COMPARATIVE STUDY OF EFFICACY OF INTRAVENOUS METHYL ERGOMETRINE WITH RECTAL MISOPROSTOL IN THE PREVENTION OF PPH IN AT RISK PPH MOTHERS

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DECLARATION

I hereby declare that the dissertation entitled, **"COMPARATIVE STUDY OF EFFICACY OF RECTAL MISOPROSTOL VERSUS INTRAVENOUS METHYLERGOMETRINE IN THE PREVENTION OF PPH IN AT RISK PPH MOTHERS"** was prepared by me under direct guidance and supervision of Prof. Dr. P.M. Santhamani, M.D. D.G.O., Superintendent Govt. Kasturba Gandhi Hospital for women and Children Triplicane, Chennai-5.

This dissertation submitted to Tamilnadu Dr. M.G.R. Medical University in partial fulfillment of the university regulation for the award of M.D. Degree in Obstetrics and Gynecology

This dissertation has not been submitted for the award of any Degree or Diploma.

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CERTIFICATE

This is to certify that this dissertation entitled "**COMPARATIVE STUDY OF EFFICACY OF INTRAVENOUS METHYL ERGOMETRINE WITH RECTAL MISOPROSTOL IN THE PREVENTION OF PPH IN AT RISK PPH MOTHERS "** has been done by **Dr.M. Vanitha**, Post Graduate in M.D. (Obstetrics and Gynecology) under my overall supervision and guidance at Govt. Kasturba Gandhi Hospital , Madras Medical College, Chennai in partial fulfillment of regulation of Tamilnadu Dr. M.G.R. Medical University for the award of M.D. Degree in Obstetrics and Gynecology.

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INTRODUCTION

Postpartum hemorrhage is a major obstetrical emergency and one of the important but preventable causes of maternal morbidity and mortality. It is often sudden, frequently unpredictable and catastrophic. Unless timely action is initiated, maternal death could occur in a short period. It is the leading cause of maternal death in developing countries and ranks third or fourth cause in the developed countries. Thus worldwide 1, 25,000 die due to postpartum hemorrhage each year. (WHO 1999) . Maternal mortality ratio in India during 2004 was 430/1,00,000 and the same in Tamil Nadu was 110/100,000. There were 1230 maternal deaths in Tamil Nadu out of which 21.6% was due to postpartum hemorrhage .

The primary aim in the management of PPH should be its prevention (Chamberlain 1992). Uterine atony remains the major cause of PPH. Adequate contraction and retraction of uterus is essential for the prevention of postpartum hemorrhage .

In modern obstetrics, active management is strongly recommended especially in women who are at risk of atony. The drugs commonly used in the active management of third stage of labor are oxytocin, methyl ergometrine or their combination, syntometrine.

Misoprostol, an analogue of PGE_1 is an alternative in the prevention and management of PPH. To date there has been few

prospective trials [1] and several randomized controlled trials comparing misoprostol with placebo[2] or misoprostol with standard therapies, oxytocin and methylergometrine alone or in combination)[3] for prevention of PPH. It has also been reported to control PPH unresponsive to oxytocin and methylergometrine.

Rectal misoprostol is an effective, easily administrable drug, which has shown, promises of being an efficacious drug in the management of PPH. This drug has the added advantage that it can be safely administered even by paramedical personnel during referral of a mother with PPH to higher institutions.

This preliminary study was undertaken to assess the efficacy of rectally administered misoprostol at a dose of 800ug in the management of III stage of labor to prevent PPH and to analyze the superiority or otherwise of intravenous methylergometrine in the active management of third stage of labor with rectal misoprostol.

REVIEW OF LITERATURE

The introduction of oxytocics for the management of PPH has contributed to a marked reduction in maternal mortality from 1:3000 in 1930s ; to 1:20,000 in 1950s (Green hill, 1951) and further falling to 1 in 60,000 in1980s. Uterine atony accounts for 80% of cases of PPH (Arulkumaran & Decruze, 1999)[5] and hence most of the studies were concentrated on treating this condition with various drugs and methods.

Prendiville et al in 'Bristol third stage trial'[6] found an incidence of postpartum bleeding of 5.9% in actively managed group and 17.9% in physiologically managed group. They concluded that active management of third stage of labor reduces the risk of PPH by 30-40%.

Primary aim here is its prevention. Active management of third stage of labor reduces the risk of PPH by 30-40% (Prendiville et.al, 1988)[7]

Routine active management was shown to be superior to expectant management in that there was a statistically significant reduction in the amount of postpartum blood loss, postnatal blood transfusion, the need for therapeutic oxytocics and the duration of third stage. These findings were confirmed in general population and also in women considered to be at risk of third stage complications (Prendivillie et al 2002)[8]

For the prophylactic and therapeutic management of PPH, various oxytocics were tried in different doses and routes like

- Oxytocin – 5 units IV bolus.
- Oxytocin 10-20 units IV drip
- Methylergometrine 0.2mg IM/IV
- 15- Methyl PG $F_2 \propto$ 125-250mcg IM.
- Latest in trials is misoprostol

All the above drugs except misoprostol, need refrigeration to maintain its potency. This facilities may not be available in developing countries at all times & places.

Thus the search for a thermostable uterotonic has thrown light on misoprostol which is shown to be stable at room temperature and it has been evaluated for both the prevention and the treatment of PPH.

Randomized controlled trial by O' Brien[9] revealed the efficacy of misoprostol in the treatment of severe PPH. 14 women with continued uncontrolled blood loss unresponsive to standard oxytocics were given 1000 ugm of misoprostol rectally and bleeding was found to be arrested within 3 minutes of administration.

Another randomized controlled study comparing syntometrine with rectal administration of 400 mcg of misoprostol showed that the third stage duration, post partum blood loss, postpartum hemoglobin estimation were similar in both groups - (Bamingboye, Hofmeyr et al 1998).[4]

A descriptive study [10] carried out with 1000 ug of misoprostol in 41 women with severe PPH unresponsive to oxytocics revealed control of hemorrhage in 63% (26/41) of mothers within 10minutes of administration.

From the study conducted at Aim shams university, Cairo, [11] Egypt it was concluded that rectal misoprostol may be used safely in the management of the third stage of labor because estimated blood loss was lower with misoprostol group, duration of third stage was similar in both groups, and post partum hypertension occurred in oxytocin - methergine group.

Randomized controlled trial [12] of rectal misoprostol versus oxytocics in third stage management conducted in 240 parturient women at Toronto hospital concluded that the rectal misoprostol is of equivalent efficacy to potential oxytocics for the prevention of primary postpartum hemorrhage and rectal misoprostol is an appropriate uterotonic agent for routine management of third stage of labour. The duration of third stage, blood loss, need for additional oxytocics were similar in both groups.

