises in the abdomen because the placenta, having separated, passes down into the lower uterine segment and vagina where its bulk pushes the uterus upwards. The fundus of the uterus rises above the umbilicus.
- There will be a soft elevation above the symphysis with a depression immediately above, indicating that the placenta has separated from the fundus and is lying in the lower uterine segment.
- The extra-vulval portion of the cord lengthens.

If the fundus of the uterus is gently grasped and raised, the cord will not recede if the placenta has separated whereas if the placenta is still adherent to the uterus, the portion of the cord just outside the vulva will be drawn into the vagina.

Expulsion of the Placenta:

Placental expulsion should never be forced before the placental Separation[35]. Only when the features of placental separation and its descent into the lower segment are confirmed, the patient is asked to bear down simultaneously with the hardening of the uterus. As soon as the placenta passes through the introitus, it is grasped by the hands and twisted round and round with gentle traction, so that the membranes are stripped intact. If the membranes threaten to tear, they are caught hold by sponge holding forceps and in similar twisting movements the rest of the membranes are delivered.

Gentleness, patience and care are the prerequisites for the complete delivery of the membranes. If the patient fails to expel, one can wait safely up to 20 minutes if there is no bleeding. But if the spontaneous expulsion fails or is not practicable, anyone of the following methods can be used to expedite expulsion.

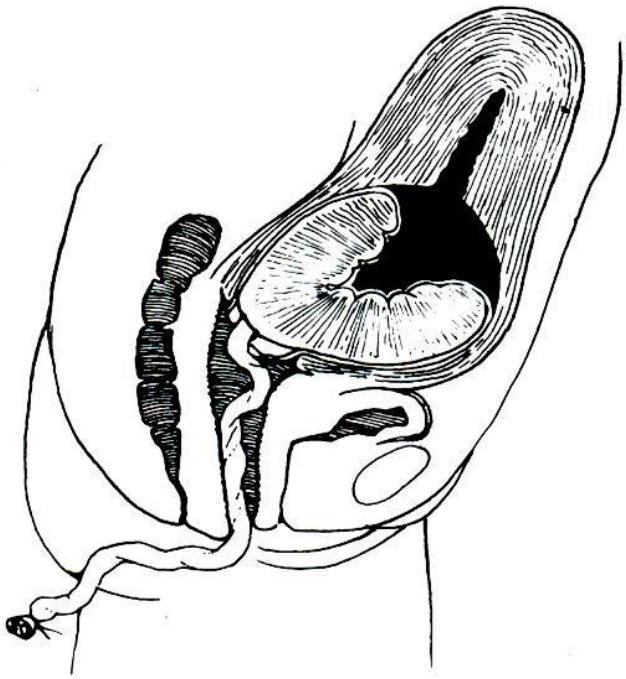


Fig.6: Third stage. Placenta in lower uterine segment

1.Brandt-Andrews Technique (Controlled Cord Traction):

Checks to be made before proceeding to controlled cord traction:

- That an uterotonic drug has to be administered
- That it has been given time to act
- That the uterus is well contracted
- That countertraction is applied
- That the signs of placental separation and descent are present[45].

It is the most commonly employed method of assisted expulsion of placenta by controlled cord traction. The uterus is palpated to confirm its contraction and once it is confirmed, controlled cord traction is instituted with attendant standing on the right side of the patient. The palmar surface of the fingers of the left hand is placed above the pubic symphisis approximately at the junction of upper and lower uterine segment. The body of the uterus is pushed upwards and backwards, towards the umbilicus while by the right hand steady tension is given in downward and backward direction holding the clamp until the placenta comes outside the introitus. It is thus more of an uterine elevation which facilitates expulsion of placenta[39].

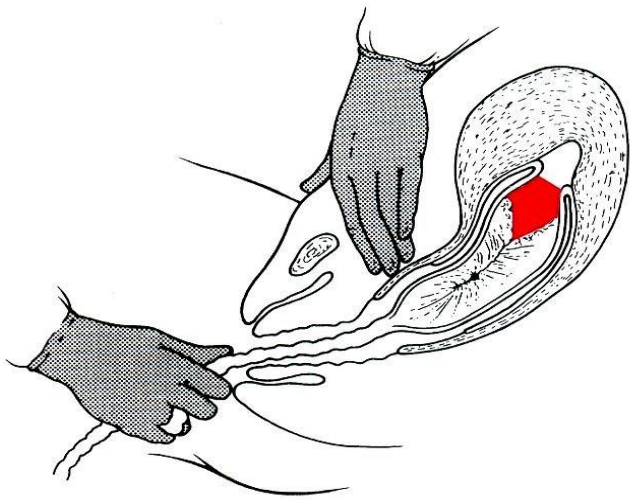


Fig. 7 Controlled cord traction

2. Crede Method:

Crede‟s method of delivering the placenta *was* associated with many complications like inversion of uterus, hour glass contraction and shock. Because of these complications it was abandoned and has now disappeared from practice.

A common method is to pass the fingers behind the body of the uterus and to squeeze the front wall with the opposed thumbs. The upper part of the uterus should be squeezed first, and in doing so the uterus should not be driven down into the depth of the pelvis, which is both shocking and ineffectual[36].

Crede‟s expression should never be attempted unless the uterus has contracted.

3. Manual Removal of Placenta:

If placenta is not expressed with these usual methods in a usual time limit or if patient is bleeding excessively before the expulsion of placenta, then one can proceed in a matter of seconds to manual removal of placenta. If there is time to give anesthesia, the patient is anaesthetized with some quick-acting anesthetic or can also be done under intravenous sedation. Bladder should be catheterized. Under aseptic precaution, one hand in the shape of a cone is insinuated into the vagina, cord is followed until the placenta is found. The other hand meanwhile should steady the fundus of the uterus and prevent it, from being pushed up towards the costal margin. During manual removal of the placenta the uterus is very much inclined to relax, with the result that the internal hand has to be introduced almost to the entire length of fore arm if this precaution is not taken. Having reached the insertion of the cord in the placenta the periphery is sought and now proceeded to separation by working from above downwards, so far as possible the fingers should be kept together. Once whole of the placenta is detached within the uterine cavity, it is best delivered traction on the cord, retaining the hand inside the uterus for final exploration of the cavity[46].

COMPLICATIONS OF THIRD STAGE OF LABOUR

Of all the stages of labour, third stage is the most crucial one for the mother.

The Complications of the Third Stage of Labour are[46]:

1. Postpartum Haernorrhage
2. Retention of placenta
3. Shock
4. Pulmonary embolism
5. Uterine inversion

POSTPARTUM HAEMORRHAGE

In spite of marked improvements in management, postpartum haemorrhage remains a significant contributor to maternal morbidity both in developing countries and in hospitals equipped with all modern medicine has to offer[47].

Prevention, early recognition and prompt appropriate intervention are keys to minimizing its impact.

Postpartum haemorrhage is the third major cause of maternal mortality next to pregnancy induced hypertension (preeclampsia) and infection[48].

Primary postpartum haemorrhage is the loss of blood in excess during the first 24 hours after birth of the infant. When it occurs between 24 hours after delivery and within puerperium it is designated as secondary postpartum haemorrhage[46].

Pritchard has shown that mean blood loss with vaginal and caesarean section is 500m1 and 1000 ml respectively[48]. Any greater loss is termed as postpartum hemorrhage.

Another proposed definition for PPH is a 10% change in haematocrit[49].

Coombs has suggested a clinical definition of "need for blood transfusion".

This definition is complicated by large variations in practice patterns and attitudes towards transfusion by both patients and physicians[49].

The diagnosis of PPH therefore remains a clinical assessment that includes any amount of blood loss that threatens the women's haemodynamic stability. Any amount of bleeding from or into the genital tract following birth of the baby up to the end of the puerperium which adversely affects the general condition of the patient as evidenced by rise in pulse rate and falling blood pressure is called postpartum hemorrhage.

However, the degree of haemodynamic compromise or shock parallels the amount of blood lost. Some women experience mild symptoms and maintain their blood pressure at a blood loss of 500 to 1000 ml (10 to 15percent of circulating volume), losses of 2000 to 3000 ml (35 to 45 percent of circulating volume) will cause marked hypotension, with cardiovascular collapse, air hunger, anuria and severe shock[47].

Table 1: Clinical findings in PPH[47]

Findings	**Degree of Shock**			
	Compensation	**Mild**	**Moderate**	**Severe**
Blood loss	500 - l000ml 10 - 15%	1000 - l500 ml 15-25%	l500 – 2000ml 25-35%	2000- 3000 ml 35-45%
Blood Pressure Change (systolic pressure)	None	Slight fall (80 – 100 mmHg)	Marked fall (70 – 80 mm Hg)	Profound fall (50-70 mmHg)
Symptoms and signs	Palpitations Dizziness Tachycardia	Weakness Sweating Tachycardia	Restlessness Pallor Oliguria	Collapse Air hunger Anuria

Incidence:

The incidence of Postpartum haemorrhage varies from 2 - 11 %[50]. Postpartum haemorrhage complicates approximately 4% of deliveries in most large obstetric services. While haemorrhage was the cause of maternal death in 19.8% cases, postpartum haemorrhage and retained placenta were responsible in 13.7% and 3% cases respectively of all complications noticed during labour. The incidence is 0.5% amongst hospital deliveries and Post-partum haemorrhage causes 10 - 16% maternal deaths in India.

Postpartum haemorrhage complicates approximately 3.9% of caesarean deliveries and is responsible for most of the use of blood and blood products in obstetric units. Postpartum bleeding has serious consequences and the proportions range from less than 10 percent to nearly 60 percent of maternal death in various countries[51].

Table 2: Maternal Deaths due to PPH: Selected countries

Country	Maternal Deaths due to PPH (%)	Maternal Deaths per 100, 000 Live Births
Hong Kong	30	7
India	16	570
Indonesia	43	650
Philippines	53	280
Burkina Faso	59	930
Egypt	32	170
Kenya	16	650
Morocco	29	610
Nigeria	20	1000
South Africa	15	230
Brazil	20	220
Guatemala	2	200
Honduras	33	220
Mexico	24	110

Epidemiology[47]

The etiologies of primary PPH are most easily understood as abnormalities of one or more of four basic processes.

- Tone
- Tissue
- Trauma
- Thrombin

Table 3: Risk factors in PPH[47]

	Etiology process	Clinical risk factors
Abnormalities of uterine contraction (tone)	- Over distended uterus	- Polyhydromnios - Multiple gestation - Macrosomia
	- Uterine muscle exhaustion	- Rapid Labour - Prolonged labour - High parity
	- Intra amniotic infection	- Fever - Prolonged ROM
	-Functional / anatomic distortion of the uterus	- Fibroid uterus - Placenta previa - Uterine abnormalities
Retained products of conception (tissue)	- Retained products - Abnormal placenta - Retained cotyledon or succinturiate lobe	- Incomplete placenta at delivery - Previous uterine surgery - High parity - Abnormal placenta on US
	- Retained blood clots	- Atonic uterus

Genital tract trauma (trauma)	- Lacerations of the cervix, vagina or perinium	- Precipitous delivery - Operative delivery
	- Extensions, lacerations at caesarean section	- Malposition - Deep engagement
	- Uterine rupture	- Previous uterine surgery
	- Uterine inversion	- High parity - Fundal Placenta
Abnormalities of coagulation (thrombin)	- Pre – existing states - Hemophilia A - Von willebrand‟s disease	- H/O hereditary - coagulation H/O of liver diasese
	- Acquired in pregnancy - ITP - Thrombocytopenia with - pre – eclampsia - DIC - Pre – eclampsia - Dead fetus in utero - Severe infection - Abruption Amniotic fluid embolus	- Bruising - Elevated BP - Fetal demise - Fever, WBC Antepartum - hemorrhage - Sudden collapse
	- Therapeutic anti - coagulation	- H/O blood clot

Bleeding will occur, if for some time the uterus is not able to contract well enough to arrest the bleeding at the placental site. Retained products of conception or blood clots, or genital tract trauma may cause large blood losses postpartum, especially if not promptly identified.

The types of postpartum haemorrhage are[46]:

1. Atonic
2. Traumatic
3. Mixed
4. Blood coagulopathy

ATONIC UTERUS:

Atonicity of the uterus is the commonest cause of postpartum hemorrhage. As long as the placenta remains unseparated, bleeding is unlikely. With the separation ofthe placenta, the uterine sinuses which are torn cannot be compressed effectively due to imperfect contraction and retraction of the uterus and bleeding continues[46].

The following are the conditions which often interfere with the retraction of the uterus as a whole and of the placental site in particular [40,46,52].

Grand multipara:

Atonic haemorrhage may result due to increase in the fibrous tissue of the uterus and decrease in the muscle for contraction. Associated malnutrition and chronic anemia probably play a role.

Over distension of uterus:

As in multiple pregnancy, hydramnios and large baby, imperfect retraction and a large placental site are responsible for excessive bleeding. In these cases overstretching of the myometrium may disrupt the bundles of actin and myosin in Individual smooth muscle cells and decrease the efficacy of the uterine contractions leading to poor uterine tone postpartum.

Malnutrition and Anemia:

Patient tolerates badly even a minimal amount of blood loss. It is associated with the debility which is more directly the cause of uterine atony.

Prolonged labour

Prolonged labour has been found to be associated with an increased risk of PPH. There is muscle exhaustion, lactate build up and glycogen depletion may be implicated. Calcium is an important regulator of smooth muscle tone and hypocalcaemia can be implicated as one of the cause of uterine atony.

Induced labour with syntocinon:

This resulted in excessive oxytocin insensitivity. Normal oxytocin regime also makes the uterus contract much harder than usual; this causes exhaustion of the muscle leading to uterine atony.

Precipitate Labor:

Women whose labour is characterized by vigorous uterine activity is likely to bleed excessively from uterine atony after delivery due to delay in uterine retraction.

Antepartum Hemorrhage

Placenta previa, where part or whole of the placenta is in the lower uterine segment which is a non-retractile portion, resulting in poor control of bleeding. In cases of abruptio placenta, the blood may sweep between the muscle fiber interfering with effective contraction.

Age: Age ≥ *35* years. In older age groups the muscle fibers loose their retractile capacity leading to uterine atony.

Previous uterine surgeries

The presence of scar on the uterus is commonly associated with placenta accreta thereby causing uterine atony.

Uterine malformation:

Implantation of the placenta in the uterine septum of a septate uterus or in the cornual region of a bicornuate uterus may cause excessive bleeding.

Preeclampsia/Eclampsia.

Although the magnitude of the association may have been exaggerated by ante partum haemoconcentration and postpartum heamodilution, the women with pre-eclampsia also had a much greater mean estimated blood loss, a nearly threefold increased incidence of clinically defined postpartum hemorrhage, and four fold increased incidence of transfusion. Several explanations might be proposed.

1. Women with pre-eclampsia were more often nulliparous and more likely to have induced labour and operative vaginal delivery.

2. Hypertension and platelet abnormalities might be expected to contribute to excessive bleeding.

3. Management by magnesium sulphate used to prevent convulsions in eclampsia may predispose to uterine atony.

ACTIVE MANAGEMENT OF THIRD STAGE OF LABOUR

Adequate management of the third stage of labour is important for the prevention of postpartum bleeding in patients undergoing vaginal delivery. Investigators have compared the effect on postpartum bleeding of active versus expectant management of third stage of labour. The authors found an incidence of postpartum bleeding of 5.9%in actively managed group and 17.9% in physiologically managed group[53]. The conclusion is that active management of third stage reduces the incidence of postpartum bleeding. The incidence of maternal mortality rate due to post partum hemorrhage has dramatically reduced in western countries with the introduction of oxytocic drugs. Active management of third stage helps prevent post partum hemorrhage and routine administration of oxytocics (Oxytocin, Ergometrine) reduces the risk of post partum hemorrhage by 40%. Hence active management of third stage of labour has become the rule.

Background &Pathophysiology:

About 8.7 million cases of severe maternal bleeding occurred in 2015[54] resulting in 83,000 maternal death[55]. Between 2003 and 2009, bleeding accounted for 27% of maternal deaths globally[56].

Albeit, cesarean sections (CSs) should be possible with no issues until unless excessive bleeding occurs in obvious cases. There are a few potential reasons that

reason over the top dying, that might be from the anterior abdominal wall, because of placental attachments variations in the from i.e placenta percreta or increta or from the whole uterus because of uterine atony.

There can be incisional site bleeding or placental site, Incision site due to extension over upper segment that involves uterine arteries, and classical incisions. Placental site bleeding can cause atonicity of uterus or retained placenta , or abnormal placental implantation [57.]