Another study conducted at Division of Maternal and Fetal Medicine, Imperial College School of Medicine, London[13] to characterize the pharmacokinetics and adverse effect profile of rectally administered misoprostol concluded that the mean maximum serum concentration of misoprostol of 144pg/ml was achieved on average of 23 minutes later

than in oral group and the incidence of shivering is significantly reduced in rectal group.

Randomized controlled trial [14] comparing rectal misoprostol 600mcg with conventional oxytocics in the treatment of third stage of labor revealed that rectal misoprostol is significantly less effective than oxytocin plus methylergometrine for the prevention of PPH because the incidence of postpartum hemorrhage was 9.8% in rectal misoprostol group compared with 3.5% in the group that received oxytocics and methylergometrine therapy. Significantly more women needed additional oxytocics in the misoprostol group.

Another descriptive study [15] conducted at Djibouti Army hospital showed that arrest of hemorrhage in PPH due to atony unresponsive to syntocinon occurs within 5 minutes of administration of rectal misoprostol.

Cochrane database systemic review 2000 [16] concluded that 'active management is superior to expectant management' in terms of blood loss, PPH and other serious complications of third stage. It is however associated with an increased risk of unpleasant side effects and hypertension, where ergometrine is used. Active management should be the routine management of choice for women expecting to deliver a baby in a maternity hospital.

Gerstenfeld TS. Wing et al., (2001) [17] revealed that rectal misoprostol 400 mcg was no more effective than intravenous oxytocics in

prevention of postpartum hemorrhage .

Cochrane database systemic review 2004 [18] concluded that neither intramuscular prostaglandins nor misoprostol are preferable to conventional injectable uterotonics as part of active management of third stage of labor especially for low risk women.

POST PARTUM HEMORRHAGE

Definition: Hemorrhage occurring after the delivery of the fetus is termed as postpartum hemorrhage . Primary PPH is defined as loss of 500ml or more of blood per vaginum during the first 24hrs after the delivery of the baby or even if the blood loss is less than 500ml but associated with significant hemodynamic changes in the mother. Massive postpartum hemorrhage is defined as loss of greater than 1000 or 1500 ml of blood. ACOG-defines PPH as blood loss which decreases the hematocrit by 10% or needs a transfusion.

The blood loss is often estimated visually. The visual estimation underestimates the actual blood loss by 50% (Pritchard and associates 1962) [25] .The problem of estimating the amount of blood loss accounts for the wide range of incidence of PPH quoted in literature, which varies from 2-11% (Gilbert et al 1987, Hall et all 1985)[26] . When quantitative measurements of blood loss are taken the incidence rises up to 20% (Newton et al 1961)[27] . Life threatening hemorrhage occurs in 1 in 1000 deliveries (Lewis and Drife 1998).[28]

More than half of the maternal deaths occuring within 24hrs of delivery are mostly due to PPH .

Causes of PPH

1. Uterine atony
2. Genital tract trauma
3. Coagulopathy
4. Retained placenta
5. Uterine inversion

Normally the control of hemorrhage following delivery is by contraction and retraction of myometrial fibers. This causes kinking of blood vessels and so cuts off the blood flow to the placental site. Failure of this mechanism resulting from disordered myometrial function is called uterine atony and is the most common cause of PPH. This complicates approximately 1 in 20 deliveries. 20% of women who develop uterine atony has no apparent risk factors for this condition. Predisposing factors include

- High parity
- Uterine over distension secondary to
    1. Multiple pregnancy

2. Hydramnios

3. Fetal macrosomia

- Prolonged labour
- Precipitate labour
- Antepartum hemorrhage
- Retained placenta
- Uterine abnormalities or fibroids
- Previous history of PPH (risk of recurrence is 25%), manual removal of placenta.
- General anaesthesia
- Uterine inversion
- Chorioamnionitis
- Myometrial relaxants- $MgSO_4$, B-agonists, diazoxide, halothane, calcium channel blockers.
- Mismanagement of third stage by pulling the cord in an subcontracted uterus leads to partial separation of placenta.
- Anemia and
- Operative vaginal delivery

Prophylactic management of PPH

The aim in the management of PPH should be prediction & prevention.

- Women at risk of PPH should be identified
- On admission, blood should be taken up for full blood count, grouping and cross matching.
- Wide bore cannula should be inserted for administration of ecbolics and fluids if needed.
- Active management of third stage of labor is recommended. (to all women)
- Early sucking (breast feeding)

Therapeutic Management of PPH

It requires multidisciplinary team for optimum management. It involves simultaneous resuscitation of the patient and identification of cause and instituting definitive treatment.

Resuscitation: Quick assessment of

- ❖ General condition
- ❖ Blood loss and
- ❖ Call for assistance

1. Insert 2 large bore intravenous cannula & administration of fluids (crystalloids/colloids)

2. Nasal O_2 6-8 liters of 100% oxygen through mask.

3. Catheterize the bladder.

4. Transfusion of blood / blood products.

5. Monitoring of vital parameters.

To identify the cause:

- Check the contractility of uterus.
- Rule out lower genital tract lacerations
- Make sure the entirety of placenta & membranes

Definitive treatment:

If uterine atony is the underlying cause, then vigorous uterine massage followed by bimanual compression is to be given.

Medical methods should be instituted in a step wise manner followed by other surgical methods. It one method fails, other method should be tried, with minimum loss of time.

Clinical diagnosis

Signs and symptoms are related to the amount of blood loss.

Class	Blood loss	BP change	Signs & symptoms
Class I (compensatory)	10-15% 500-1000ml	None	Tachycardia
II	15-30%	Slight fall in systolic BP	Cold & clammy skin, weakness, tachycardia, postural hypotension, thirst, decreased pulse pressure, delayed capillary refilling time
III	30-40%		Oliguria, restlessness confusion, , HR 120-160 /minute RR 30-50 / minute
IV	> 40%		Anuria, collapse, coma, death

INVESTIGATION

- Hemoglobin %
- Packed cell volume
- Blood grouping & typing, cross matching
- Coagulation profile

Medical methods:

1. Intravenous infusion of 20-40 units of oxytocin in 1000ml normal saline.
2. Intramuscular PG F2∝ - 250 mcg once in 15-90 minutes
3. Rectal misoprostol 800 mcg.

Surgical management:

1. The tamponade test with Senkstaken- Blackmore tube or Rusch balloon catheter.
2. Laparotomy

   a) If bimanual compression of uterus reduces the bleeding, brace sutures can be applied

      1. B- lynch sutures

      2.Multiple square sutures

   b) If the PPH follows placenta previa apply

      I. Isthmus- cervical apposition sutures

      II. Under suturing of placental bed.

   c) If bimanual compression fails to control the bleeding following procedures to be undertaken.

Step wise ligation of blood vessels including

1. Uterine artery

2. Infundibulo pelvic vessels.

3. Internal iliac artery ligation.

d) Uterine artery embolization

e) Hysterectomy – which is the last resort.

THE THIRD STAGE OF LABOUR

It commences with the delivery of the infant and ends with the delivery of the placenta. The mean length of third stage of labor is 6minutes and the ninety seventh percentile is 30minutes . [19] The duration of third stage is very important because direct relationship has been observed between the time interval and the risk of significant maternal morbidity.

Physiology:

After delivery of the infant, the uterine muscles contract and retract with a resultant reduction in the size of upper segment. This shortening reduces the area of uterine surface to which the relatively incompressible placenta is attached. Separation of placenta occurs through spongy layer and it is forced down towards the dilated lower uterine segment. (Mac person and Wilson 1965). The main uterotonic hormones responsible for uterine contraction are oxytocin and prostaglandin.[20]

Normal volume of blood flow through the placenta at term is 700ml/ minute.[21] This has to be arrested within seconds following placental separation. Otherwise serious hemorrhage will occur. The three inter-related physiological mechanisms responsible for the arrest of hemorrhage are

1. Retraction of oblique muscle fibers in upper segment which acts as a ligature to the torn vessels that intervene through

the muscle.

2. Following separation, the strong uterine contractions brings the uterine walls into apposition so that further pressure is exerted on the placental site.

3. There is transitory increase in the activation of the coagulation and fibrinolytic system around the placental site. So, clot formation in the torn vessels is intensified. Placental site is covered by fibrin mesh utilizing 5-10% of the circulating fibrinogen.

Any impairment in these mechanisms predisposes to severe post partum hemorrhage .

Mechanisms of placental separation:

1. Schultz mechanism:

During the process of separation there is formation of retroplacental haematoma. First the central portion, later the rest of the placenta is delivered inversely. So the fetal surface appears first with the membranes covering the maternal surface.

2. **Mathew Duncan mechanism:**

Edge of the placenta separates first and the maternal surface appears at the vaginal outlet first.

Signs of placental separation:

Because attempts to express the placenta prior to its separation are futile and possibly dangerous, it is important to recognize the following signs of placental separation, which appear within about one minute after delivery of the infant and usually within 5 minutes .

1. The uterus becomes globular and firm. This is the earliest sign to appear.
2. Sudden gush of blood.
3. 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 upward.
4. Extra vulval lengthening of umbilical cord.

Physiological or expectant management:

As long as the uterus remains firm and there is no unusual bleeding, an attitude of watchful waiting until the placenta gets separated and delivered by maternal efforts. If the efforts fail to deliver the placenta, after ensuring the firm contraction of uterus, pressure is exerted with the hand on fundus to propel the detached placenta into the vagina. It does not recommend uterotonics until after delivery of placenta (if at all) and not cord traction and cord is clamped after cessation of pulsation - Roger J, Wood. J et al., 1998 [22]

Active management of third stage of labour

It was first described by Thilaganathan & collegues,[23] in 1993 and includes the following:

2. Prophylactic use of oxytocics.
3. Early clamping of cord
4. Controlled cord traction

Prophylactic use of oxytocics:

Standard management is to administer oxytocics with the delivery of anterior shoulder in a vaginal delivery in cephalic presentation and following delivery of the head in vaginal breech delivery. The objectives of prophylactic oxytocics are:

1. to ensure efficient contraction of the uterus, thus minimizing the amount of blood loss.
2. To promote rapid and complete separation and the descent of the placenta.
3. To be more effective, oxytocics should be given before the placental separation.

Early clamping of cord:

Active management of third stage of labor entails the early clamping and dividing the umbilical cord before commencing controlled

cord traction. The duration of third stage is reduced by early cord clamping (Enkin et al, 1995).[24] However the time of clamping does not appear to influence the rate of PPH. The efficacy of this intervention is however, questioned.

Brandt- Andrew's technique for the delivery of placenta:

When the signs of placental separation has appeared, after ensuring the firm contraction of uterus, gentle but steady downward traction is applied to the cord and at the same time countertraction is exerted over the body of uterus in upward direction to prevent the inversion of uterus.

Examination of the placenta

The placenta should be examined after its removal for any missing cotyledons. If it is there, then immediate exploration is necessary.

Abnormalities of the third stage

- Retained placenta
- Inversion of uterus
- Post partum hemorrhage .

Any amount of stored blood cannot equate for a few ml of patient's own blood. So adequate management of third stage is crucial for the prevention of post partum hemorrhage .

PHARMACOLOGY OF UTEROTONICS

The primary mechanism by which hemostasis is achieved at the site of placental separation during the third stage of labor is compression of blood vessels by well contracted myometrium. The following drugs are used in various ways to promote myometrial contractions (Philips and Kinch 1994). They are given alone or in combination.

1. oxytocin
2. Methyl ergometrine
3. Syntometrine

Oxytocin:

- The synthetic form of the octapeptide of oxytocin is commercially available as syntocinon or pitocin.
- It is not effective by mouth.
- The half life of intravenous oxytocin is 3-5 minutes .
- Onset of action: Intravenous dose: within 30 –40 seconds

  Intramuscular dose: after 3 minutes .
- Mechanism of action: It increases the frequency and strength of uterine contraction and augments retraction of uterus.
- No absolute contraindications for its use.

- Deleterious effects can occur with inadvertent use of intravenous oxytocics.

    1. In utero death of fetus
    2. Rupture of uterus

- Side effects:

    1. Maternal hypotension
    2. Cardiac arrhythmias
    3. Water intoxication

- Water intoxication occurs when the rate of infusion is more than 40mU/mt and oxytocin is administered in large volume of electrolyte free solution (Whally and pritchand 1963).[29]

- It should not be given intravenously as a large bolus but rather as a much more dilute solution by continuous intravenous infusion.

- When oxytocin is to be administered in high doses for a considerable period of time, it should be used either in normal saline or ringer lactate solution.

Ergometrine and methyl ergometrine:

- It is an alkaloid obtained from ergot, a fungus that grows in rye and some other grains or it is synthesized from lysergic acid.
- Mechanism of action: causes tetanic contraction of uterus
- Onset of action: Intravenous dose: 30-40 seconds

  Intramuscular dose: 7 minutes
- Maximum dose: 5 doses, total of 1 mg.
- It requires storage at 2 to 8^{o} C and must be protected from light.[30]
- Ergometrine loses 90% of its potency after 1 year of storage at 21^{o}C to 25^{o}C [31]

Side effects

- Nausea, vomiting, dizziness
- Headache
- Transient but severe hypertension rarely
- Intracerebral hemorrhage
- Myocardial infarction
- Cardiac arrest

- Postpartum eclampsia
- Pulmonary edema
- Paraesthesia, tingling, numbness, frank gangrene.

Contraindications:

Absolute:

Before the third stage of labour

Relative:

Liver disease

Heart disease

Hypertension

Vascular disorders

Renal disease

Syntometrine:

- Combination of 5 units of oxytocin with 0.5mg ergometrine.
- It is given intramuscularly.
- Hypertension is not a significant problem with it.