Once atonic haemorrhage has developed the management is the same as after a vaginal delivery. In caesarean section direct visualisation and manipulation of uterus and adnexas are possible. By manual compression of uterus blood loss can be minimised, gently massaging the uterine fundus and if it remains flabby,or we can put hot mop for sometime till it start getting contracted. Simultaneously, uterotonics should be administered. If these measures fail, one must then consider about surgical steps in a sequential manner [58.]

Placenta accreta is another cause of peripartum and postpartum hemorrhage which may leads to maternal morbidity and mortality. The incidence of PA increases with placenta previa (PP) especially with prior CSs or multiple check curretage [59.] Even with antepartum diagnosis and with adequate blood reserve for CS, it is not uncommon for a patient to be at risk during this kind of delivery due to massive bleeding and on table death. Many haemostatic techniques like bilateral uterine artery and internal iliac artery ligation [60,] hypogastric and uterine arterial embolization by balloon occlusion [61], interrupted circular sutures such as Hayman and B-Lynch procedures[62,63,] stepwise uterine devascularization [64,] and argon beam coagulation techniques [65] have been used to minimize blood loss .However,excessive bleeding

during CS is still challenging and makes it more difficult for obstetricians to select the relevant procedure.

High quality and expensive equipment are available mostly in tertiary centers. There is a need for a simple haemostatic and quick life saving technique that any physician can do for appropriate result, because rapid onset of profuse bleeding makes it difficult to decide and put in dilemma for further operations such as peri-partum hysterectomy.

Cesarean section is one of the major obstetric surgeries where there is change of 4-4.2% of haematocrit [66.] As consistent with literature, we detected a change of 3.43±3.32 in Haematocrit and 1.36±1.06 g/dl in Hb levels.

It has been reported that in cases of CS under spinal anesthesia, maternal hemorrhage risk is lower than that of general anesthesia [67]. All these findings seem to be associated with two potential effects of anesthetic agents; first, inhibitory effects on uterine contractions and second, disruptive effects on platelet functions and haemostasis. Our findings indicate that CS under general anesthesia result in a more explicit and profound blood loss.

Study of Imarengiaye CO et al[68], showed no difference between the primary cesarean patients and those with a prior cesarean in terms of hemorrhage. This finding might have stemmed from selective measures to have taken against uterine atony which is the most important reason of intraoperative hemorrhage, by exclusion of grand multiparity, polyhydramnios, fetal macrosomia, prolonged labor and multiple gestations. In some studies, uterine scar formation is indicated to affect contraction and to increase significantly intraoperative bleeding whereas some others express previous SC to be of no clinical significance for postoperative period [69].

Pearson GA et al detected the frequency of blood transfusion to be 0%. This rate has usually been reported as 3% in studies reporting cesarean-related transfusion rates [70]. Their results indicate that the probability of transfusion is much lower in patients of low risk group after an uneventful SC.

Monitoring of Hb/Hct levels has become a settled clinical practice for many years to have an idea about postoperative blood loss in patients or to identify any possibility of haemorrhage and to provide an opportunity of treating anemia at thean early stages. But it was previously found unnecessary to follow Hb/Hct levels in low-risk patient population [71].

Standardization of intraoperative procedures is important for obtaining a steady achievement, because some techniques or even used materials might have potential effects on patient outcomes.Traditionally, CS begins through a Pfanenstiel incision**,** but in a **2013 review Joel-Cohen** incision was found to be superior to Pfanenstiel incision in terms of postoperative outcomes [72]. Performing a bladder flap was found to be associated with greater (1 g/dl vs 0.5 g/dl) change in Hb levels compared to conventional incision that is 1 cm above the bladder fold [73]. In a recent study with a level of evidence, omission of the bladder flap was associated with non-significant change in haemoglobin levels [14]. In our CSs, bladder flap was formed when seemed necessary especially in previous CSs. Previous CS was not found to be one of the confounding factors of postpartum haemorrhage.

Saad AF et al prefered to use transverse uterine incision in the lower segment as it is usually recommended in obstetrics [75]. This was found that low vertical incision and classical incision have been associated with increased blood loss as compared with the low transverse incision [76].

The expansion of uterine incision is generally recommended to be performed bluntly, which is associated with more maternal blood loss[77.] In the **CORONIS study**, led on randomized 15,935 ladies, done investigation on mediation sets, as gruff versus sharp passage, exteriorization of uterus versus intra-abdominal uterine suture , single-layer conclusion versus twofold layer conclusion of the uterus, conclusion of peritoneum versus non-conclusion of the peritoneum and suture material as chromic catgut versus polyglactin-910 for uterine fix, were analyzed and no factually huge contrasts were found inside any of the intercessionss [78.]

Murphy DJ, et al[79] Prevention of uterine atony has not been studied for cesarean delivery and also the optimal rate of infusion of oxytocin in CS is still not clear. In a recent randomized study infusion of 30 units of oxytocin in addition to five units of bolus may provide additional benefit in elective CSs.

Placental removal options of either spontaneous or manual removal at CS have been studied in 15 randomized trials including over 4600 women[80.] Spontaneous placental removal was found to be associated with less blood loss as compared to manual removal. After spontaneous removal of placenta, the uterus was sutured after exteriorization and performing uterine massage simultaneously[81]. The Uterus closed in a double layer suturing with a polyglycolic acid (Vicryl-Ethicon) 1-0 continuous suture. There was no any significant difference noted between single layered uterine closure and two layered closure in terms of blood loss [82.]

In general speaking for a low risk CS population we found a blood loss level around 500 ml, which was slightly below the Class I hemorrhage as defined by **American College of Surgeons**[83.] Class I hemorrhage represents a blood loss up to 750 ml in which minimal physiological changes occur,for which body can compensate well. So

we could conclude that it could be reasonable to feel confidence after an uneventful CS.

How much misoprostol is effective in controlling PPH study of its efficacy:

It has been seen that reductions in maternal deaths in the past decade the annual rate of change in the maternal mortality ratio was greater between 2003 and 2013 with the most substantial improvement from 2012 to 2013 noted by Kassebaum etal [84]. Majority in reducing maternal mortality can be attributed to developments in preventing and treating postpartum hemorrhage. It is because of achievements in controlling PPH.

As PPH remains the most common cause of maternal mortality in all over world[85] and has more prevalence in developing countries since 1990.[84] This is mostly due to the prevalence of home deliveries and ,poor hygiene lack of facilities and access to conventional uterotonics at time .[86-88] There is also grounds of retained placenta and poor active management of third stage of labor leads to PPH.[89,90]

.**According to concentrate done in 13European nations** demonstrated that the utilization of blood gatherer sack has not been decreased the pace of PPH because of bigger difficulties in the administration [91]. In developing countries with authenticity of volume of blood loss post-partum can be an important initial measure toward managing the case.[92]

A recent multinational study led by World Health Organization (**WHO)** to explore the clinical practices, risks, and maternal outcomes that are associated with PPH included 275,000 births in 28 low- and middle-income countries. Of all the women included in the analysis 95.3% received an uterotonic prophylaxis and among them

1.2% reported PostPartum Haemmorhage. The overall death rate because of post partum haemmorhage is 38 per100,000 births. Not only uterotonic treatment is important in the reduction of PPH and adverse maternal outcomes but it can also lessen the need of emergency intervention, such as additional uterotonics ,extra fluid management, blood transfusion and any other surgeries[93].

Because of several benefits of rectal Misoprostol (prostaglandin E1 analogue) has emerged over time in low resources area with limited skill workers, with its advantage of long shelf life , different routes of administration, and stability at room temperature making its use more convinient.[94,95] The use of rectal misoprostol has been supported by researchers in 2007 for PPH in cases where other treatments were not available. Treating PPH with misoprostol has shown its as a good prophylactic use.[96]

Misoprostol:

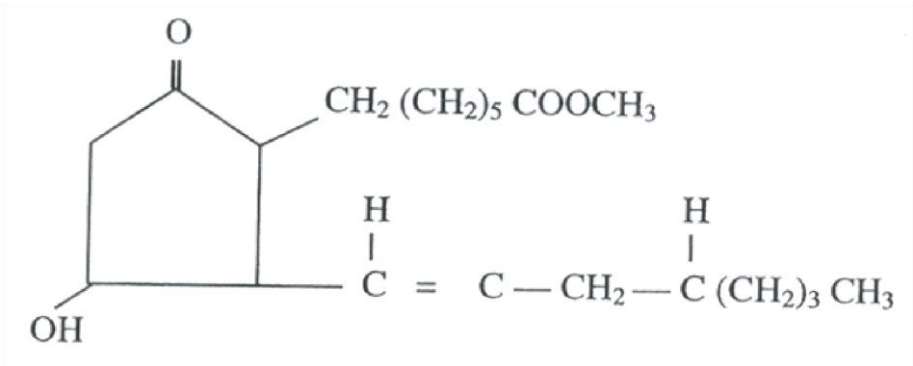


Fig.8: Chemical structure of misoprostol

[Misoprostol: 15-deoxy, 16-dehydroxy methyl-PGE1 Ester]

Synthetic analogue of prostaglandin E1 is a racemate of four stereoisomer. It is a strong myometrial stimulant.

First indication for its powerful uterotonic properties came from Latin

America when it was utilized to terminate pregnancy.

Misoprostol is a prostaglandin E1 analogue that has been approved by the Food and Drug Administration (FDA) initially to be taken orally for the prevention & treatment of gastric ulcers associated with the use of nonsteroidal anti-inflammatory drugs (1982). It has also become now an important drug in Obstetrical and Gynaecologic practice because of its uterotonic and cervical-ripening actions.

Now the drug is being used successfully in prevention and treatment of post partum haemorrhage.

Characteristic of Misoprostol:

- It is inexpensive.
- Easily stored (Shelf life : 3 years) at room temperature.
- In comparison with other prostaglandins, it has minimal effects on cardiovascular and bronchial tree smooth muscle and can be safely used in hypertensive patients and asthmatics.
- It is not affected by ambient temperature and needs no refrigeration, needles or syringes for its storage and administration respectively.
- Mode of administration - oral, vaginal, intracervical, intrauterine, sublingual, buccal, rectal. Although the formulation available in India is labeled for oral use only, oral, vaginal and rectal routes of administration are being used liberally.

Misoprostol is useful for;

1. Cervical ripening and labour induction.
2. Labour induction for post-dated or post-term pregnancy.
3. Labour induction in cases of second trimester termination in postcesarean pregnancies.
4. Induction in second and early third trimester termination of pregnancies with fetal abnormalities.
5. Induction in Intrauterine fetal death.
6. Management of spontaneous abortions and missed abortion.
7. Medical abortion - alone or in combination with mifepristone CRU-486).
8. Management of 3rd stage of labour prophylactically.
9. Management of atonic post-partum haemorrhage.
10. Misoprostol stimulates myometrium of the pregnant uterus by selectively binding to EP-2/EP-3 prostanoid receptors.

Misoprostol is easily stored at room temperature and possess a half life of several years. Misoprostol is manufactured as an oral preparation in 100 µgm and 200 µgm strength tablets.

Pharmacokinetics, Physiology and Teratogenicity :

After oral administration this drug is absorbed quickly and then deesterified to be converted into its active pharmacological form misoprostol acid, less than 90 percent of which remains bound to serum protein. Misoprostol acid is responsible for different chemical activities.

Concentration of this metabolite reaches its peak in plasma approximately by next 30 minutes and declines rapidly thereafter (half life 21 minutes).

Maximum plasma concentration of misoprostol acid is diminished when the drug is taken with food and total availability of the active metabolite is reduced by concomitant antacid. Primary site of metabolism of this drug is in liver and less than 1 percent of this metabolite is excreted in urine.

Dose of drug needs adjustment when used in patients with liver disease whereas it is not required in patient with renal insufficiency who do not require dialysis.

This drug has no known drug interaction and does not induce the hepatic cytochrome P-450 enzyme system.

The effect of misoprostol on reproductive tract are increased and gastrointestinal adverse effects are decreased if the oral preparation of misoprostol is administered vaginally or rectally.

The use of misoprostol for the treatment of PPH:

The use of misoprostol for the treatment of PPH has been promoted by women's health organizations, the International Confederation of Midwives and the International Federation of Gynecology and Obstetrics (FIGO) in 2006 recommended that " misoprostol for the treatment of PPH may be as good as for use in low-resource settings as a single treatment" or may be used in combination with oxytocin as a last resort for PPH treatment[97]. At the same time, the American Congress of Obstetricians and Gynecologists included role of misoprostol as a uterotonics as a first-line treatment in the event of uterine atony.[98] A few years later, the Royal College of Obstetricians and Gynaecologists also agreed that misoprostol may be an appropriate alternative for PPH treatment where parenteral prostaglandins are not available or in case of any contraindications or in low settings[99] . Guidelines published by FIGO for

treatment of PPH with misoprostol. “one dose of misoprostol 800 μg sublingually is can be used for the treatment of PPH where 40 IU IV oxytocin is not available (irrespective of the prophylactic measures)” published in 2012.[100]

In 2014, the Cochrane collaboration published a systematic review on the treatment of primary PPH.[101] The review assessed the effectiveness and safety regarding the treatment of PPH. Using different doses of misoprost from 600 μg to 1000 μg by alternative methods of administration, including combination of sublingual and rectal. 4052 women reviewd through ten RCT amon them seven out of ten studies on estimation of effectiveness of misoprostol suggests that the role of misoprostol has been one of the most studied interventions regarding management of post partum haemmorhage in recent decades. The misoprostol was been added to Essential Medicines in WHO Model List for the treatment of PPH in april 2015. EML(Essential Medicines List) recommends that misoprostol can be used as “prevention and treatment of PPH where oxytocin is not available or cannot be safe to use”.[102]

“Viability proof of misoprostol for the treatment of PPH”

The results from all the published RCTs on the use of misoprostol for treatment of primary PPH after vaginal deliveries or CS. RCTs have used multiple dose regimens and routes in addition to controlling against placebo or another conventional uterotonics agents as oxytocin and/or Ergometrine or combined.

A comparative study between 800 mg of misoprostol per rectal vs 5 IU oxytocin and 500 μg ergometrine intramuscular plus 10 IU oxytocin diluted in 500 mL normal saline IV infusion. The results got from this relatively small sample size (n=32 in

each arm) were promising, showed that misoprostol is an effective uterotonic studied through **The first RCT was published in 2001**[103].

A trial done between Placebo and control group over high-dose misoprostol administration but the study was underpowered to show any significant differences as published **In 2004 by Hofmeyr et al**[104].

Ccombined oral (200 μg) of misoprostol and sublingual (400 μg) of misoprostol were used and also showed the therapeutic effectiveness of misoprot against a placebo **a study by Walraven et al**[105] .

It was ventured to examine whether sublingual misoprostol had extra benefits over a standard routine oxytocin. They had detailed a critical blood loss in misoprostol groups, the investigation did not arrive at the proposed test size because of much lower PPH rate than anticipated through a study **Four years later, an RCT in Pakistan**[106] .

Till **2010 it was unclear** that any strong evidence became available from three RCTs regarding therapeutic potential of misoprostol. In a double-blind non-inferiority trial, **Blum et al** showed that use of 800 μg misoprostol is clinically equivalent to 40 IU IV oxytocin in women who received prophylactic oxytocin during the third stage of labor. However, while the time to cessation and additional blood loss of 300 mL and 500 mL was equivalent the number of women in the misoprostol group with >1,000 mL of additional blood loss was significantly higher (relative risk [RR]: 3.6; 95% confidence interval [CI]: 1.02–12.88).

The women enrolled in misoprostol group were more likely to undergo intrauterine clinical exploration under anesthesia (RR: 1.66; 95% CI: 1.00–2.76).[107]

Among women who have not been exposed to oxytocin during the third stage of labor, showed that misoprostol is slightly superior to oxytocin.[108] .Authors concluded that in the absence of oxytocin misoprostol might be a good alternative for first-line treatment for PPH.

Regardless of whether 600 μg misoprostol can be utilized as an aide treatment to standard uterotonics. Results demonstrated that when contrasted with other utero-tonic misoprostol offer extra benefits by RCT in 2010[109].

It was seen that for the treatment of PPH, utilized a solitary portion (1000 μg) of per rectal misoprostol and demonstrated the compelling utilization of misoprostol for PPH treatment at spots where other customary utero-tonics isn't accessible for the third phase labor. **Prooved by Prata et al through a community based study,**[110] .

Winikoff et al's[108] through RCT with lower dose and different routes of administration proved that misoprostol is best in settings where oxytocin is not available. The use of high-dose rectal misoprostol was also as an adjunct therapy to oxytocin as compared to ergometrine through a retrospective cohort study design.[111] Results showed no significant differences between the two groups.