Time taken by various drugs to act and their mode of action can be summarized as follows:

Drug	**Onset of action**	**Mode of action**
Oxytocin IM	3 minutes	Induces rhythmic contraction and augments retraction
Ergometrine IM IV	7 minutes 20-40 sec	More prolonged tetanic contraction
Syntometrine IM	2 minutes	Minimal maternal side effects
PG $F_2 \alpha$ IM	5 minutes	Myometrial contraction vasoconstriction.

Though prophylactic methyl ergometrine has its own advantage of reducing the post partum blood loss its major disadvantage is transient but severe hypertension. However evidence[32] suggests that the benefits of routine oxytocin administration outweigh the less likely risks.

Mitchell and Elbourne et al 1993 [33] found Intramuscular syntometrine to be more effective than oxytocin alone in the prevention of postpartum hemorrhage .

PHARMACOLOGY OF MISOPROSTOL

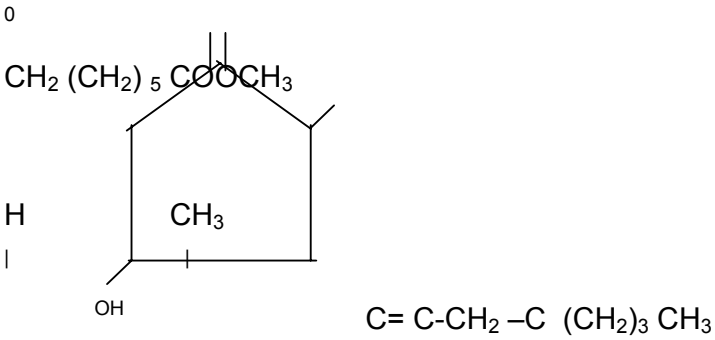
Introduction:

Prostaglandin was the name given by Von Euler in 1935 to a substance found in extracts and secretions from the human prostate and seminal vesicles. They are derived from arachidonic acid.

Chemistry

Prostaglandin (PG) are 20 carbon atom polyunsaturated fatty acids with a five membered cyclopentane ring and two side chains. Depending upon the structure of the carbon ring, PGs are named A to I. PGE_1, E_2, E_3 are named according to the number of double bonds respectively.

The chemical formula of misoprostol is $C_{22}\ H_{38}O_5$



Mechanism of action:

1. It binds to both E2 and E3 prostanoid receptors and stimulates myometrial contraction.

2. It exerts a protective effect on the gastro intestinal mucosa by increasing mucus and bicarbonate ion secretion and it also inhibits acid secretion.

Characteristics of misoprostol

Misoprostol

- Is inexpensive
- Is easily stored (shelf-life- 3 years)
- Has a minimal effect on cardiovascular and bronchial smooth muscle and hence can be used in hypertensive and asthmatic patients.
- Available as 100mcg and 200mcg tablets.
- Route of administration - oral, vaginal, rectal, sublingual.
- Stable at room temperature. So no need for refrigeration.

Pharmacokinetics

The exact time of onset, peak and duration of action following the administration of misoprostol rectally have not been studied in detail so far. But various clinical studies [9,10] have shown that arrest of hemorrhage occurs within 3-10minutes of rectal administration of 800-1000ug of misoprostol in PPH patients.

- Following the absorption, it is de-esterified and converted to its active pharmacological form misoprostol acid, which is responsible for various clinical activities.

- Primary site of metabolism of this drug is in liver and less than 1% is excreted in urine. So dose has to be adjusted in patients with liver disease.[34] Since presystemic hepatic metabolism does not occur with rectal administration there is greater bioavailability and less side effects.

- This drug has no known drug interaction.

Side effects:

- Nausea
- Vomiting
- Headache
- Diarrhoea
- Uterine cramps
- Shivering
- Pyrexia

Gastrointestinal side effects are more with oral administration. Most common side effects with rectal administration are pyrexia and shivering .

Contraindications:

Absolute: Hypersensitivity

Relative:

- Cardiovascular disease
- Liver disease
- Bronchial asthma
- Hypertension
- Renal disease
- Convulsive disorders
- Prior uterine surgery.

Other uses of misoprostol

- Cervical ripening and induction of labour
- First and second trimester abortion
- Treatment of peptic ulcer.

AIM OF THE STUDY

To determine the effectiveness and safety of misoprostol administered rectally for the prevention of PPH.

To compare the efficacy of rectal misoprostol with the intravenous methyl ergometrine in reducing the blood loss during the third stage of labor in mothers at risk for PPH.

MATERIALS AND METHODS

This randomized prospective comparative study was carried out at Govt. Kasturba Gandhi Hospital, Madras Medical College, Chennai, during the period of October 2004 to August 2005 on hundred patients who were admitted to labor ward with any of the risk factors for PPH. All the patients included in the study had vaginal delivery.

The patients were assigned into two groups:

Group I: Includes fifty patients in whom prophylactic methyl

(Control) ergometrine was used intravenously as part of the active management of labor.

Group II: includes fifty patients in whom 800 mcg of misoprostol

(Study) was kept rectally immediately after delivery of anterior shoulder.

Inclusion criteria:

Following were the inclusion criteria on the basis of which the patients were included in the study:

- Overdistended uterus as in big baby, multiple pregnancy hydramnios.

- Prolonged labour
- High parity (5 and above)
- Abruptio placenta
- Precipitate labour
- Chorioamnionitis
- Prolonged use of oxytocin
- Previous history of PPH
- Where vaginal or instrumental delivery is not contra indicated

Exclusion Criteria:

Patients with following risk factors were excluded from the study.

- Heart disease
- Epilepsy
- Severe anemia
- Traumatic PPH
- Hepatic disorders
- Disorders of blood coagulation
- Previous scarred uterus
- Where vaginal delivery is not contemplated

Procedure of drug administration

In group I 0.2 mg of methyl ergometrine was administered intravenously soon after delivery of the anterior shoulder of the baby.

In group II , four 200 mcg of misoprostol tablets soaked in saline were kept rectally soon after delivery of the anterior shoulder of the baby.

Estimation of blood loss:

Immediately after delivery of the baby when all liquor was drained out, the patient was brought to the edge of the table where an inflated kelley's pad was kept ready to be placed under the patient's gluteal region. The lower end of pad was inserted into a measuring jug of 2 litre capacity with every 20ml graduations. The blood, which escapes per vaginum, gets collected in the jug. After 20-30 minutes , the clots in the jug was weighed separately and added to the amount of blood in the jug. The average immeasurable blood loss due to episiotomy was taken as 50ml (from the average calculated from normal vaginal delivery with episiotomy) and the same is not included in the blood loss calculated. Similarly, when there was profuse bleeding following episiotomy, such patients were excluded from the study.

The following factors were noted in all patients:

1. Time taken for the delivery of placenta from the time of administration of prophylactic methyl ergometrine in group-I and the

rectal administration of misoprostol in group II

2. The amount of blood loss.
3. The blood pressure measurements taken 5minutes after the drug administration.
4. Any complications.
5. Side effects of drugs (if any) – noted
6. Need for medical / surgical interventions and blood transfusion.
7. Difference in antepartum and the post partum hemoglobin levels measured 48 hrs after delivery.

All these factors were compared between the two groups.

RESULTS

This study was carried out at Govt Kasturba Gandhi Hospital, during the period of October 2004 – August 2005. 100 women were included in this study and the outcome analyzed using various parameters. The results are subjected to statistical analysis using the *t* test and chi-square test.

Table I – Age distribution n=100

S.no	Age	Group I		Group II	
		No.of cases	%	No.of cases	%
1.	<20	3	6%	5	10
2.	20-25	25	50%	19	38
3.	26-30	17	34%	21	42
4.	30-35	4	8%	5	10
5.	>35	1	2%		

- Most of the patients in both the control and study group were in the age group of 20-30 years. (80-84%)
- 6% cases in control group and 10% cases in study group were in the age group of less than 20 years.
- Only 1 case (2%) in control group was above 35 years.
- Youngest in this study was 18 years old and eldest was 37 years old.

Table II Booking status n=100

S.no	Booking status	Group I		Group II	
		No. of cases	%	No. of cases	%
1.	Booked	50	100%	49	98
2.	Un Booked	-	-	1	2%

- All of the patients except one in study group were booked cases though they were selected at random basis.

Table III Socio economic status n=100

S.No	Socio economic status	Group I		Group II	
		No. of cases	%	No. of cases	%
1.	I				
2.	II				
3.	III				
4.	IV	6	12%	8	16%
5.	V	44	88%	42	84%

- 88% of cases in control group and 84% of study group were belonged to class V socio economic status.

Table IV - Distribution of gravidity n=100

S.No	Gravida	Group I		Group II	
		No. of cases	%	No. of cases	%
1.	G1	15	30	18	36
2.	G2	22	44	20	40
3.	G3	7	14	8	16
4.	G4	4	8	3	6
5.	5 above	2	4	1	2

- 44% of cases in control group and 40% of cases in study group were second gravida.
- 30% of cases in control group and 36% of cases in study group were primigravida.
- 2 cases in control group and, 1 case in study group were grand multipara.

Table V – Risk factors n=100

S.No	Risk factors	Group I		Group II	
		No. of cases	%	No. of cases	%
1.	Over distended uterus a. Big baby b. Hydramnios c. Multiple pregnancy	28 18 4 6	56%	29 17 5 7	58%
2.	Prolonged labour	20	40	17	34
3.	Abruptio placenta			3	6
4.	Grand multi	2	4	1	2

- 56% of cases in control group and 58% of cases in study group had over distended uterus in the form of either fetal macrosomia, hydramnios or multiple pregnancy.
- 40% of cases in control group and 34% of cases in study group had prolonged labor.
- 3 cases of abruption were included in study group.
- 2 cases in control group and 1 case in study group were grand multipara.

Table VI – Onset of labor n=100

S.No	Onset of labour	Group I		Group II	
		No. of cases	%	No. of cases	%
1.	Spontaneous	38	76	32	64
2.	ARM & oxytocin	7	14	12	24
3.	PGE_2 alone	3	6	3	6
4.	PGE_2 + oxytocin	2	4	3	6

- 76% of cases in control group and 64% of cases in study group had spontaneous onset of labor.
- In 14% of cases in control group and 24% of cases in study group, labor was induced with ARM and oxytocin.
- In 6% of cases in control group and 6% of cases in study group, labor was induced with PGE_2 gel alone.
- In 4% of cases in control group and 6% of cases in study group, labor was induced with both PGE_2 gel and oxytocin.

Table VII – Nature of delivery n=100

S.No	Nature of delivery	Group I		Group II	
		No. of cases	%	No. of cases	%
1.	LN	19	38	23	46
2.	LN with episiotomy / LPII°	27	54	20	40
3.	Vacuum	1	2	5	10
4.	Forceps	3	6	2	4

- 38% of cases in control group and 46% of cases in study group had normal vaginal delivery.
- 54% of cases in control group and 40% of cases in study group were delivered by labor natural with episiotomy or perineal lacerations of II°.
- 8% of cases in control group and 14% of cases in study group had assisted vaginal delivery either vacuum extraction or forceps. In all these patients, traumatic PPH had been ruled out.

Table VIII – Duration of III stage of labor n=100

S.No	Duration of III stage (in minutes)	Group I		Group II	
		No. of cases	%	No. of cases	%
1.	< 2	15	30	2	4
2.	2 – 4	30	60	23	46
3.	4 – 6	4	8	19	38
4.	6 – 8	-	-	6	12
5.	>8	1	2	-	-

- In 90% of cases in control group, the duration of third stage of labor was less than 4 minutes , whereas in study group only in 50% of cases the duration of third stage of labor was less than 4 minutes .
- In significant number of cases in study group (50%) the duration of third stage was more than 4 minutes .

Table IX Comparison between duration of III stage of labor in both the groups n=100

S.No	Group	No. of cases	Mean duration in minutes	SD	't' value	P value
1.	I	50	3.25	2.633	2.943	0.01
2.	II	50	4.5	1.446		

- Mean duration of third stage of labor in control group was 3.25 minutes and in study group it was 4.5 minutes.

- The difference in the mean duration of third stage of labor between control and study group was 1.25 minutes . which is not statistically significant (p=0.01).

Table X – Amount of blood Loss n=100

S.No	Amount of blood loss in ml	Group I		Group II	
		No. of cases	%	No. of cases	%
1.	<100 ml	3	6	-	-
2.	100 – 200	25	50	6	12
3.	200 – 300	15	30	19	38
4.	300 – 400	3	6	16	32
5.	400 – 500	2	4	5	10
6.	>500 – 1000	1	2	4	8
7.	>1000	1	2	-	-

- Only 6% cases in control group had blood loss of less than 100ml. All the patients in study group had blood loss of more than 100ml.
- 50 % cases in control group had blood loss in the range of 100 – 200ml.
- 38% of cases in study group had blood loss in the range of 200 – 300ml.
- 8% of cases in study group had blood loss of more than 500ml, which is significant.

- Only 4% of cases in control group had blood loss of more than 500ml.
- One case in control group had severe postpartum hemorrhage of about 1400ml.

Table XI – Risk factors n=100

S.No	Risk factors	Group I	Group II
		Blood loss in ml	Blood loss in ml
1.	Over distended uterus	191.78	286.20
2.	Prolonged labor	315	361.17
3.	Abruption	-	350
4.	Grand multi	150	220

- Mean blood loss in cases with overdistended uterus in control group was 191.78 ml, whereas in study group it was 286.2 ml.
- Mean blood loss in cases with prolonged labor in the control group was 315 ml and it was 361.17ml in study group .
- 3 cases in study group with abruption had average blood loss of 350ml.
- In cases of grand multipara, the mean blood loss in control group was 150ml and in the study group was 220ml.
- There was significantly increased blood loss in study group when compared to the control group.