Women with PPH due to uterine atonicity and who are not received any other utero-tonics during the third phase of labor 800 μg of misoprostol through sublingual route arrested bleeding within 20 minutes of administration in 85% of the PPH cases, the remaining needed additional utero-tonics proved **by a cohort study in three Nigerian hospitals**[112].

The safety profile of misoprostol in obstetrics has been established since a long ago and is associated to the pharmacokinetic profile of E2 prostaglandin analog.[113]

Compared to placebo misoprostol showed increased RR of side effects as seen by study done through RCT. Although side effects were reported as transient and dose limited in a small group of women, pooled data from a Cochrane review show average increases in vomiting (RR: 1.84; 95% CI: 1.16–2.95), shivering (RR: 2.25; 95% CI: 1.76–2.88), pyrexia of 38°C (RR: 3.12; 95% CI: 2.66–3.67), and pyrexia of 40°C or more (RR: 13.58; 95% CI: 4.93–37.44).[101]

PPH associated with Other conditions during labor and delivery :

Results from a systematic review and meta-analysis evaluating the potency and assurance of misoprostol proved that misoprostol combined with oxytocin seems to be more efficacious than oxytocin alone in cases with intra and post-operative bleedings and even in cases of retained placenta.[114]

Through a methodical revision included 17 studies total of 3,174 women were included in a trial among them seven studies assessed misoprostol vs oxytocin, seven with misoprostol plus oxytocin vs oxytocin alone. Subsequent RCTs found similar results while comparing misoprostol with oxytocin and only through oxytocin while cesarean sections in women at risk of PPH.[115,116]

Through a Cochrane review in 244 women by using prostaglandin for retained placenta, of whom 194 received a dose of 800mcg misoprostol, showed that prostaglandins were not superior compared to placebo. No statistically striking discrepancy were noted [117].However the authors noted that the quality of the evidence was low and called for much larger and sufficiently evidence based studies to make any recommendations.

“Implications for management guidelines and health care planning”

Although RCTs and non-randomized trials have used different routes of dispension and doses but current evidence suggsets a dosage of 800mcg of per rectal misopostol is optimal and effective for the treatment of PPH, was recommended by **FIGO**.[100] This drug has sufficient assurance profile regarding routes and doses but shivering and vomiting may occur as dose related adverse effects.[101]

Misoprostol is clinically equivalent to 40 IU IV oxytocin when used for the treatment of PPH in women who have received a prophylactic dose of oxytocin during the third stage of labor this is a big advantage in poor site .Such as ill-equipped background, site with unqualified supervision and lack of IV infusion convenience, amenity providers can use intramuscular oxytocin during third stage of labor with sublingual misoprostol in case of PPH .

The long shelf life of misoprostol and relatively better stability at room temperature [113,] health care providers can adjust purchasing of the drug assuming all estimated primary PPH cases will be treated with misoprostol, making it as a first-line treatment.

Current evidence supports that in absence of 40 IU i.v oxytocin as a prophylactic drug for the treatment of PPH, in poor settings where it is not available then misoprostol as sublingual or per rectal is an alternative first-line treatment.Where a maximum number of deliveries occurs at home without any skilled provider or with a minimally trained one, as well as in places where health care facilities are not determinable for referral due to the lack of transportation, road security at night, and other issues.

Contrary to the evidences based of RCT regarding misoprostol prior to 2010, don't bolster the utilization of misoprostol in perspective on standard utero-tonics either oxytocin or ergometrine for the treatment of essential PPH after vaginal deliveries[109] .However if there should arise an occurrence of caesarean conveyances it was demonstrated opposite showed that job of misoprostol contrasted with traditional utero-tonics is significant in lessening intra-and postoperative bleeding[114-116].

Current evidences on effectiveness of misoprostol is efficacy and good enough to move programs forward such as in developing countries, places where highest rate of PPH related morbidities, the management of PPH is more challenging through ease of its administration ant its storage advantage despite knowledge of efficacy of the drug. The efficacy from clinical trials assumes relatively accurate blood loss measurement, leading to a specific point of time when treatment should started. By standardizing clinical protocols with culturally appropriate ways to measure blood loss after delivery could increase effectiveness for the treatment of PPH. Task shifting or sharing with providers at lower-level health centres and health posts including community health workers should also be considered especially when referrals to health facilities are difficult. In many countries where access to misoprostol for PPH is being scaled up[118] providers could benefit from learning not just about prevention but also about the treatment for PPH, including clinical officers providing emergency caesarean sections in rural or district hospitals. Other ways to potentially increase program effectiveness to treat PPH in women who deliver at home would certainly include the use of community health workers and/or accustomed birth custodian who are skilled in determining and handling Post Partum Haemorrhage.

A Cochrane review with the objective of determining the safety and effectiveness of misoprostol for prevention and treatment of PPH found sufficient evidence to support such system.[119] The review identified three studies and none of them met the inclusion criteria – randomized or quasi RCTs. So, the conclusion is based on lack of evidence rather than results from existing evidence. However according to insight of PPH-related mortality and the role of misoprostol to treat PPH, a randomized placebo-controlled experiment for advance distribution at community level might need some ethical concerns.

Diffrent programs are needed to make informed decisions about the realm of interventions to implement in each setting it is needed to compare the effectiveness of misoprostol and other conventional uterotonics at the level of human services framework. Anyway one significant inquiry still remains that can misoprostol be given for the treatment of PPH for prevention during the third stage of labor, Even though conventional uterotonics are more widely being used then what will the relative contribution of misoprostol as compared to other interventions for management of PPH. Such as the non-pneumatic antishock garment, hemostatic drugs, and surgical approach, reviews regarding these interventions showed that more data is needed for the best ways to treat where uterotonics are not responding adequately.[101]

Oxytocin:

Oxytocin is a hormone produced by hypothalamus and secreted by pituitary gland.This is an important hormone plays a crucial role in the process of childbirth,responsible for signalling contractions of uterus during labor by stimulating uterine muscles. It is responsible for making us feel good can also stimulate nurturing

behaviour and feelings. It is the key hormone responsible for forging a loving bond between new moms and their babies as it promotes lactation.When baby sucks mother's breast oxytocin helps in releasing of milk. Oxytocin through its receptors on uterus helps in delivery of placenta by adequate contractions of uterus and minimises blood loss .

Role of Oxytocin During Labour:

Oxytocin plays a crucial role during labour in the following ways:

1. In case of insufficient uterine contractions, oxytocin can help induce labour which facilitates dilation of the cervix, enabling the baby to be stirred out of the mother's body.
2. Oxytocin may help the uterus to contract to seal many of the blood vessels in the placenta thereby preventing extreme bleeding after childbirth.
3. Oxytocin may help the placenta to detach from the uterus's wall so that it can be expelled from the mother's body after childbirth.
4. Oxytocin can obstruct pain receptors which may prove beneficial during childbirth.

Side Effects of Using Oxytocin in Labour:

Synthetic oxytocin may not suit all pregnant women. Certain side effects of using synthetic oxytocin in labour can be:

- High blood pressure
- Allergic reactions
- Vomiting
- Uterine ruptures particularly in multiple pregnancies
- Post-labour bleeding
- Foetal distress

Concerns While Taking Oxytocin in Labour:

It is very important to take special care while taking oxytocin in labour. Some concerns that you may like to keep in mind are as follows:

1. Different pregnant women may need a diverse dosage of oxytocin for labour induction and for regulating post-labour.

2. Use of oxytocin during pregnancy should be limited only for inducing labour and managing post-birth bleeding.

3. Oxytocin can trigger unmanageable contractions (uterine hypertonicity) which may then require medications. The doctor can also discontinue oxytocin dose if the needed.

4. Oxytocin should be discontinued right away in case of any distress to the unborn child or any occurrence of hyperactivity in the uterus.

5. It is advisable for patients to disclose if they are taking any other medication before taking oxytocin as certain medicines can interfere with the use of oxytocin.

6. Some women may have concerns regarding their newborn child consuming oxytocin through breastfeeding. It is always a good idea to discuss any such concerns in detail with your doctor before taking oxytocin in labour.

Physiology and pharmacology of Oxytocin:

Historically, oxytocin is hormone of posterior pituitary gland release in the presence of postpartum haemorrhage [120].In 1901 this "extract" was separated into two

fractions as oxytocic and vasopressor by Kamm et al In 1928 [121], its structure was defined in 1953 [122] andafter 1957 pure oxytocin came into clinical purpose .

The paraventricular and supraoptic nucleus of the hypothalamus synthesizes polypeptide form of oxytocin and stored in neurohypophysis[122]. Because of its structure of its molecule has a ring conformation that makes it biologically effective. Similarity of its molecule with the Antidi-uretic diuretic hormone (ADH), varying just by swap of two amino acids,that explicate its anti diuretic and vasoactive properties when directed in higher dosages, in addition both are metabolised by the equivalent aminopeptidases.

However neurohypophysis secretes Oxytocin in pulsatile manner, which is controlled by neurosensory stimuli, such as nipple sucking , stimulation of the lower genital tract and during dilatation of cervix. The release of oxytocin and ADH triggered by in plasma osmolality[124] . On the other hand, secretion of both oxytocin and ADH is inhibited by ethanol, thats why in past ethanol was used as labor supressant.

Synthetic oxytocin (pitocin) can stimulate the frequency and the strength of contraction of uterine muscle , during early trimesters high doses are needed for contractions due to lack of receptors with decrease in resting membrane potential [125]. Estrogen was also responsible for resistance of the uterine smooth muscle because of its relation to its action.

Under the influence of estrogen, receptors which are specific for oxytocin in myometrium varies at different stages of labor. As a consequence of this hormonal influence the uterine reaction with respect to its quality of contraction increments around multiple times between the twentieth and 39th weeks of gestational age. In

spite of the fact that there is singular inconstancy, work can be increased with little portion of oxytocin, for example, 0.5mUpermin[126]. When oxytocin binds to its receptor it activates phosphor-lipase C and intracellular release of Ca^{++} via inositol-1,4,5-triphosphate which direct activation or activation induced by depolarization of voltage-gated Ca^{++} channels. It was possible to describe those events after cloning the human receptor for oxytocin, although the signaling mechanisms that mediate the effects of oxytocin in the hypothalamus, pituitary gland, and uterus are unknown [126].

In uterus,contractile activity of the myometrium and production of prostaglandins by endometrial/decidual cells is also regulated by oxytocin [127]. Prostaglandins has significant task in the contraction of myometrium similar to oxytocin, as to prostaglandins enhances the susceptibility of the uterus with the progression of gestational age. But compared with oxytocin they seems to be more effective in the first weeks of pregnancy as a contractile agent [124].

Oxytocin has half life of 15-17minutes and its activated molecules binds to plasma protein. It is cleared by the kidneys and liver, and only a small fraction is excreted unchanged in the urine. Although there is evidence that oxytocin crosses the placental barrier in primates, it is unknown the extension of this crossing in the human placenta [128].

During pregnancy, the plasma concentration of oxyticinase(cystil aminopeptidase) increases approximately ten times [129]. This enzyme is derived from the placenta and it helps in metabolising both antidiuretic hormone and Oxutocin it is responsible for regulating the uterine concentration by oxytocin. Apparently its metabolism is not a ffected by presence of aminopeptidase in plasma concentration [130,131].

Extra-uterine properties of oxytocin:

Oxytocin has systemic effects, it also helps as of smooth muscle relaxant of uterine muscle and for vessels leads to its dilatation which promotes in lowering systolic as well as the diastolic blood pressure mostly, due to reflex tachycardia. The vasodilation effect is seen when oxytocin given in bolus, and may lead to increase in coronary perfusion and prevents from cardiac shutdown these impacts are more pronounced in the presence of general anesthesia[124]. In addition with general anesthesia , Oxytocin could reduce mean arterial pressure by up to 30% in 10 to 40 seconds after the injection[132].

The effects of oxytocin on cardiovascular system have been published [132-135]. Although it has a wide therapeutic index, increase in cardiac output is basically caused by decrease in peripheral vascular resistance and l auto –transfusion of blood from placental site too after delivery of the placenta, but it has been shown that cardiac output also increases with bolus dose of Oxytocin when administered during early pregnancy while performing uterine currattage. Due to b-stimulating action of synthetic Oxytocin which has chronotropic , inotropic in nature through which there is peripheral vasodilation is seen . Although it has not been proven yet but after10 to 20 seconds of vasodilation cardiac changes occurs, which is mostly due to reflex phenomena. Mostly this cardiovascular effects seems to be due to excessive administration of oxytocin at its maximum dose limit[136].

Thus maximum dose of oxytocin and its consequences can be tolerated by the parturients who don't have any cardiac related comorbidities . Parturients under anaesthesia (may it be spinal block or general anaesthesia) who presents with hypovolemia or with preexisting cardiac disorders it can be fatal , such as

valvuloplasty,uncontrolled hypertension, fixed cardiac output, or disease of the myocardium.

On its high dose antidiuretic action is also noted that may leads to water intoxication, hyponatremia secondary to antidiuretic effect of oxytocin, resulting in pulmonary edema, seizures, coma, and death[137-140]. However, with its physiological doses ,and in the absence of any co-morbidities , pure synthetic Oxytocin rarely has any anti-diuretic action[141,142].

The prophylactic use of oxytocin in caesarean section has been proved in controlling hemorrhage in up to 40% of patients by reducing uterine atony, when compared to placebo or any non prophylactic administration of drugs..

Some circumstances may leads to increase incidence of uterine atonicity as in case of multiple gestation , polyhydramnios, fetal macrosomia, and etc. However, it is seen that uterine atonicity is the main factor of PPH and it has been documented that 74% of the patient who evolved for hysterectomy immediately postpartum had any risk factor for obstetric bleeding.Among them one quarter of these patients did not have any risk factors indicating the need of prophylactic utero-tonics [143].

"Oxytocin should be slowly infused at a dose of 5 IU after delivery of anterior shoulder" According to the British National Formulary[144]. As of its wide use in caesarean sections there is no consensus regarding the adequate doses and infusion rate. Its use on pragmatic basis on the experience of each institution and dose and regimes set accordingly.

There are few works who compared the dosage and rate of infusion of oxytocin. Continous infusion of large dosage of oxytocin for example 80 IU in 500

mL of Ringer's lactate was found to be superior to lesser doses (10 IU in 500 mL of Ringer's lactate) in the prevention of post-cesarean section hemorrhage by Munn et al. but they have not mentioned the differences regarding side effects.,It was documented that by using higher dose bound the use of other utero-tonics [145]., there was little benefit by using higher dosesof oxytocin in elective CS than 5 IU when the speed of infusion was fixed (1 IUpermin) [146]. Because need of higher doses probably not necessary because concentration of myometrial receptors,which reaches its peak at term under the influence of Estrogen[147].

The current protocol is based on low dosage oxytocin to promote effective uterine contraction, as smaller dosage acts as a physiological dose and are more effective in induction and maintainance of labor. Sarna et al., described several cases of hypotension after delivery by dose of 1 IUpermin, for which vasopressor was needed [146]. Clinically satisfactory results were obtained infusing a smaller dose, 0.024 IUpermin without any side effects in parturients who are undergoing cesarean section with epidural anesthesia [148,149]. Carvalho et al. Showed that adequate uterine contraction can be achieved with 0.35 IU of oxytocin in women who are undergoing elective caesarean section under spinal anaesthesia. However some authors stressed about the importance of the method of placental extraction, because in their studies there was a considerably long time between delivery of the baby and placental extraction, providing sufficient time to reduced dose of oxytocin and allowing satisfactory uterine contraction [150]. On the other hand, the parturients undergoing cesarean section due to induction failure and had already received oxytocin during second stage there is desensitization of the oxytocin receptor after exogenous administration during labor as a continous infusion rate of minimal dose was nine times greater (rapid infusion of 3 IU) in them[151].

The problem occur especially due to use of high dosage and especially with bolus administration. A death case has been reported after using 10 units of oxytocin in bolus form in already hypovolemic parturient[152]. The dose of 5 IU of oxytocin in slow rate has been recommended for good contraction and lessens the blood loss volume[153]. The definition of "slow", rate of infusion, has not been determined yet[154]. That is been achieved by mixing the drug in the infusing bottles and titrating rate of infusion according to the evaluation of the obstetrician. According to study done by Bolton et al. that there was a change in the use of oxytocin in the United Kingdom. In the first phase of the study,87% of the obstetricians used a bolus dose of 10 IU of oxytocin, both in elective caesarean sections and in cases of postpartum bleeding. After noticing few reports of maternal death as of inadequate use of drug [38], clinical regulation of the obstetricians has been changed [155].