- Among all the risk factors, patients with prolonged labor had significantly increased blood loss.

Table XII: Blood loss statistical analysis n=100

S.No	Group	No. of cases	Mean in ml	Standard Deviation	't' value	P value
1.	I	50	241.4	191.19	2.366	0.05
2.	II	50	315.44	111.35		

- The difference in mean blood loss between the study and control group was 74 ml.
- Though, the mean blood loss of 74 ml is high in study group, it is not statistically significant.
- Intravenous methyl ergometrine is superior to rectal misoprostol in reducing the third stage blood loss.

Table XIII – Analysis of complications n=100

S.No	Group	PPH	%
1.	I	2	4%
2.	II	4	8

- In this study, the incidence of post partum hemorrhage was 8% in study group, compared to only 4% in control group.
- One case in the control group had severe postpartum hemorrhage .

Table XIV – Interventions and Blood transfusion n=100

S.No	Interventions	Group I		Group II	
		No. of cases	%	No. of cases	%
1.	Medical	2	4	6	12
2.	Surgical	1	2	-	-
3.	Blood transfusion	1	2	1	2

- 12% of cases in the study group required additional oxytocics for the control of bleeding, whereas only 4% of cases in the control group required additional oxytocics either in the form of 10-20U of oxytocin infusion or $PGF_{2\propto}$ 250mcg IM.
- One case in the control group had severe PPH and required 5 units

of blood. Subsequently, she had undergone subtotal hysterectomy as the bleeding was not controlled with other medical methods.

- One case in study group required one unit of blood for treatment of anemia.

Table XV - Side effects n=100

S.No	Side effects	Group I		Group II	
		No. of cases	%	No. of cases	%
1.	Increase in BP	8	16	0	0
2.	Pyrexia	-	-	7	14
3.	Shivering	-	-	10	20
4.	Nausea	6	12	2	4
5.	Vomiting	2	4	-	-

- Most common side effect noted (16%) in control group was significant increase in blood pressure (10 – 20mm of Hg either systolic or diastolic or both)
- 12% of cases in control group had nausea and 4% of cases in study group had vomiting.
- Most common side effect in study group was shivering noted in 20% of cases.
- 14% of cases in study group had increase in body temperature, but not exceeding 100°C.

Table XVI - Hemoglobin difference n=100

S.No	Hemoglobin difference in gm %	Group I		Group II	
		No. of cases	%	No. of Cases	%
1.	<0.5	39	78	19	38
2.	0.6-1	7	14	23	46
3.	1.1 – 1.5	3	6	6	12
4.	1.6 – 2	0	0	2	4
5.	>2	1	2	0	0

- Hemoglobin difference of less than 0.5% was noted in 78% of control group and 38% of study group.
- Hemoglobin difference of 0.5 to 1gm% was noted in 14 % of cases in control group and 46% of cases in study group.
- Hemoglobin difference of 1.6 –2gm% was noted in 4% of cases in study group.
- One case in control group had severe atonic PPH and the hemoglobin difference of more than 2 gm% was noted in her.

Table XVII: Hemoglobin difference statistical analysis n=100

S.No	Group	Mean hemoglobin (gm %)	SD	T value	'P' value
1.	I	0.53	.702	0.653	0.01
2.	II	0.84	.456		

- Mean hemoglobin difference in control group was 0.53gm%
- Mean hemoglobin difference in study group was 0.84 gm%
- Mean hemoglobin difference between study group and control group was 0.3 gm%, which is not statistically significant.

DISCUSSION

This randomized prospective “Comparative study of efficacy of rectal misoprostol with intravenous methyl ergometrine in the prevention of PPH in at risk PPH mothers” was undertaken in hundred patients , who had any of the risk factors for PPH.

The results of this study were discussed as follows.

- Most of the patients in this study were in the age group of 20-30 years (80-84%)
- Though patients were selected at random basis, 99% of patients were booked cases
- 86% of patients in this study were belonged to class V socio economic status.
- 33% cases were primigravidae and 42% cases were second gravidae and only 3% cases were grand multipara.

- 57% of cases in this study had overdistended uterus as a risk factor (big baby 35%, hydramnios 10%, multiple pregnancy 13%). 37% of cases had the prolonged labor(II stage) as a risk factor .

- According to various literature,

  20% of women have no risk factors for PPH (Varner,M et al).[35]

  PPH was reported to occur in 6-22% of twin deliveries (Newton 1986)[36].

  Recurrence of PPH is 25% (Dewhurst, CJ et al)[37]

- 70% cases in this study group had spontaneous onset of labor and in 30% cases, labor was induced with either ARM & oxytocin , PGE_2 gel alone or PGE_2 gel with oxytocin.

- 89% cases in this study had normal vaginal delivery and 11% of cases had instrumental vaginal delivery (6% vacuum, 5% forceps). Incidence of atonic PPH was 7.3 in vacuum and 12.5% in forceps deliveries (Williams et al 1981)[38]

- In 90% cases in control group, and 50% cases in study group the duration of third stage was less than 4 minutes .

- The mean duration of third stage of labor in control group was 3.25 minutes and in study group was 4.5 minutes . The difference in the mean duration of third stage of labor between the control and study group was 1.25 minutes which is not statistically significant and this study well correlates with the study conducted by Bamigboy et all in 490 low risk women comparing the effectiveness of syntometrine and 400 mcg of rectal misoprostol which showed no difference in the duration of third stage of labor.

- 56% of cases in group I and only 12% of cases in group II had blood loss of less than 200 ml. 50% of cases in study group had blood loss of 200-400 ml which is significant. So rectal misoprostol is less effective in reducing the third stage blood loss when compared to intravenous methyl ergometrine.

- The mean blood loss is relatively high in both the groups who had prolonged II stage when compared to other risk factor

- The mean blood loss in control group was 241.4ml and the mean blood loss in study group was 315.4ml. Though clinically the mean blood loss of about 74.8ml was significantly high with rectal misoprostol, it is not statistically significant

- Arulkumaran and associates, 2004 concluded that oral / rectal misoprostol was less effective than conventional oxytocics. Until alternative regimes of misoprostol are studied in large controlled trials, misoprostol is not recommended for routine use in third stage of labor.

- In this study the incidence of postpartum hemorrhage was 4% in control group and 8% in study group which correlates with a following study.

  In a randomized controlled study comparing the effectiveness of parenteral oxytocics and rectal misoprostol, the incidence of postpartum hemorrhage was 9.8% with rectal misoprostol group and only 3.5 % in the group who received parenteral oxytocics either oxytocin or methyl ergometrine therapy.

- 4% of cases in control group and 12% of cases in study group required additional oxytocics in the form of either 10-20U of oxytocin infusion or PGF_2 ∝250 mcg IM, which differs slightly from the following study.
- Significantly more women needed additional oxytocics in the group that received only rectal misoprostol therapy when compared with the group that received oxytocin and ergometrine therapy (8.3% Vs 2.2%) - Caliskan E et al.[14] Gerstenfeld TS et al compared the rectally administered 200 mg misoprostol to intravenously administered oxytocin for the management of third stage of labor. In this study 23% of misoprostol group and 11% of oxytocin group were required at least one additional agent to control the bleeding.
- One patient in control group had severe atonic PPH. As the bleeding was not controlled with other medical methods, being the multipara subtotal hysterectomy was done. She had prolonged second stage as a risk factor for PPH. 3 units of blood transfused preoperatively and 2 units of blood transfused postoperatively to this patient.
- One case in study group required one unit of blood for anemia

- Postpartum hypertension is the most common side effect noted in control group (16%)

  Chong YS. Su LL, Arulkumaran S et al., 2004 – Active management of third stage of labor though it is superior to expectant management in terms of blood loss and postpartum hemorrhage , it is associated with unpleasant side effects and hypertension when ergometrine is used.

  Most common side effects noted in study group were shivering (20%) and pyrexia (14%)

  Cochrane database systemic review 2001 – Shivering and elevated body temperature (>38°C) are the main side effects of misoprostol and are dose related.

  Khan RU, El Refaey H et al. 2003 - Misoprostol administered rectally is associated with less adverse effects compared to oral misoprostol group . Incidence of severe shivering was significantly reduced by 72%.

- Hemoglobin difference of less than 1gm% was noted in 92% of cases in control group and 84% of cases in study group.

- Mean hemoglobin difference was 0.53 gm% and 0.84gm% in control and study group respectively . The difference between these 2 groups was 0.31gm% which does not have any statistical significance.

- Karkanis SG associates, 2002 - No difference in hemoglobin was observed between the 400 mcg rectal misoprostol group (0.16 gm%) and the parenteral oxytocin group 0.14gm%

From this study, rectal misoprostol was found to be less effective in reducing the postpartum blood loss.

Viller and collegues 2002 reviewed prophylactic use of misoprostol to prevent postpartum hemorrhage and concluded that oxytocin or oxytocin – ergot prepartions are more effective.

SUMMARY

This present prospective study “Comparative study of efficacy of rectal misoprostol versus intravenous methylergometrine in the prevention of PPH in at risk PPH mothers” was carried out at Govt. Kasturba Gandhi Hospital Madras Medical College, Chennai during the period October 2004 – August 2005.

Total of hundred cases who had any of the risk factors for PPH were included in the study.

Group I

Included fifty patients in whom intravenous methyl ergometrine was administered following delivery of anterior shoulder.

Group II

Included fifty patients in whom, 800 mcg of misoprostol was kept rectally following delivery of the anterior shoulders.

The efficacy of prophylactic intravenous methyl ergometrine, and rectal misroprostal in reducing the postpartum blood loss were compared in terms of duration of third stage, amount of blood loss, need for additional oxytocic therapy and change in prenatal and postnatal hemoglobin level in gm % and the results were statistically analyzed.

Observations of this study includes,

- Most of the patients were in the age group of 20-30 years.
- 99% of cases were booked and most of the patients were belonged to class V socio-economic status.
- 42% of cases were second gravida 33% of cases were primigravida and 3 case were grand multipara.
- 54% of cases had overdistended uterus and 37% of cases had prolonged labor as the risk factor for PPH.
- 70% of cases had spontaneous onset of labor and in remaining 30% of cases labor was induced with either ARM & oxytocin, PGE_2 gel alone or PGE_2 with oxytocin.
- 47% of patients were delivered by labor natural with episiotomy or perineal laceration of II^o. 11% of cases had operative vaginal delivery either vacuum extraction or forceps delivery in whom traumatic PPH had been ruled out.
- The duration of third stage in 90% of cases in control group was less than 4minutes , and only in 50% of cases in study group it was less than 4 minutes .
- The difference in the mean duration of third stage of labor between the two group was 1.25 minutes .
- 56% of cases in control group had blood loss of lessthan 200ml. Only 12% of cases in study group had blood loss of lessthan200ml.

70% of cases in study group had blood loss of 200 - 400ml.

- Prolonged labor is associated with significantly increased blood loss, when compared to other risk factors.
- The difference in mean blood loss between the two groups was 74ml. Comparing the absolute blood loss, parenteral methyl ergometrine appears to be more effective than rectal misoprostol in reducing postpartum blood loss.
- Incidence of PPH was 8% in study group as compared to only 4% in control group.
- 12% cases in study and 4% cases in control group required additional parenteral oxytocic drugs.
- The major side effects noted in study group were pyrexia (14%) and shivering (20%)
- Common side effect noted in control group was increase in blood pressure. (16%)
- Hemoglobin difference of less than 1gm% was noted in 92% of cases in control group and 84% of cases in study group.
- Mean hemoglobin difference between control and study group was 0.31gm%, which has no statistical significance.

CONCLUSION

- Active management of third stage of labor should be the routine management of choice for women expecting to deliver a baby by vaginal route in a maternity hospital.
- Rectal misoprostol is less effective than intravenous methyl ergometrine as part of the active management of third stage of labor for prevention of postpartum hemorrhage .
- Misoprostol need not replace oxytocin or ergometrine for prophylaxis in hospitals where these drugs could be properly stored.
- Misoprostol is a very valuable drug in the armamentarium of doctors in rural setting and especially midwives, who work in the periphery in developing countries, where these parenteral drugs could not be stored at the desired temperature and where parenteral drugs are impractical to administer or simply not available.
- In above situations, misoprostol which is inexpensive, thermo stable with good safety profile will have clear advantages over other conventional injectable oxytocics like methyl ergometrine .
- This drug can be safely administered even by paramedical personnel while referring a mother with PPH to higher

institutions.

- So, misoprostol deserves a special place in every pharmacy, health post and midwifery list and has considerable potential to reduce the maternal mortality from postpartum hemorrhage in developing countries.

So, in countries with high maternal mortality and limited resources, introducing low cost, evidence based practices that prevent PPH is an important way to improve women's health.

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PROFORMA

"COMPARATIVE STUDY OF EFFICACY OF RECTAL MISOPROSTOL VERSUS INTRAVENOUS METHYLERGOMETRINE IN THE PREVENTION OF PPH IN AT RISK PPH MOTHERS "

Name: Age Unit IP No.