It has been seen that contractility after inta-myometrial route is as efficient as the intravenous route but hemodynamic changes such as low blood pressure and tachycardia can be fatal in cases with decreased stroke volume [156]. As we know as a utero-tonic Oxytocin is not the only available drug but due to confinement of the use of other drugs and their side effects. For example Ergot derivatives can cause hypertension so contraindicated in hypertensive patients. On the other hand, prostaglandins can cause hypotension, bronchospasm and gastrointestinal symptoms (nausea, vomiting, diarrhea). It is reported that incidence of acute pulmonary oedema after the use of prostaglandin F2a (Carboprost) as intramyometrial route in parturients with uterine atonicity in resistive cases of oxytocin or ergot derivatives [157].

Oxytocin may be the first line of drug in the arresting uterine atonicity in parturients undergoing cesarean sections because of good therapeutic index.Its

prophylactic use is justified in reducing post partum heammorhages. Since clinical use of Oxytocin is being available but drawback is with improper infusion regimen for caesarean sections. Avoiding the bolus administration and use of low doses as continous infusion is the current protocol .

COMPARATIVE STUDY OF RECTAL MISOPROSTOL VERSUS INTRAVENOUS OXYTOCIN :

Study of **Vimala et al,**[158] estimated those who are receiving per rectal misoprostol 400mcg (819±236ml) during CS has significantly less blood loss than among those with 20IU oxytocin (974±285ml, p=0.004) soon after delivery of the neonate.

Also in Owonikoko et al study[16], the two groups received either IV infusion of 20IU Oxytocin and another group 400mcg of misoprostol soon after delivery of the baby but there were no significant differences in the two groups estimated regarding blood loss during the surgery. It was noted that mean blood loss in the first 4 h after the surgery was significantly less in the misoprostol group than in the oxytocin group (58.2±20.7vs 80.5± 26.8ml; P=0.02).

The study of Vimala et al[158] showed that level of haemoglobin was decreased significantly among both groups manifested by the highly significant p value in comparison of pre and postoperative Hb level in the two groups-(p=0.001) But the loss in blood volume in misoprostol group was higher than oxytocin group, manifested by significant postoperative difference between the two groups (p=0.004).

In Vimala et al[158] according to them no difference was noted between the two groups in terms of the pre-delivery and post-delivery hemoglobin values. The mean reduction of hemoglobin was 0.4gm/dl in the misoprostol group and 0.6gm/dl in

oxytocin group. There were more women who needed additional oxytocics in oxytocin group and had blood loss was in excess of 1000ml. However this difference did not reach statistical significance.

In Vimala et al study[158,] In misoprostol group incidence of side effects such as pyerexia,shivering and metallic taste wassingnificantely higher as compared to oxytocin group.20 In Owonikoko et al study, the incidence of adverse effects such as shivering, pyrexia was also significantly higher in misoprostol group than in the oxytocin group (27/50 vs 1/50, $p< 0.001$).

There are very few studies who performed to assess the role of misoprostol in prevention of excessive intra-operative blood loss during CS.

In 2009, a study was done by Quiroga et al,[159] in Spain to evaluate the efficacy of per rectal misoprostol for prevention of obstetrical hemorrhage. in this study, the efficacy of misoprostol was compared with a placebo, and both groups received 10IU oxytocin as IV infusion. Results showed that addition of misoprostol diminished the necessity of additional uterotonics by 50%, and decreased the loss of hemoglobin, and the fall in hematocrit value by 39.6% and 40.6% respectively. A potential weakness in Quiroga study was the application of 10IU of oxytocin intravenously after cord clamping in both groups, which could have had an influence on intraoperative blood loss. Quiroga concluded that combination of misoprostol and oxytocin diminishes the post-cesarean blood loss with few adverse effects.

In a study conducted in China done by Xueqin[160] in 2010,Misoprostol when administered per rectal misoprostol was competent in decreasing blood loss intra-operatively and after 2 hours of the cesarean section with no adverse reactions. In this randomized trial 180 cases of hospital patients who underwent elective CS and who

were at risk for PPH were randomly assigned into three groups, 800mcg Misoprostol per rectal administration group, 20IU IV infusion oxytocin group and 600mcg Misoprostol oral administration group, with 60 cases in each group. Results showed that blood loss of the misoprostol group intra-operatively and 2 hours after the operation were significantly less than the oxytocin group (P=0.01), and there were no adverse reactions in two groups. There were no significant differences between the per rectal misoprostol group and the oral misoprostol group as regards blood loss intra-operatively and 2 hoursafter operation (P>0.05), but the side effects in the oral group were significantly higher.

MATERIALS & METHODS

Type of Study: It was prospective comparative study.

Place of Study: _____ UNIVERSITY'S in Dept. of OBG. _____ Medical College Hospital and Research Centre, _____.

Period of Study: 1st Dec2017– 30th June 2019.

Sample Size: As per study done by Minoo Rajei et.al[5.] With Anticipated Mean Difference of postoperative blood loss between the two study Groups as 28.1 and Anticipated SD as 54.6,the minimum sample size is 300 with 90%power and 5% level of significance.

Following formula is used to estimate the sample size for proposed project.

$$n = \frac{(Z_{\alpha}+Z_{\beta})^2 \times 2 \times \sigma^2}{MD2}$$

Here, Z=Z statistic at a level of significance

MD=Anticipated mean difference

SD= Anticipated standard deviation.

After calculation, total **300** women of low risk pregnancy were included undergoing caesarean section in whom Post-Partum Hemorrhage (PPH) was anticipated. Women were counselled about their participation in the study. Written informed consent was obtained before cesarean section.

STATISTICAL ANALYSIS

All characteristics was summarized descriptevely. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and data

was analyzed by Chi square test for association, comparison of means using t test, ANOVA and diagrammatic presentation.

Inclusion criteria:

- Singleton term pregnancy (37 -40) weeks undergoing elective LSCS.

Exclusion criteria:

- Previous rupture uterus
- Coagulopathy
- Fetal Distress
- Presence of Comorbid diseases like Cardiac, Respiratory,Renal or Hepatic disease.

Methodology:

The following study included 300 women undergoing elective LSCS in DEPPARTMENT OF OBSTETRICS AND GYNAECOLOGY, _____. Detailed history of all the patients were taken according to the performa and complete examination and all necessary investigations was done. After having met all the inclusion and exclusion criteria and obtaining written consent.

The study will include two groups.

Group (A) MISOPROSTOL Group-150:

In group A, preoperatively tablet misoprostol 400 microgram per rectal was kept after spinal anaesthesia before painting and draping was done in women who underwent elective LSCS .

Group (B) –OXYTOCIN Group -150

In group B, women were given intravenous oxytocin 10 IU in 500ml RL after the baby was extracted in caesarean section.

Assesment of blood loss-

1. Assessment of number of tetras soaked .Amount of clot removed. Amount of blood collected in suction apparatus[4].

   1g clot considered equivalent to 4ml of blood.
2. Pre and post operative haemoglobin levels.
3. Need of blood transfusion postoperatively.
4. Pre and post operative haematocrit
5. Need of additional interventions.
6. Vitals pulse ,blood pressure,urine output.

Hemoglobin level was measured before and after 24 hours of the operation. Side effects like shivering, nausea and vomiting along the operation and up to 2 hours after the operation was recorded. Temperature was monitored routinely and noted in the data sheet when greater than 37.5°C.

The amount of blood loss during caesarean section and 2 hours postoperatively was assessed. Total blood loss during caesarean delivery was measured by adding the volume of the suction bottle with the blood soaked sponges. Blood loss 2 hours after caesarean delivery was also measured by using blood collection drape. The whole blood loss was estimated by adding the blood in the suction bottle, blood soaked sponges and blood collection drapes.

Haematocrit values were noted before and 24 hours following surgery. Vital signs were observed continuously intraoperative and every 30 minutes after that.

Study outcomes:

The primary outcome of this study was estimation of blood loss during and after CS following administration of per rectal misoprostol or intravenous oxytocin.

The secondary outcome measures included the need for any additional oxytocic drugs or changes in hematocrit value after delivery and incidence of side effects.

Statistical analysis:

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables.

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript "c" are the degrees of freedom. "O" is observed value and E is expected value. C= (number of rows-1)* (number of columns-1)

The difference of the means of analysis variables between two independent groups was tested by unpaired t test.

The t statistic to test whether the means are different can be calculated as follows:

$$t = \frac{(\overline{x_1} - \overline{x_2}) - (\mu_1 - \mu_2)}{\sqrt{\frac{{s_1}^2}{n_1} + \frac{{s_2}^2}{n_2}}}$$

where $\bar{x}_1$ = mean of sample 1

$\bar{x}_2$ = mean of sample 2

n_1 = number of subjects in sample 1

n_2 = number of subjects in sample 2

$$s_1^2 = \text{variance of sample 1} = \frac{\Sigma(x_1 - \bar{x}_1)^2}{n_1}$$

$$s_2^2 = \text{variance of sample 2} = \frac{\Sigma(x_2 - \bar{x}_2)^2}{n_2}$$

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft office 2007.

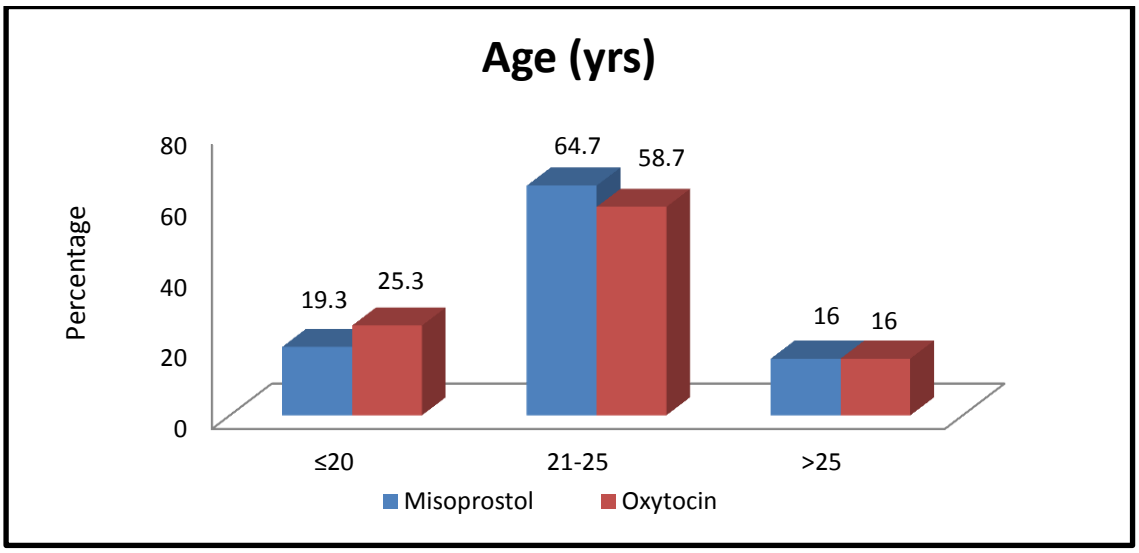
RESULT

After selection of study population data were collected and analyzed. Total 300 patients were selected where 150 of them received misoprostol and another /150 received oxytocin. Data is tabulated in the following section.

TABLE4. : DISTRIBUTION OF AGE BETWEEN STUDY GROUPS

Age (yrs)	Misoprostol		Oxytocin		p value
	N	%	N	%	
≤20	29	19.3%	38	25.3%	0.439
21-25	97	64.7%	88	58.7%	
>25	24	16.0%	24	16.0%	
Total	150	100.0%	150	100.0%	

FIGURE:9. DISTRIBUTION OF AGE BETWEEN STUDY GROUPS

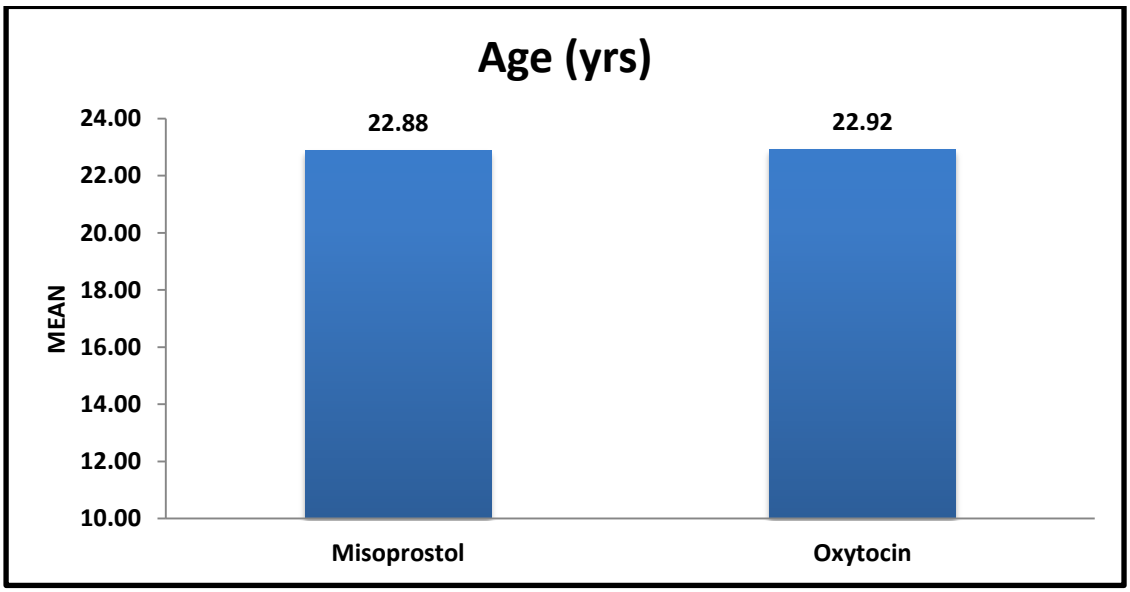


The above table shows the age distribution of the study participants of both groups. In Misoprostol group of the present study ≤20 years, 21-25 years and >25 years constituted 19.3%, 64.7% and 16% patients respectively. In Oxytocin group ≤20 years, 21-25 years and >25 years constituted 25.3%, 58.7% and 16% patients respectively.

TABLE:5. MEAN AGE BETWEEN STUDY GROUPS

Paramaters	Misoprostol		Oxytocin		p value
	Mean	SD	Mean	SD	
Age (yrs)	22.88	2.62	22.92	2.89	0.900

FIGURE:10. MEAN AGE BETWEEN STUDY GROUPS

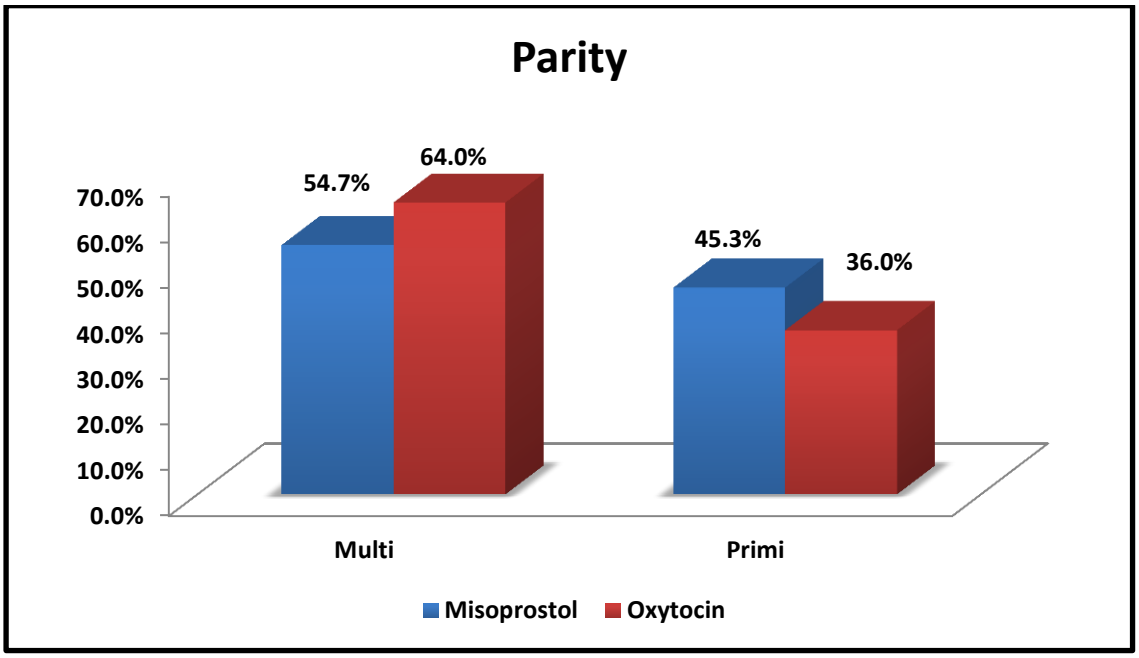


The above table shows the mean age of misoprostol and Oxytocin Group was 22.88 and 22.92 years respectively. Above analysis for mean age of both groups we found no significant difference as the p value was 0.900.

TABLE:6. DISTRIBUTION OF PARITY BETWEEN STUDY GROUPS

Parity	Misoprostol		Oxytocin		p value
	N	%	N	%	
Multi	82	54.7%	96	64.0%	0.100
Primi	68	45.3%	54	36.0%	
Total	150	100.0%	150	100.0%	

FIGURE:11. DISTRIBUTION OF PARITY BETWEEN STUDY GROUPS



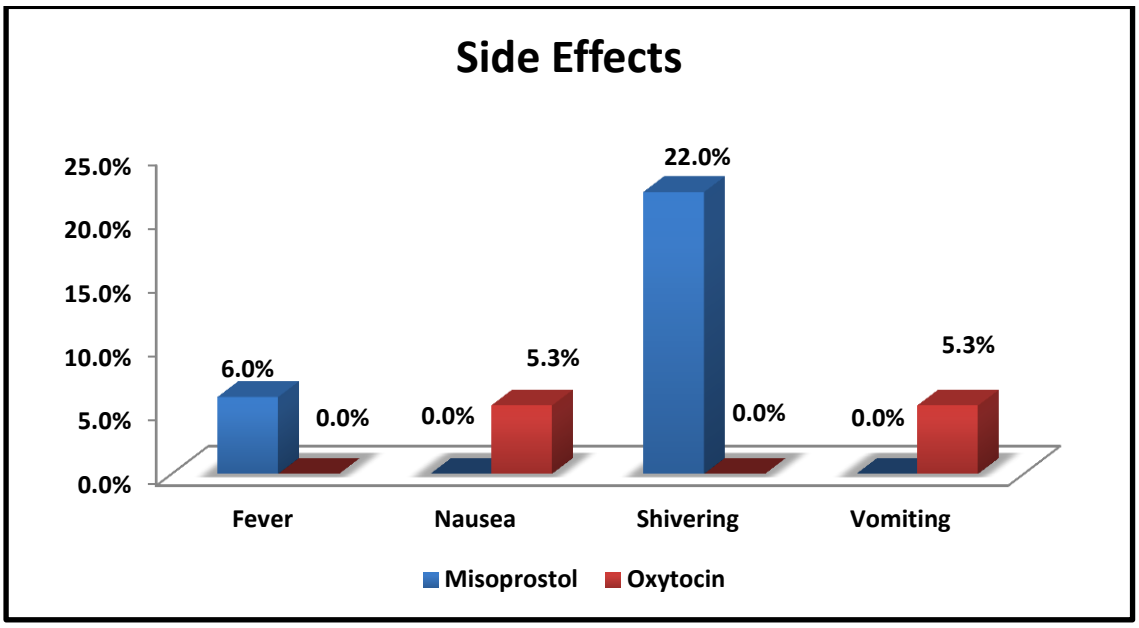
Parity distribution of study participants is mentioned in the above table. Multiparous and primiparous women were 54.7% and 45.3% respectively in Misoprostol group; 64% and 36% in Oxytocin group.

TABLE:7.DISTRIBUTION OF SIDE EFFECTS BETWEEN STUDY GROUPS

Side Effects	Misoprostol		Oxytocin		p value
	N	%	N	%	
Fever	9	6.0%	0	0.0%	<0.001*
Nausea	0	0.0%	8	5.3%	
Shivering	33	22.0%	0	0.0%	
Vomiting	0	0.0%	8	5.3%	

Note: * significant at 5% level of significance (p<0.05)

FIGURE:12. DISTRIBUTION OF SIDE EFFECTS BETWEEN STUDY GROUPS



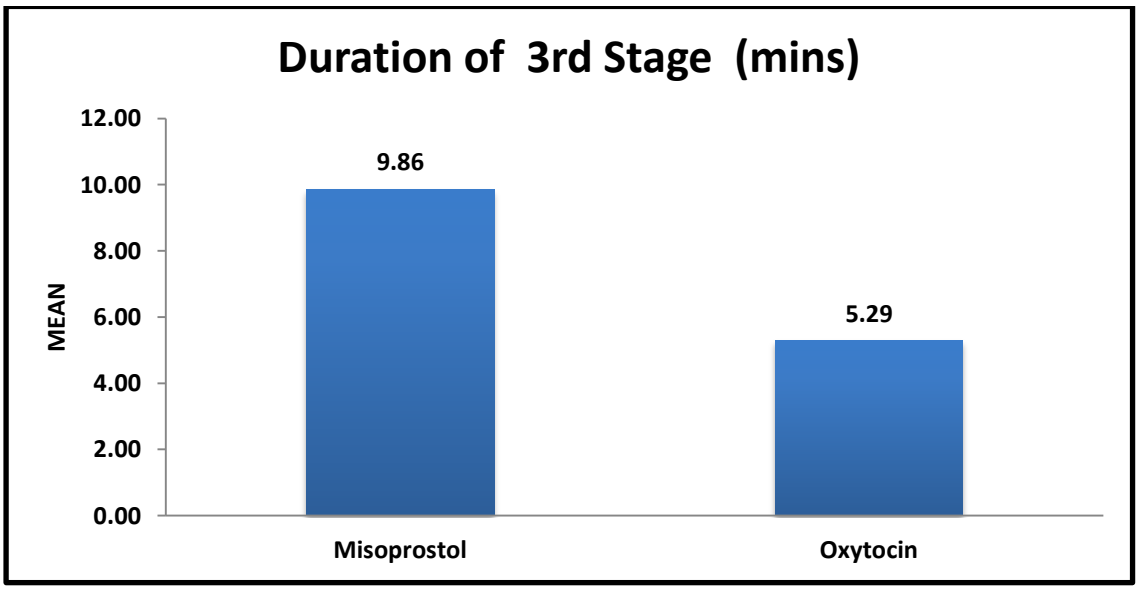
The above table shows the side effects of the drugs among the study subjects. In Misoprostol group the most common side effect was shivering accounts for 22% (33) patients followed by fever accounts for 6% (9) patients. In Oxytocin group nausea and vomiting were the commonest side effect account for 5.3% (8) patients each. While analyzing we found statistically insignificant difference for side effects in both groups as the p value was <0.001.

TABLE:8. MEAN DURATION OF 3RD STAGE BETWEEN STUDY GROUPS

Paramaters	Misoprostol		Oxytocin		p value
	Mean	SD	Mean	SD	
Duration of 3rd Stage (mins)	9.86	2.64	5.29	1.59	<0.001*

Note: * significant at 5% level of significance (p<0.05)

FIGURE:13. MEAN DURATION OF 3RD STAGE BETWEEN STUDY GROUPS

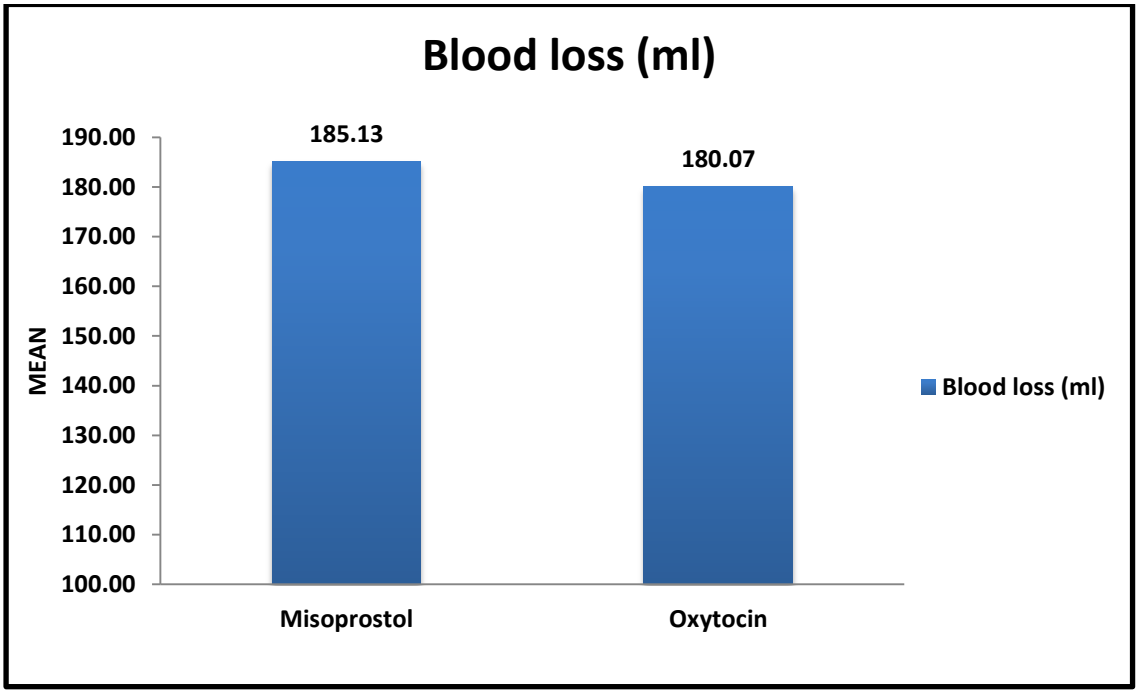


The mean duration of 3rd stage labour of both groups is mentioned in the above table. The mean duration of 3rd stage labour for Misoprostol and Oxytocin group was 9.86 and 5.29 minutes respectively. Above analysis we found statistically significant difference for duration of 3rd stage labour in both groups as the p value was <0.001.

TABLE:9. MEAN BLOOD LOSS BETWEEN STUDY GROUPS

Paramaters	Misoprostol		Oxytocin		p value
	Mean	SD	Mean	SD	
Blood loss (ml)	185.13	49.68	180.07	52.51	0.391

FIGURE:14. MEAN BLOOD LOSS BETWEEN STUDY GROUPS

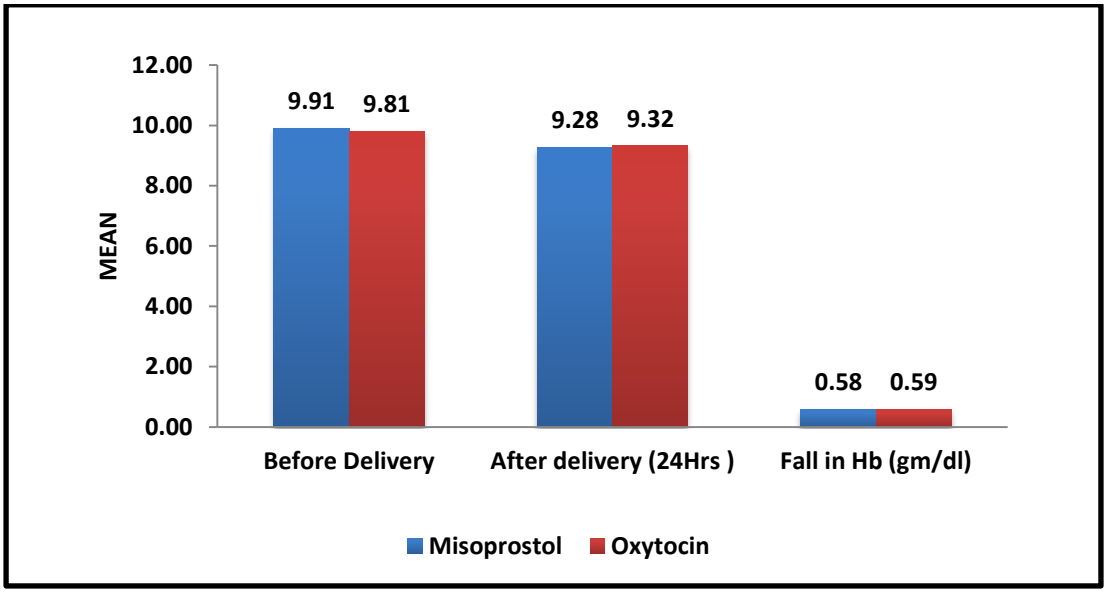


Mean blood loss level for Misoprostol and Oxytocin group was 185.13 and 180.07 ml respectively. The difference in blood loss was statistically insignificant between the two groups as the p value was 0.391. Data is tabulated in the above table.

TABLE: 10.Hb PARAMETERS BETWEEN STUDY GROUPS

Paramaters	Misoprostol		Oxytocin		p value
	Mean	SD	Mean	SD	
Before Delivery Hb	9.91	0.87	9.81	0.81	0.307
After delivery Hb (24Hrs)	9.28	0.85	9.32	0.77	0.633
Fall in Hb (gm/dl)	0.58	0.17	0.59	0.26	0.549

FIGURE: 15. Hb PARAMETERS BETWEEN STUDY GROUPS



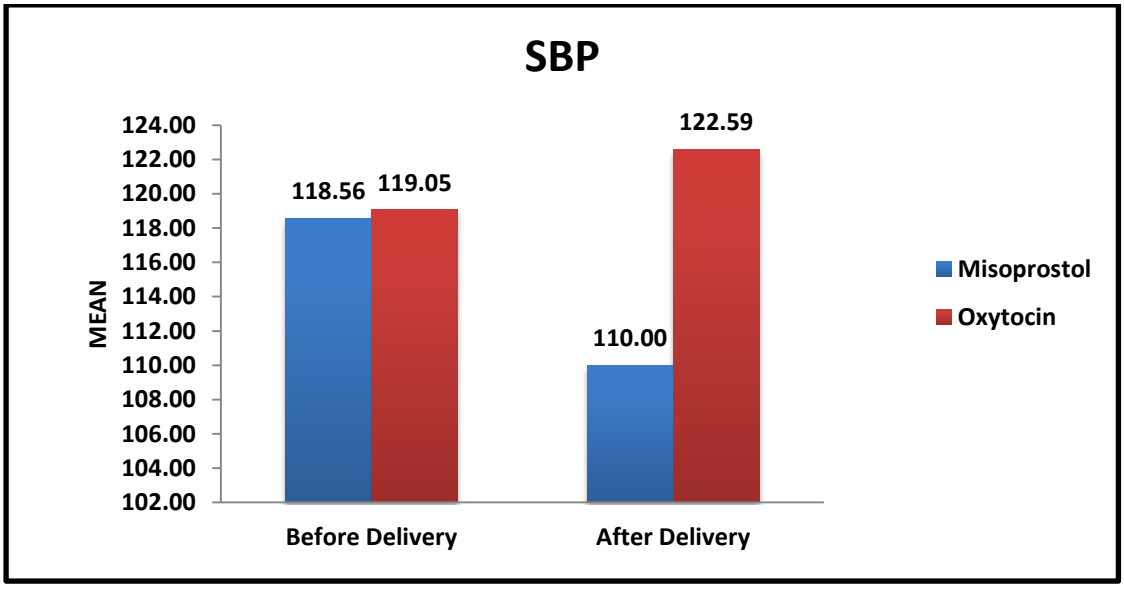
The above table shows the mean Hb status of both groups before and after delivery (24hrs) and the mean fall of Hb level. The mean Hb level of misoprostol group before and after 24 hrs of delivery was 9.91 and 9.28 respectively. In Oxytocin group the mean Hb level before and after 24 hrs of delivery was 9.81 and 9.32 respectively. The mean fall of Hb level for Misoprostol and Oxytocin group was 0.58 and 0.59 mg/dl respectively. The difference in mean Hb level before and after 24 hrs of delivery and fall in Hb level was insignificant as the p value was >0.05.