Socioeconomic status Married: Booked / Unbooked

Obstetric Formula :

LMP :
EDD :

At Risk Factors :
- Big baby
- Hydramnios
- Multiple pregnancy
- Abruption
- Previous History of PPH
- Prolonged labour
- Grandmulti

Onset of labour ;
- Spontaneous
- Induced – ARM and oxytocin
- PGE2 gel without oxytocin
- **PGE 2 with Oxytocin**

Duration of labour :
- First stage
- Second stage

Nature of delivery :

Management of third stage of labor: Active management

1. Phylactic intravenous methyl ergometrine-0.2mg
2. Rectal misoprostol-800 mcg

Duration of third stage :

Amount of blood loss :

Complications : PPH
Retained placenta
Others

Any other drugs given : Ergot
Oxytocin
Inj. prostagladin

Surgical intervention : Manual removal of placenta
: Stepwise ligation
Hysterectomy

Blood transfusion : No. of units

Side effects :

Outcome : Maternal

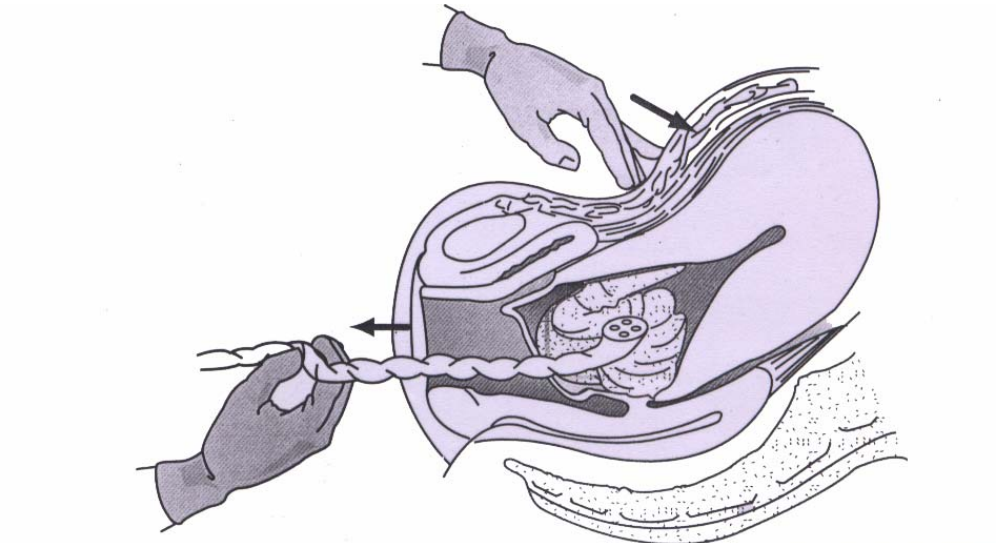
: Fetal

Investigation :

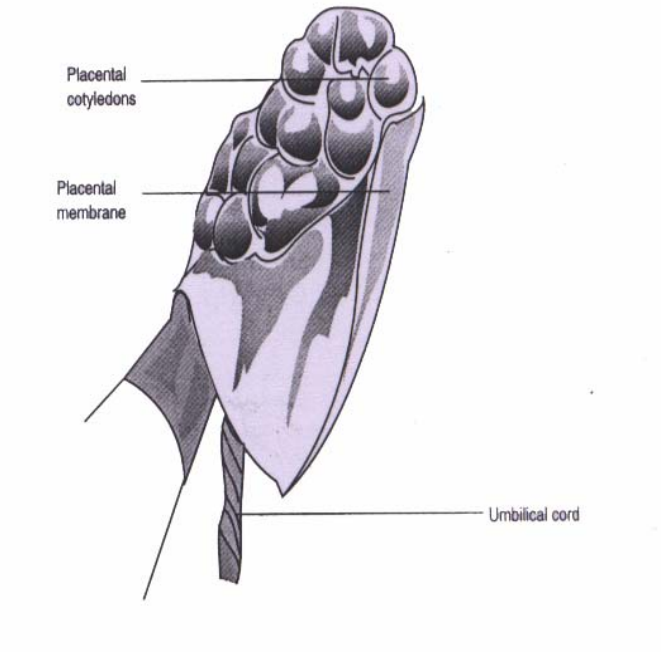
Antenatal hemoglobin
Postnatal hemoglobin
Hemoglobin difference

GLOSSARY

PPH	:	Postpartum hemorrhage
WHO	:	World Health Organization
PGE_1	:	Prostaglandin E_1
PGE_2	:	Prostaglandin E_2
$PGF_2 \alpha$	:	Prostaglandin $F_2 \alpha$
ARM	:	Artificial rupture of membranes
LN	:	Labor naturale
LP II°	:	Perineal Laceration II °
mcg	:	Micro gram.
mU/mt	:	Milliunits / minutes
IV	:	Intravenous
IM	:	Intramuscular



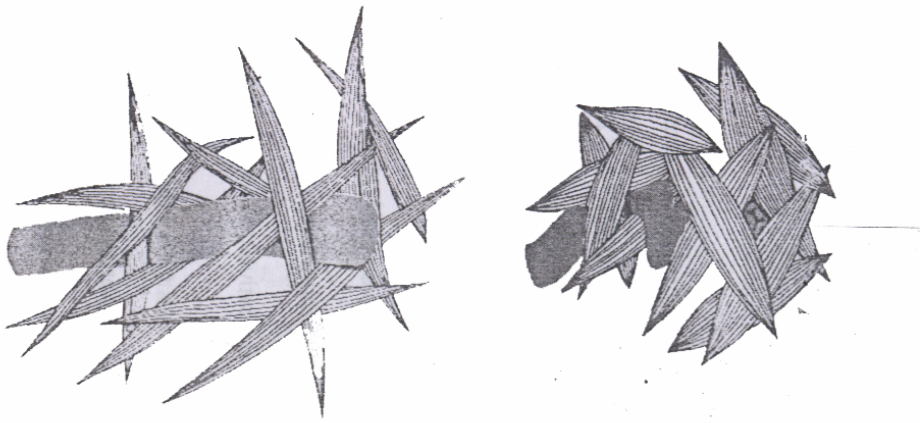
Brandt – Andrews Maneuver : Delivery of Placenta

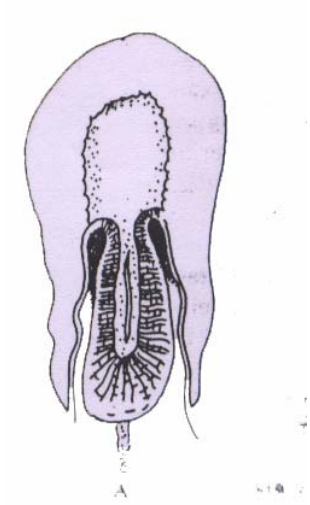


Examination of the Placenta

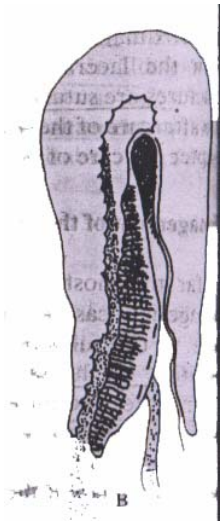
Brandt – Andrews Maneuver : Delivery of Placenta

Mechanism of Control of Bleeding in Third Stage (Living Ligatures)





Schultz mechanism



Duncan mechanism