TABLE:11. MEAN SYSTOLIC BLOOD PRESSURE BETWEEN STUDY GROUPS

SBP (mmHg)	Misoprostol		Oxytocin		p value
	Mean	SD	Mean	SD	
Before Delivery	118.56	9.87	119.05	8.98	0.651
After Delivery	110.00	0.00	122.59	9.73	<0.001*

Note: * significant at 5% level of significance (p<0.05)

FIGURE:16. MEAN SYSTOLIC BLOOD PRESSURE BETWEEN STUDY GROUPS



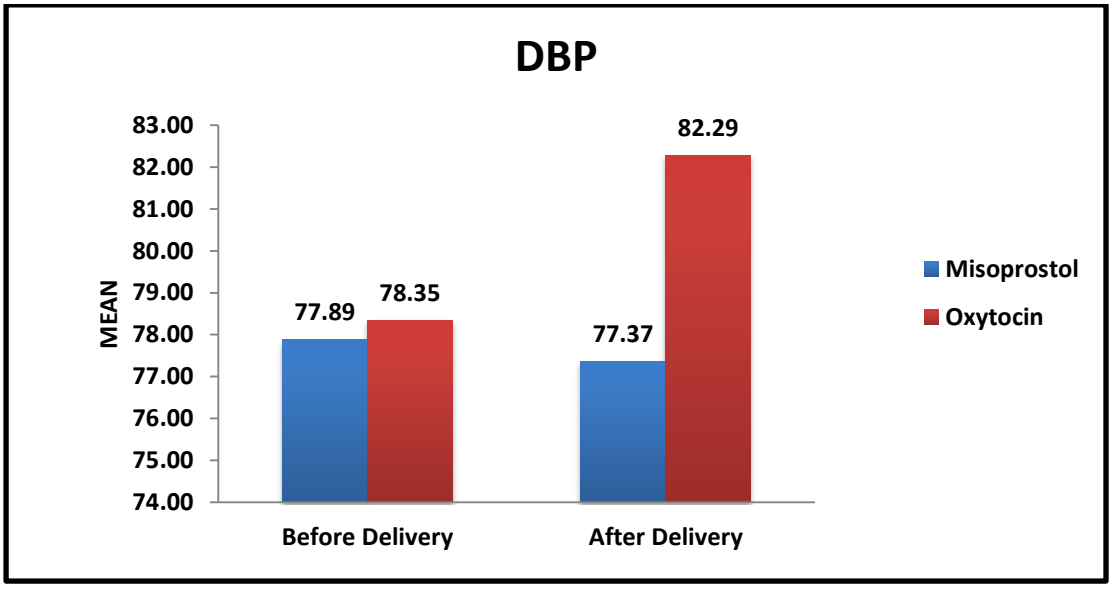
The mean SBP of Misoprostol group before and after delivery was 118.56 and 110 mm of Hg respectively. In Oxytocin group the mean Systolic BP before and after delivery was 119.05 and 122.59 respectively. Above analysis we found statistically significant difference for mean SBP only after delivery in both groups as the p value was <0.001. The difference in mean SBP before delivery in both groups was statistically insignificant as the p value was 0.651.

TABLE:12. MEAN DIASTOLIC BLOOD PRESSURE BETWEEN STUDY GROUPS

DBP (mmHg)	Misoprostol		Oxytocin		p value
	Mean	SD	Mean	SD	
Before Delivery	77.89	5.72	78.35	5.42	0.481
After Delivery	77.37	5.31	82.29	5.97	<0.001*

Note: * significant at 5% level of significance (p<0.05)

FIGURE:17. MEAN DIASTOLIC BLOOD PRESSURE BETWEEN STUDY GROUPS



The mean DBP of Misoprostol group before and after delivery was 77.89 and 77.37 mm of Hg respectively. In Oxytocin group the mean DBP before and after delivery was 78.35 and 82.29 respectively. Above analysis we found statistically significant difference for mean DBP only after delivery in both groups as the p value was <0.001. The difference in mean DBP before delivery in both groups was statistically insignificant as the p value was 0.481.

DISCUSSION

Labor should be a safe event and tend to be a happy ending after a long journey of pregnancy; unfortunately sometimes it might turn into a tragic event when it became complicated by postpartum hemorrhage. There is a worldwide trend toward minimizing the incidence of such tragedy. So many international researches concerning this condition were published during the last few years, where data results were controversial in their conflict, but all of them admitted the importance of the active management of the third stage of labor.

The present study was a prospective comparative type study where we assessed the safety and efficacy of preoperative per rectal 400mcg Misoprostol versus 10U intravenous Oxytocin in 500ml RL used for elective cesarean section to reduce intra and post operative bleeding under the following headings:

According to age distribution in this study, we found that almost two thirds of patients were in their third decade. Mean age of Misoprostol and Oxytocin group was 22.88 and 22.92 years respectively. This is consistent with the fact that during this age group, ladies are in their highest fertility and sexual activity[161].

Nialm S et al[162] in a similar study also found the mean age of Misoprostol and Oxytocin group was 23.3 ±3.57 and 24.28 ±4.49 respectively which is quite consistent with our study. Similar findings were observed in a study by **Rahim AYHA et al**[163] where 67.1% patients were in their third decade of life.

In the present study multiparous and primiparous women were 54.7% and 45.3% respectively in Misoprostol group; 64% and 36% in Oxytocin group. **Rahim AYHA et al**[163] also found similar observation where primiparous and multiparous women were 28.6% and 71.4% respectively in their study. **Diallo M et al**[164]in a similar study

found the man parity of Misoprostol and Oxytocin group was 2.49 and 2.51 respectively which is in an agreement with the present study.

The commonest side effect of Misoprostol in the study subjects was shivering accounts for 22% (33) patients followed by fever constituted for 6% (9) patients. In Oxytocin group nausea and vomiting was observed as side effects constituted 8% patients each. While analyzing for side effects we found a highly significant difference in two groups. Shivering was significantly higher with per rectal Misoprostol which was similar with study done by **Kundodyiwa, and Chaudhuri et al**[165,166].

Diallo M et al[164]in their study foundthe occurrence of side effects was mostly observed in the misoprostol group: 13.64% against 3.4% in the oxytocin group (p = 0.004). Shivering occurred significantly more (p = 0.001) in patients who received misoprostol compared to those who received oxytocin. 7.14% against 2% respectively. No significant difference was observed for other side effects: hyperthermia (p=0.123). Nausea (p=0.123). Vomiting (p=0.498) in their study.

Nialm S et al[162] in their study,also showed the occurrence of side effects is much higher in misoprostol group than oxytocin group. **E.R. Othman et al**[167], in their study showed shivering and metallic taste were reported in the misoprostol group more than in the oxytocin group.

The present study found the mean duration of 3rd stage labour for Misoprostol and Oxytocin group was 9.86 and 5.29 minutes respectively and above analysis significant difference was found in respect to mean duration of 3rd stage labour. This observation is in a contradiction with a study by **Rahim AYHA et al**[163] where the shortest mean duration of the third stage of labor was seen in patients who received misoprostol

(3.89±0.37 min), followed by oxytocin (4.6±0.9 min),. The difference in duration was statistically significant between groups.

In the present study the mean blood loss level for Misoprostol group (185.13) was higher while compared to Oxytocin group (180.07). While analyzing in terms of mean blood loss level in both groups we found no statistically significant difference.

Diallo M et al[164] in their study showedthere was no significant difference in the amount of blood loss between the two groups during our trial. The dose of 400 mcg of misoprostol administered per os, per lingual. Or even rectally (10-22) was as effective as oxytocin 10 IU IM[168-171]. In these studies, the average volume of blood loss varied between 155 ml and 193.5 ml in patients who received misoprostol; close to the average volume of 185.13 ml in observation of our study**.**

However, **Villar** in a systematic review that focused on the use of misoprostol in preventing early postpartum haemorrhage indicated the greater effectiveness of other conventional uterotonics (oxytocin, methylergometrine) for the reduction of blood loss during delivery compared to misoprostol[172].

We noted no statistically significant difference between the two groups based on the average hemoglobin levels before and after delivery. Cook who noted a higher reduction in hemoglobin levels in the misoprostol group (400 mcg per oral) compared to the control group (oxytocin or syntometrine) suggested a greater effectiveness of this combination therapy[11]. However. Our results are consistent with those of **Bulgaho, Walley, Zachariah, Afolabi** and **Caliskan** who orally or rectally administered doses of 400 to 500 mcg of misoprostol comparing it to oxytocin or syntometrine[168,169,174,175]. **Bellad** observed a greater effectiveness of 400 mcg of misoprostol per rectal over 10 IU IM oxytocin[171].

The two groups were comparable in terms of changes in systolic and diastolic blood pressures before and after delivery. An average reduction of systolic blood pressure by 7.0 mm of Hg was observed in the misoprostol group against 3.54 mm of Hg in the oxytocin group. There was no significant difference in the average reduction of diastolic blood pressure for both groups: 0.52 mm of Hg in the misoprostol group against 3.94 mm of Hg in the oxytocin group.

The relevance of measuring blood pressure is to assess the impact haemorrhage has on the general condition which is one of the criteria proposed to define postpartum haemorrhage[16]. This assessment is particularly useful in the context of anaemia where haemorrhagic shock can occur when less than 500 ml of blood is lost. **Cookand El Refaey** observed similar results to ours when they respectively compared 500 and 400 mcg of oral misoprostol to higher doses of oxytocin (10 IU IM) administered on its own or associated with methylergometrine[173,177].

However these findings differ from those of **Diab** in Egypt who reported a higher drop in the blood pressure of the group receiving 400 mcg of rectally administered misoprostol than the group receiving 5 IU oxytocin associated with 0.25 mg of methylergometrine administered by intramuscular route[178]. This could be due to the methylergometrine which has hypertensive properties.

The present study demonstrates that preoperative per rectal misoprostol was a safe & effective alternative to 10 units of Oxytocin intravenous in 500ml RL in routine active management of 3rd stage labour.

SUMMARY

The present study was a prospective comparative study, conducted on 300 pregnant women who were elected for caesarean section. All the patients were divided in two groups randomly; Group A constituted 150 patients in whom 400mcg Misoprostol was kept per rectal preoperatively before skin incision within one minute after giving spinal anesthesia. In Group B 150 patients received i.v 10 Units of Oxytocin in in500ml (RL) drip during operation. The present study summarizes:

- The age range varied from ≤20 years to >25 years. Most common age group was 21-25 years constituted total 185 (61.7%) patients. The mean age of Misoprostol and Oxytocin group was 22.88 and 22.92 years respectively.
- In the present study we observed the number of multiparous women were hign than primiparous women. Multipaous and primiparous women were 54.7% and 45.3% respectively in Misoprostol group; 64% and 36% in Oxytocin group.
- The commonest side effect of Misoprostol in the study subjects was shivering accounts for 22% (33) patients followed by fever constituted for 6% (9) patients. In Oxytocin group nausea and vomiting was observed as side effects constituted 8% patients each. While analyzing for side effects we found a highly significant difference in two groups.
- The mean duration of 3rd stage labour in Misoprostol (9.86) was higher than that of Oxytocin (5.29) group. Above analysis we found statistically significant difference for duration of 3rd stage labour in both groups as the p value was <0.001.was

- In the present study the mean blood loss level for Misoprostol group (185.13) was higher while compared to Oxytocin group (180.07). While analyzing for the mean blood loss level in both groups we found insignificant difference as the p value was 0.391.
- The mean fall of Hb level for Misoprostol and Oxytocin group before and after 24 hours of delivery was almost same and above analysis we found insignificant difference as the p value was >0.05.
- In our study above analysis we found statistically insignificant difference for mean SBP and DBP only after delivery in both groups as the p value was <0.001.

CONCLUSION

Our study concludes:

The above results indicate that in the context of active management of 3rd grade labour, Misoprostol has comparable effectiveness to oxytocin (10IU IV in 500ml RL) in the prevention of early postpartum haemorrhage However, misoprostol was associated with higher incidence of shivering and pyrexia but no other serious adverse effects occurred. Hence, per rectal misoprostol can be safely used in low risk caesarean deliveries as an alternative to 10 IU oxytocin in AMTSL It should be included as an alternative in delivery protocols and also added to the list of essential drugs for affordable access. In the future it may be an important and effective option for the management of third stage labour particularly in women where oxytocin is contraindicated.

REFERENCES

1. Ramadani H. Cesarean section intraoperative blood loss and mode of placental separation. Int J Obstet Gynecol 2004; 87(2): 114-8.
2. Assali N., Dougls R., Baid W. Measurement of uterine blood flow and uterine metabolism. Am J Obstet Gynecol 1953; 66: 248-53.
3. Pritchard J A., Baldwin R M., Dickey J C. and Wiggins K M. Blood volume changes in pregnancy and peurperium : II. Red cell loss and changes in apparent blood volume during the following vaginal delivery, caesarean section, and cesarean section plus total hysterectomy. Am J Obstet Gynecol 1962; 84: 1271-82.
4. Vimala N, Mittal S, Kumar S. Sublingual misoprostol versus oxytocin infusion to reduce blood loss at cesarean section. Int J Obstet Gynecol 2005; 90 (1): 322- 29.
5. Brecher M E, Monk T, Goodnough L T.A standardized method for calculating blood loss. Transfusion 1997; 37(10): 1070-4.
6. Ashlesha P.A calibrated drape versus visual assessment for estimating postpartum hemorrhage. From The 132nd annual Meeting (November 6-10, 2004) of APHA (American Public Health Association).
7. Duthie S J, Ven D, Yung G L, Guang D Z, Chan S Y. Discrepancy between laboratory determination and visual estimation of blood loss during normal delivery. Eur J Obstet Gynecol Reprod Biol 1991; 38 (2): 119-24.
8. Duthie S J, Ghosh A, Ng A, Ho P C. Intra-operative blood loss during elective lower segment cesarean section. Br J Obstet Gynecol 1992; 99 (5): 364-7.
9. Karoshi M, Keith L. Challenges in managing postpartum hemorrhage in resource-poor countries. *Clin Obstet Gynecol*. 2009;52(2):285–298.

10. Candio F, Hofmeyr G. *Treatments for Iron-Deficiency Anaemia in Pregnancy: RHL Commentary*. *The WHO Reproductive Health Library*. Geneva: World Health Organization (WHO); 2007.

11. Frass KA. Postpartum hemorrhage is related to the hemoglobin levels at labor: observational study. *Alexandria J Med*. 2015;51(4):333–337.

12. Sanghvi TG, Harvey PW, Wainwright E. Maternal iron-folic acid supplementation programs: evidence of impact and implementation. *Food Nutr Bull*. 2010;31(2 suppl):S100–S107.

13. Kalaivani K. Prevalence & consequences of anaemia in pregnancy. *Indian J Med Res*. 2009;130(5):627–633.

14. Magann EF, Evans S, Hutchinson M, Collins R, Lanneau G, Morrison JC. Postpartum hemorrhage after cesarean delivery: an analysis of risk factors. South Med J 2005;98:681–5.

15. Acharya G, Al-Sammarai MT, Patel N, Al-Habib A, Kiserud T. A randomized controlled trial comparing effect of oral misoprostol and intravenous syntocinon on intra-operative blood loss during cesarean section. Acta Obstet Gynecol Scand 2001;80:245–50.

16. Owonikoko KM, Arowojolu AO, Okunlola MA. Effect of sublingual misoprostol versus intravenous oxytocin on reducing blood loss at cesarean section in Nigeria: a randomized controlled trial. J Obstet Gynaecol Res 2011;37:715–21.

17. Thomas JS, Koh SH, Cooper GM. Haemodynamic effects of oxytocin given as i.v.bolus or infusion on women undergoing caesarean section. Br J Anaesth 2007;98:116–9.

18. Svanstrom MC, Biber B, Hanes M, Johansson G, N € €aslund U, Balfors EM. Signs of myocardial ischaemia after injection of oxytocin: a randomized double-blind comparison of oxytocin and methylergometrine during caesarean section. Br J Anaesth 2008;100:683–9.

19. Senior J, Marshall K, Sangha R, Clayton JK. In vitro characterization of prostanoid receptors on human myometrium at term pregnancy. Br J Pharmacol 1993;108:501–6.

20. Gulmezoglu AM, Forna F, Villar J, Hofmeyr GJ. Prostaglandins for € preventing postpartum haemorrhage. Cochrane Database Syst Rev 2007;18:CD000494.

21. Walraven G, Blum J, Dampha Y, Sowe M, Morison L, Winikoff B, et al. Misoprostol in the management of the third stage of labour in the home delivery setting in rural Gambia: a randomised controlled trial. BJOG 2005;112:1277–83.

22. Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB, et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet 2006;368:1248–53.

23. Enakpene CA, Morhason-Bello IO, Enakpene EO, Arowojolu AO, Omigbodun AO. Oral misoprostol for the prevention of primary post-partum haemorrhage during third stage of labour. J Obstet Gynaecol Res 2007;33:810–7.

24. Gulmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, Adetoro L, € et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 2001;358:689–95.

25. Langenbach C. Misoprostol in preventing postpartum hemorrhage: a meta-analysis. Int J Gynaecol Obstet 2006;92:10–8.

26. Sloan NL, Durocher J, Aldrich T, Blum J, Winikoff B. What measured blood loss tells us bout postpartum bleeding: a systematic review. BJOG 2010;117:788–800.

27. Lumbiganon P, Hofmeyr J, Gulmezoglu AM, Pinol A, Villar J. € Misoprostol dose-related shivering and pyrexia in the third stage of labour. WHO collaborative trial of misoprostol in the management of the third stage of labour. Br J Obstet Gynaecol 1999;106:304–8.

28. World Health Organization (WHO). WHO Recommendations for the Prevention of Postpartum Haemorrhage. Geneva (Switzerland): World Health Organization, 2007.

29. Lokugamage AU, Paine M, Bassaw-Balroop K, Sullivan KR, Refaey HE, Rodeck CH. Active management of the third stage at caesarean section: randomised controlled trial of rnisoprostol versus Syntocinon. Aust N Z J Obstet Gynaecol 2001;41:411–4.

30. Vimala N, Mittal S, Kumar S. Sublingual misoprostol versus oxytocin infusion to reduce blood loss at cesarean section. Int J Gynaecol Obstet 2006;92:106–10.

31. Lapaire O, Schneider MC, Stotz M, Surbek DV, Holzgreve W, Hoesli IM. Oral misoprostol versus intravenous oxytocin in reducing blood loss after emergency cesarean delivery. Int J Gynaecol Obstet 2006;95:2–7.

32. Eftekhari N, Doroodian M, Lashkarizadeh R. The effect of sublingual misoprostol versus intravenous oxytocin in reducing bleeding after caesarean section. J Obstet Gynaecol 2009;29:633–6.

33. Chaudhuri P, Banerjee GB, Mandal A. Rectally administered misoprostol versus intravenous oxytocin infusion during cesarean delivery to reduce intraoperative and postoperative blood loss. Int J Gynaecol Obstet 2010;109:25–9

34. AL Mudaliar, Causation and stages of Labour, Clinical obstetrics, 9th edition, ;Madras Orient longman; 1994: p.85 – 96.

35. Cunningham FG. Parturition. Williams , 20th Edn, USA, Appleton and Lange : 1997. p. 261 – 317.

36. Donald I. Postpartum hemorrhage. Practical Obstetric Problems, 5th Edn. New Delhi. B.I. Publications. 1998 p. 748 – 794.

37. Cunningham FG. Leveno.K.J, Bloom SL, Hauth J.C. Williams Obstetrics, 22nd Edn, Philadelphia, W.B. Saunders Company ;.p. 826 – 865.

38. Fraser DM, Cooper MA. Physiology and management of the third stage of labour in Myles textbook for midwives. 14th edn. China, Churchill Livingstone; p. 507-530.

39. Dutta DC. Textbook of Obstetrics. 6thedn. Calcutta, New Central Book

a. Agency Pvt. Ltd; 2004. p. 114 – 144.

40. McDonald S. Physiology and management of the third stage of labour. Myles Textbook for Midwives, 13th Edn. China, Churchill Livingstone; 1999. p. 465 – 488.

41. Dutta DC. Normal Labour, Textbook of Obstetrics. 4th edn. Calcutta, New Central Book Agency Pvt. Ltd; 1998. p. 118 – 152.

42. Myles M. The third stage of labour. Textbook of Midwives, 10th Edn. USA English Language Book Society/Churchill Livingstone; 1985. P. 328 – 342.

43. Bonnar J. Coagulation and fibrinolytic mechanisms during and after childbirth. Br Med J 1970; 25:200 – 203.

44. AL Mudaliar, Conduct of Normal Labour, Clinical obstetrics, 9th edition, Madras Orient longman; 1994: p.103-113.

45. Fraser DM, Cooper MA. Physiology and management of the third stage of labour in Myles textbook for midwives. 15th edn. China, Churchill Livingstone; p. 531 – 554.

46. Dutta DC. Complication of the third stage of labour. Textbook of Obstetr. 6thEdn. Calcutta, New Central Book Agency Pvt. Ltd.; 2004. p. 411 – 421.

47. Schuurmans N. Prevention and management of postpartum hemorrhage. J Soc Obstet Gynecol Can 2000;22(4):271-281.

48. Samil RS. Postpartum hemorrhage and management. J Pediatr Obstet Gynecol 1988; 4 – 7.

49. Combs CA. Factors associated with postpartum hemorrhage with vaginal birth. Obstet Gynecol 1991; 77:69-76.

50. Mukherjee S. Postpartum Haemorrhage: Its management in Rural Postpartum Haemorrhage, 1st Edn. FOGSI Publication; 2000. p. 33-3 8.

51. Abou Zahr C. Antepartum and postpartum Haemrnorhage. He dimensions of sex and reproduction Boston, Harvard University Press.

52. Arulkumaran S. The management of postpartum Haemorrhage. Management of labour,1st Edn. Chennai, Orient Longman; 1997. p. 183-196.

53. Elbourne D, Prendiville W, Chalmers I. Choice of oxytocic preparations for routine use in the management of the third stage of labour : An overview of the evidence from controlled trials. Br J Obstet Gynaecol 1998; 95:17-30.

54. "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015". *Lancet*. **388** (10053): 1545–1602. October 2016.

55. "Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. **388** (10053): 1459–1544. October 2016.

56. Say, Lale; Chou, Doris; Gemmill, Alison; Tunçalp, Özge; Moller, Ann-Beth; Daniels, Jane; Gülmezoglu, A Metin; Temmerman, Marleen; Alkema, Leontine (2014). "Global causes of maternal death: a WHO systematic analysis". The Lancet Global Health. **2** (6): e323–e333.

57. G. Kayem, D. Clément, and F. Goffinet, "Recurrence following conservative management of placenta accreta," International Journal of Gynecology and Obstetrics, vol. 99, no. 2, pp. 142–143, 2007.

58. S. Timmermans, A. C. van Hof, and J. J. Duvekot, "Conservative management of abnormally invasive placentation," Obstetrical and Gynecological Survey, vol. 62, no. 8, pp. 529–539, 2007.

59. S. Wu, M. Kocherginsky, and J. U. Hibbard, "Abnormal placentation: twenty-year analysis," American Journal of Obstetrics and Gynecology, vol. 192, no. 5, pp. 1458–1461, 2005.

60. S. L. Clark, J. P. Phelan, S.-Y. Yeh, S. R. Bruce, and R. H. Paul, "Hypogastric artery ligation for obstetric hemorrhage," Obstetrics & Gynecology, vol. 66, no. 3, pp. 353–356, 1985.

61. E. Hansch, U. Chitkara, J. McAlpine, Y. El-Sayed, M. D. Dake, and M. K. Razavi, "Pelvic arterial embolization for control of obstetric hemorrhage: a five-year experience," American Journal of Obstetrics and Gynecology, vol. 180, no. 6 I, pp. 1454–1460, 1999.

62. C. B-Lynch, A. Coker, A. H. Lawal, J. Abu, and M. J. Cowen, "The B-Lynch surgical technique for the control of massive postpartum haemorrhage: an alternative to hysterectomy? Five cases reported," British Journal of Obstetrics and Gynaecology, vol. 104, no. 3, pp. 372–375, 1997.

63. R. G. Hayman, S. Arulkumaran, and P. J. Steer, "Uterine compression sutures: surgical management of postpartum hemorrhage," Obstetrics & Gynecology, vol. 99, no. 3, pp. 502–506, 2002.

64. S. A. AbdRabbo, "Stepwise uterine devascularization: a novel technique for management of uncontrollable postpartum hemorrhage with preservation of the uterus," American Journal of Obstetrics and Gynecology, vol. 171, no. 3, pp. 694–700, 1994.

65. S. E. Scarantino, J. G. Reilly, M. L. Moretti, and V. T. Pillari, "Argon beam coagulation in the management of placenta accreta," Obstetrics and Gynecology, vol. 94, no. 5, pp. 825–827, 1999.

66. Berg CJ, Callaghan WM, Henderson Z, Syverson C. Pregnancy-Related Mortality in the United States, 1998 to 2005. Obstet Gynecol. 2011;117:1230.

67. Afolabi BB, Lesi FE. Regional versus general anaesthesia for caesarean section. Cochrane Database Syst Rev. 2012;10:CD004350.

68. Imarengiaye CO, Ande AB. Risk factors for blood transfusion during c-section in a tertiary hospital in Nigeria. Med Sci Monit. 2006;12:CR269–72.

69. Api O, Unal O, Api M, Dogance U, Balcik O, Kara O, Turan C. Do asymptomatic patients require routine hemoglobin testing following uneventful, unplanned cesarean sections? Arch Gynecol Obstet. 2010;281:195–9.

70. Pearson GA, MacKenzie IZ. Blood loss and blood transfusion at caesarean section: a prospective observational study covering 30 years. Eur J Obstet Gynecol Reprod Biol. 2014;181:72–7.

71. Anzaku AS, Edem BE, Ngwan SD, Galadima SJ. Do patients require routine hematocrit testing following uncomplicated cesarean delivery? Afr J Med Health Sci. 2015;14:24–8.

72. Mathai M, Hofmeyr GJ, Mathai NE. Abdominal surgical incisions for caesarean section. Cochrane Database Syst Rev. 2013;5:CD004453.

73. Walsh CA. Evidence-based cesarean technique. Curr Opin Obstet Gynecol. 2010;22:110–5.

74. Tuuli MG, Odibo AO, Fogertey P, Roehl K, Stamilio D, Macones GA. Utility of the bladder flap at cesarean delivery: a randomized controlled trial. Obstet Gynecol. 2012;119:815–21.

75. Saad AF, Rahman M, Costantine MM, Saade GR. Blunt versus sharp uterine incision expansion during low transverse cesarean delivery: a metaanalysis. Am J Obstet Gynecol. 2014;211:684, e1–11.

76. Bakhshi T, Landon MB, Lai Y, Spong CY, Rouse DJ, Leveno KJ, Varner MW, Caritis SN, Meis PJ, Wapner RJ, Sorokin Y, Miodovnik M, Carpenter M, Peaceman AM, O'Sullivan MJ, Sibai BM, Langer O, Thorp JM, Mercer BM. Maternal and neonatal outcomes of repeat cesarean delivery in women

with a prior classical versus low transverse uterine incision. Am J Perinatol. 2010;27:791–6.

77. Asıcıoglu O, Gungorduk K, Asıcıoglu BB, Yıldırım G, Gungorduk OC, Ark C. Unintended extension of the lower segment uterine incision at cesarean delivery; a randomized comparison of sharp versus blunt techniques. Am J Perinatol. 2014;31:837–44.

78. CORONIS Collaborative Group. Abalos E, Oyarzun E, Addo V, Sharma JB, Matthews J, Oyieke J, Masood SN, El Sheikh MA, Brocklehurst P, Farrell B, Gray S, Hardy P, Jamieson N, Juszczak E, Spark P. CORONIS - International study of caesarean section surgical techniques: the follow-up study. BMC Pregnancy Childbirth. 2013;13:215.

79. Murphy DJ, MacGregor H, Munishankar B, McLeod G. A randomised controlled trial of oxytocin 5IU and placebo infusion versus oxytocin 5IU and 30IU infusion for the control of blood loss at elective caesarean section--pilot study. Eur J Obstet Gynecol Reprod Biol. 2009;142:30–3.

80. Anorlu RI, Maholwana B, Hofmeyr GJ. Methods of delivering placenta at cesarean section. Cochrane Database Syst Rev. 2008;16:CD004737.

81. Hofmeyr JG, Novikova N, Mathai M, Shah A. Techniques for cesarean section. Am J Obstet Gynecol. 2009;201:431–44.

82. Dodd JM, Anderson ER, Gates S, Grivell RM. Surgical techniques for uterine incision and uterine closure at the time of caesarean section. Cochrane Database Syst Rev. 2014;7:CD004732.

83. Kortbeek JB, Al Turki SA, Ali J, Antoine JA, Bouillon B, Brasel K, Svendsen LB. Advanced trauma life support, the evidence for change. J Trauma. 2008;64:1638–50.

84. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, et al. Global, regional, and national levels and causes of maternal mortality during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384(9947):980–1004.

85. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014;2(6):e323–e333.

86. Prata N, Passano P, Rowen T, Bell S, Walsh J, Potts M. Where there are (few) skilled birth attendants. *J Health Popul Nutr*. 2011;29(2):81–91.

87. Montagu D, Yamey G, Visconti A, Harding A, Yoong J. Where do poor women in developing countries give birth? A multi-country analysis of demographic and health survey data. *PLoS One*. 2011;6(2):e17155.

88. Crowe S, Utley M, Costello A, Pagel C. How many births in sub-Saharan Africa and South Asia will not be attended by a skilled birth attendant between 2011 and 2015? *BMC Pregnancy Childbirth*. 2012;12:4.

89. Knight M, Callaghan WM, Berg C, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. *BMC Pregnancy Childbirth*. 2009;9:55.

90. Cheung WM, Hawkes A, Ibish S, Weeks AD. The retained placenta: historical and geographical rate variations. *J Obstet Gynaecol*. 2011;31(1):37–42.

91. Zhang W-H, Deneux-Tharaux C, Brocklehurst P, et al; EUPHRATES Group. Effect of a collector bag for measurement of postpartum blood loss after vaginal delivery: cluster randomised trial in 13 European countries. *BMJ*. 2010;340:c293.

92. Prata N, Gerdts C. Measurement of postpartum blood loss. *BMJ*. 2010;340:c555.

93. Sheldon WR, Blum J, Vogel JP, et al; WHO Multicountry Survey on Maternal and Newborn Health Research Network. Postpartum haemorrhage management, risks, and maternal outcomes: findings from the World Health Organization multicountry survey on maternal and newborn health. *BJOG*. 2014;121(suppl 1):5–13.

94. Weeks A. The prevention and treatment of postpartum haemorrhage: what do we know, and where do we go to next? *BJOG*. 2015;122(2):202–210.

95. Smith JM, Gubin R, Holston MM, Fullerton J, Prata N. Misoprostol for postpartum hemorrhage prevention at home birth: an integrative review of global implementation experience to date. *BMC Pregnancy Childbirth*. 2013;13:44.

96. Blum J, Alfirevic Z, Walraven G, Weeks A, Winikoff B. Treatment of postpartum hemorrhage with misoprostol. *Int J Gynaecol Obstet*. 2007;99(suppl 2):S202–S205.

97. International Conferation of Midwives (ICM) and International Federation of Gynaecology and Obstetrics (FIGO). *Prevention and Treatment of Post-partum Haemorrhage: New Advances for Low Resource Settings*. *Joint Statement by ICM and FIGO*. The Hague and London: ICM and FIGO; 2006.

98. American Congress of Obstetricians and Gynecologists (ACOG) Committee on Practice Bulletins. *ACOG Practice Bulletin*. *Clinical Management Guidelines for Obstetrician-Gynecologists*. *Number 76*. *Postpartum Hemorrhage*. Washington, DC: ACOG; 2006.

99. Royal College of Obstetricians and Gynaecologists. *Green-top Guideline No 52. Prevention and Management of Postpartum Haemorrhage*. London: RCOG; 2009.

100. International Federation of Gynecology, Obstetrics. Treatment of postpartum hemorrhage with misoprostol. *Int J Gynecol Obstet*. 2012;119(3):215–216.

101. Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. *Cochrane Database Syst Rev*. 2014;2:Cd003249.

102. World Health Organization (WHO). *Executive Summary: The Selection and Use of Essential Medicines (2015). Report of the 20th WHO Expert Committee on the Selection and Use of Essential Medicines*. Geneva: WHO; 2015.

103. Lokugamage AU, Sullivan KR, Niculescu I, et al. A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. *Acta Obstet Gynecol Scand*. 2001;80(9):835–839.

104. Hofmeyr GJ, Ferreira S, Nikodem VC, et al. Misoprostol for treating postpartum haemorrhage: a randomized controlled trial [ISRCTN72263357]. *BMC Pregnancy Childbirth*. 2004;4(1):16.

105. Walraven G, Dampha Y, Bittaye B, Sowe M, Hofmeyr J. Misoprostol in the treatment of postpartum haemorrhage in addition to routine management: a placebo randomised controlled trial. *BJOG*. 2004;111(9):1014–1017.

106. Zuberi NF, Durocher J, Sikander R, Baber N, Blum J, Walraven G. Misoprostol in addition to routine treatment of postpartum hemorrhage: a hospital-based randomized-controlled trial in Karachi, Pakistan. *BMC Pregnancy Childbirth*. 2008;8:40.

107. Blum J, Winikoff B, Raghavan S, et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women receiving prophylactic oxytocin: a double-blind, randomised, non-inferiority trial. *Lancet*. 2010;375(9710):217–223.

108. Winikoff B, Dabash R, Durocher J, et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. *Lancet*. 2010;375(9710):210–216.

109. Widmer M, Blum J, Hofmeyr GJ, et al. Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre, double-blind randomised trial. *Lancet*. 2010;375(9728):1808–1813.

110. Prata N, Mbaruku G, Campbell M, Potts M, Vahidnia F. Controlling postpartum hemorrhage after home births in Tanzania. *Int J Gynaecol Obstet*. 2005;90(1):51–55.

111. Baruah M, Cohn GM. Efficacy of rectal misoprostol as second-line therapy for the treatment of primary postpartum hemorrhage. *J Reprod Med*. 2008;53(3):203–206.

112. Okonofua FE, Ogu RN, Akuse JT, Ujah IA, Galadanci HS, Fabamwo AO. Assessment of sublingual misoprostol as first-line treatment for primary post-partum hemorrhage: results of a multicenter trial. *J Obstet Gynaecol Res*. 2014;40(3):718–722.

113. Elati A, Weeks A. Misoprostol for the management of postpartum haemorrhage. *BMJ*. 2011;342:d2877.

114. Conde-Agudelo A, Nieto A, Rosas-Bermudez A, Romero R. Misoprostol to reduce intraoperative and postoperative hemorrhage during cesarean delivery:

a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2013;209(1):40.e41–40.e17.

115. Chaudhuri P, Majumdar A. Sublingual misoprostol as an adjunct to oxytocin during cesarean delivery in women at risk of postpartum hemorrhage. *Int J Gynaecol Obstet*. 2015;128(1):48–52

116. Ugwu IA, Enabor OO, Adeyemi AB, Lawal OO, Oladokun A, Olayemi O. Sublingual misoprostol to decrease blood loss after caesarean delivery: a randomised controlled trial. *J Obstet Gynaecol*. 2014;34(5):407–411.

117. Grillo-Ardila CF, Ruiz-Parra AI, Gaitan HG, Rodriguez-Malagon N. Prostaglandins for management of retained placenta. *Cochrane Database Syst Rev*. 2014;(5):CD010312.

118. Prata N, Bell S, Weidert K. Prevention of postpartum hemorrhage in low-resource settings: current perspectives. *Int J Womens Health*. 2013;5:737–752.

119. Oladapo OT, Fawole B, Blum J, Abalos E. Advance misoprostol distribution for preventing and treating postpartum haemorrhage. *Cochrane Database Syst Rev*. 2012;2:Cd009336.

120. Bell WB — The pituitary body and the therapeutic value of the infundibular extract in shock, uterine atony and untestinal paresis. Br Med J, 1909;2:1609.

121. Kamm O, Aldrich TB, Grote IW et al. — The active principles of the posterior lobe of the pituitary gland: I. The demonstration of the presence of two active principles: II. The separation of the two principles and their concentration in the form of potent solid preparations. J Am Chem Soc, 1928;50:573.

122. DuVigneaud V, Ressler C, Swan JM et al. — The synthesis of an octapeptide amide with the hormonal activity of oxytocin. J Am Chem Soc,1953;75:4879.

123. Shyken JM, Petrie RH — The use of oxytocin. Clinics in Perinatology, 1995;22:907-931.

124. Graves CR — Fármacos que Provocam Contração ou Relaxamento do Útero, em: Goodman & Gilman — As Bases Farmacológicas da Terapêutica, 8ª Ed, New York, McGraw-Hill, 1996; 693-700.

125. Kao CY — Electrophysiological Properties of the Uterine Smooth Muscle, em: Wynn RM — Biology of the Uterus, 2nd Ed, New York, Plenum, 1977;423-496.

126. Kimura T, Makino Y, Saji F et al. — Molecular characterization of a cloned human oxytocin receptor. Eur J Endocrinol, 1994;131: 385-390.

127. Bossmar T, Akerlund M, Fantoni G et al. — Receptors and myometrial responses to oxytocin and vasopressin in pre-term and term human pregnancy: effects of the oxytocin antagonist atosiban. Am J Obstet Gynecol, 1994;171:1634-1642.

128. Roy AC, Karim SMM — Significance of the inhibition of prostaglandins and cyclic GMP of oxytocinase activity in human pregnancy and labour. Prostaglandins, 1983;25:55-70.

129. Majkic-Singh N, Vukonic A, Spasic S et al. — Oxytocinase (CAP) in serum during normal pregnancy. Clin Biochem, 1982;15:152-153.

130. Mitchell MD, Flint APF, Bibby J et al. — Rapid increases in plasma prostaglandin concentration after vaginal examination e amniotomy. BMJ, 1977;2:1183-1185.

131. Thornton S, Davison JM, Baylis PH — Effect of human pregnancy on metabolic clearance rate of oxytocin. Am J Physiol, 1980;259:R21-R24.

132. Weiss Jr FR, Markello R, MO B et al. — Cardiovascular effects of oxytocin. Obstet Gynecol, 1975;46:211-214.

133. Bonica JJ — Principles and Practice of Obstetric Analgesia and Anesthesia. Philadelphia, FA Davis, 1972.

134. Kitchen AH — Some actions of oxytocin on the cardiovascular system in man. Clin Sci, 1959;8:399.

135. Andersen TW, DePadua CB, Stenger V et al. — Cardiovascular effects of rapid intravenous injection of synthetic oxytocin during elective cesarean section. Clin Pharmacol Ther, 1965;6: 345-349.

136. Katz RL — Antiarrhythmic and cardiovascular effects of synthetic oxytoxin. Anesthesiology, 1964;25:653-661.

137. Liggins GC — The treatment of missed abortion by high dosage syntocinon intravenous infusion. J Obstet Gynaecol Br Commonw, 1962;69:277-281.

138. Pittman GC — Water intoxication due to oxytocin: report of a case. New Engl J Med, 1963;268:481-482.

139. Heytens L, Camu F — Pulmonary edema during cesarean section related to the use of oxytocic drugs. Acta Anaesthesiol Belg, 1984;35:155-164.

140. Shahin J, Guharoy SR — Pulmonary edema possibly developing secondary to the intravenous administration of oxytocin. Vet Hum Toxicol, 1991;33:587-588.

141. Hays RM — Agents Affecting the Renal Conservation of Water, em: Gilman AG, Goodman LS, Rall TW et al. The Pharmacological Basis of Therapeutics, 7th Ed, New York, Macmillan, 1985.

142. Saunders WG, Munsick RA — Antidiuretic potency of oxytocin in women post partum. Am J Obstet Gynecol, 1966;95:5-11.

143. Clark SL, Sze-Ya Y, Phelan JP et al. — Obstet Gynecol, 1984;64: 376-380.

144. British Medical Association — British National Formulary, 44th Ed, London, British Medical Association/British Pharmaceutical Society of Great Britain, 2002.

145. Munn MB, Owen J, Vincent R et al. — Comparison of two oxytocin regiments to prevent uterine atony at cesarean delivery: Arandomized controlled trial. Obstet Gynecol, 2001;98:386-390.

146. Sarna MC, Soni AK, Gómez M et al. — Intravenous oxytocin in patients undergoing elective cesarean section. Anesth Analg, 1997;84:753-756.

147. Kimura T, Tanizawa O, Mori K et al. — Structure and expression of a human oxytocin receptor. Nature, 1992;356:526-529.

148. Zarzur E — A ocitocina e a operação cesariana. Rev Bras Anest, 1992;42:293-295.

149. Zarzur E — Intravenous oxytocin in patients undergoing elective cesarean section. Anesth Analg, 1998;86:1334.

150. Carvalho JCA, Balki M, Kingdom J et al. — Oxytocin requirements at elective cesarean delivery: a dose-finding study. Obstet Gynaecol, 2004;104:1005-1009.

151. Balki M, Ronayne M, Davies S et al. — Minimum oxytocin dose requirement after cesarean delivery for labor arrest. Obstet Gynecol, 2006;107:45-50.

152. Lewis G, Drife J, eds — Why mothers die 1997-1999. The fifth report of the confidential enquiries into maternal deaths in the United Kingdom. London: RCOG Press, 2001.

153. Wee MYK, Brown H, Reynolds F — The national institute of clinical excellence (NICE) guidelines for caeserean sections: implications for anaesthetist. Int J Obstet Anesth, 2005;14:147-158.

154. Khan MM, Gupta S, Radford P et al. — Dose of oxytocin after caesarean section. Anaesthesia, 2002;57:110.

155. Bolton TJ, Randal K, Yentis SM — Effect of the confidential enquiries into maternal deaths on the use of syntocinon at caeserean section in the UK. Anaesthesia, 2003;58:277-279.

156. Dennehy KC, Rosaeg OP, Cicutti NJ et al. — Oxytocin injection after caesarean delivery: intravenous or intramyometrial. Can J Anaesth, 1998;45:635-639.

157. De La Torre MRR, Alonso JIG, Fernández MG — Edema pulmonar em uma cesárea relacionado com la administración de 15-metil prostaglandina F2alpha. Rev Esp Anestesiol Reanim, 2004;51:104-107.

158. Vimala N, Mittal S, Kunar S. Sublingual misoprostol versus oxytocin infusion to reduce blood loss at cesarean section. Int J Gynaecol Obstet. 2006;92(2):106-10.

159. Quiroga DR, Cantú MR, Tello GHE, Puente VM, Montemayor GR, Martínez MA. Intrauterine misoprostol for the prevention of bleeding cesarean. Ginecol Obstet Mex. 2009;77(10):469-74.

160. Xueqin ZH. Clinical observation of intrauterine placement Misoprostol in prevention of intraoperative and postoperative bleeding in cesarean section. China Medical Herald. 2010;25:039.

161. Seli E, Agarwal A, eds. Fertility preservation. New York: Springer, 2012:226.

162. Nilam Subedi , Deepanjali Sharma, Rubby Das, Comparison of Misoprostol with Oxytocin in Third Stage Of Labour; Journal of Universal College of Medical Sciences (2018) Vol.06 No.01 Issue 17; page:19-21.

163. Rahim AYHA et al, Comparison between oxytocin, ergometrine and misoprostol in active management of the third stage of labour: a randomized controlled trial, Int J Reprod Contracept Obstet Gynecol. 2018 Jun;7(6):2076-2080.

164. Diallo M et al., Active management of third stage of labour with low doses of oral misoprostol and oxytocin on low: risk parturient in a Sub-Saharan hospital, Dakar, Sénégal, Int J Reprod Contracept Obstet Gynecol. 2017 Feb;6(2):516-522.

165. Kundodyiwa TW, Majoko F, Rusakaniko S. Misoprostol versus oxytocin in the third stage of labor. Int J Gynecol Obstet 2001; 75 : 235-41.

166. Chaudhuri P, Biswas J, Mandal A, et al. Sublingual misoprostol versus intramuscular oxytocin for prevention of postpartum hemorrhage in low-risk women. Int J of Gynecology and Obstetrics 2012;116: 138-142

167. E.R. Othman et al, Sublingual misoprostol versus intravenous oxytocin in reducing bleeding during and after caesarean delivery: A randomized clinical trial, Taiwanese Journal of Obstetrics and Gynecology, 55 (2016), 791-795.

168. Diab KM. Ramy AR. Yehia MA. The use of rectal misoprostol as active pharmacological management of the third stage of labor. J Obstet Gynaecol Res. 1999;25:327-32.

169. Zachariah ES. Naidu M. Seshadri L.nOral misoprostol in the third stage of labor. Int J Gynecol Obstet. 2006;92:23-6.

170. Chaudhuri P. Biswas J. Mandal A. Sublingual misoprostol versus intramuscular oxytocin for prevention of postpartum hemorrhage in low-risk women. Int J Gynecol Obstet. 2012;112(2):148-2.

171. Caliskan E. Meydanli MM. Dilbaz B. Aykan B.. Sonmezer M. Haberal A. Is rectal misoprostol really effective in the treatment of third stage of labor? A randomized controlled trial. Am J Obstet Gynecol. 2002;187(4):1038-45.

172. Villar J. Gulmezoglu AM. Hofmeyr GJ. Forna F. Systematic review of randomized controlled trials of misoprostol to prevent postpartum hemorrhage. Obstet Gynecol. 2002;100:1301-12.

173. El-Refaey H. Randa N. O'Brien P. Mona A. Geary M. Jane W. Choulnard CR. The misoprostol third stage of labour study: a randomised controlled comparison between orally administered misoprostol and standard management. BJOG. 2000;107(9):1104-10.

174. Walley RL. Wilson JB. Crane JM. Matthews K. Sawyer E. Hutchens D. A double-blind placebo controlled randomized trial of misoprostol and oxytocin in the management of the third stage of labour. BJOG. 2000;107:1111-5.

175. Singh G. Radhakrishnan G. Guleria K. Comparaison of misoprostol sublingual. intravenous oxytocin and intravenous methylergometrine in active management of third stage of labour. Int J Gynecol Obstet. 2009;107:130-4.

176. Tang OS. Schweer H. Seyberth HW. Lee SW. Ho PC. Pharmacokinetics of different routes of administration of misoprostol. Hum Reprod. 2002;17(2):332-6.

177. Afolabi EO. Kuti O. Orji O. Ogunniyi SO. Oral misoprostol versus intramuscular oxytocine in the active management of the third stage of the labour. Singapore Med J. 2010;51(3):207-11.

178. Cook CM. Spurret B. Murray H. A randomized clinical trial comparing oral misoprostol with synthetic oxytocin or syntometrine in the third stage of labour. Aust NZ J Obstet Gynaecol. 1999;39(4):414-9.

ANNEXURE

ETHICAL CLEARANCE CERTIFICATE

SAMPLE INFORMED CONSENT FORM

TITLE OF THE TOPIC : "A COMPARITIVE STUDY OF RECTAL MISOPROSTOL VERSUS INTRAVENOUS OXYTOCIN IN REDUCING INTRAOPERATIVE AND POST OPERATIVE BLEEDING IN ELECTIVE CAESERIAN SECTIONS.

DURATION OF STUDY : FROM DEC 2017 TO JUNE 2019.

PRINCIPAL INVESTIGATOR : Dr. _____

PG GUIDE NAME : Dr._____

PURPOSE OF RESEARCH

To determine preoperative per rectal misoprost in controlling of intra and post operative bleeding in cesarean sections..

PROCEDURE

I understand that I will be a part of this study. My history and physical findings will be recorded and evaluated in a systematic way. I may be given preoperative per rectal misoprostol as part of my treatment, I may be asked for follow-up.

RISK AND DISCOMFORTS

I understand that this procedure may involve risks due to fluid overload. But it will be a minor risk and transient. If any side effects occur, I will be given appropriate care and treatment.

ENEFITS

This study will help in reducing the complications associated with intraoperative and postoperative bleeding(PPH)by using 400mcg misoprostol per rectum '

CONFIDENTIALITY

I understand that the medical information produced by this study will become a part of hospital records and will be subject to the confidentiality and privacy regulation of _____ University's _____ Medical College. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file securely**.** If the data are used for publication in the medical literature or for teaching purpose no names will be mentioned**.** I understand that the relevant designated authority are permitted to have an access to my medical records and to the data produced by the study for audit purpose. However, they are required to maintain confidentiality**.**

STUDY SUBJECT CONSENT STATEMENT:

I confirm that, Dr. _____ has explained to me the purpose of research, the study procedure, that I will undergo and the possible discomforts as well as benefits that I may experience. I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(witness to signature) Date

PROFORMA FOR STUDY

Name: **IPNo:Age:**

Case.no:

Address: **Occupation:**

DOA: **Contact no:**

DO Study: **Mobile:**

Chief complaints: **Residence:**

History of present pregnancy:

Gestational age :

H/o prior PPH: YES ☐ NO ☐

Any other treatment : YES ☐ NO ☐

If yes (drug/dosage/duration)

Obstetrics history:

Married Life :

Obstetric Score:

H/O Heart disease,liver disease,renal disease: ☐ YES ☐ NO

Treatment taken : ☐ YES ☐ NO

if yes details(drug/dosage/duration):

Menstrual History

LMP: EDD BY USG

EDD: I TRIMESTER:

POG: II TRIMESTER:

III TRIMESTER:

Corrected EDD: POG:

Corrected POG:

Past History:

Family History:

Personal History:

General Physical Examination

PR: BP: RR: TEMPERATURE:

Thyroid**:**

Pallor / icterus / cyanosis / clubbing / edema / lymphadenopathy:

Systemic Examination

CVS:

RS:

Per Abdomen

Fundal height(GA):

Presentation:

Symphysiofundal height(cms):

FHS:

Fetal liquor ratio(clinical):

Moderate oligohydramnios:

Severe oligohydramnios:

INVESTIGATIONS

CBC,ABO RH TYPING,HBsAG,RVD**,BT,CT**

OGCT**:**

URINE ROUTINE:

TORCH (IF done already)**:**

USG**:**

BPD: PLACENTA

FL: POSITION:

AC: GRADE:

EFW:

IUGR(YES/NO):

DOPPLER(If done):

OUTCOME MEASURES:

HAEMATOCRIT:

Before operation :	
After24hours :	

AMOUNT OF INTRAOPERATIVE BLEEDING;

AMOUNT OF POSTOPERATIVE BLEEDING at the end of 1hr and at the end of 24 hrs.

HAEMOGLOBIN LEVEL:

Before operation :	
After24hours :	

CHANGE IN VITALS

Treatment	PR	BP	RR	OEDEMA
Before				
After 1 hours				
After 24 hours				

SIDE EFFECTS

Vomiting: YES ☐ NO ☐

Headache: YES ☐ NO ☐

Allergic reactions: YES ☐ NO ☐

Any other

If yes, treatment given:

REMARKS: