COMPARATIVE STUDY OF MISOPROSTOL VS OXYTOCIN IN INDUCTION OF LABOUR IN TERM PRELABOUR RUPTURE OF MEMBRANES

DISSERTATION SUBMITTED FOR

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BONAFIDE CERTIFICATE

This is to certify that the dissertation titled "Comparative Study of Misoprostol Vs Oxytocin in Induction of Labour in Term Prelabour Rupture of Membranes" is the bonafide work of Dr.S.Vilvapriya in the Institute of Obstetrics and Gynaecology,Madras Medical College,Chennai during the period of her postgraduate study for MD BranchII Obstetrics and Gynaecology,from 2003--2006 under the guidance and supervision of Additional Professor Dr.Mohanambal MD.DGO, Unit chief, Institute of Obstetrics and Gynecology, Madras Medical College, Chennai.

The dissertation is submitted to "The TN Dr. MGR Medical University" in partial fulfillment of University Regulations for the award MD Degree in Obstetrics & Gynecology.

This dissertation has not been submitted previously to any University by me for the award of any degree / diploma.

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CONTENTS

Introduction

Prelabour Rupture of membranes is a common obstetrical problem. It is a significant event as it transforms an ordinary pregnancy into a high risk one. Management depends upon careful weighing of fetal condition, neonatal intensive care facilities and presence of complicating factors. Overall incidence is 5-10%

Premature Rupture of membranes is defined as “Rupture of membranes prior to onset of labour” by Embrey (1953), Flowers (1962), Downley (1958), & Eastman (1966).

According to Prof. Chauha & Arulkumaran prelabour rupture of membranes is “Spontaneous breach of chorio amnion with release of amniotic fluid with latent period before the onset of labour”.

Authors like Ianios(1965) and Lebher(1963) diagnose PROM only when a latent period of 1-12 hours has elapsed following amniorrhexis occurring at anytime prior to the onset of labour, regardless of period of gestation.

Majority of Cases of PROM – of about 60% occur after 37 completed weeks. PROM is a significant event that transforms pregnancy into a high risk one by increasing maternal and neonatal morbidity and mortality. Maternal complications like Chorioamnionitis, puerperal fever are more common in PROM. Active management of PROM decreases complications and associated maternal and neonatal morbidity and mortality.

Induction of labour is artificial or non-spontaneous initiation of uterine contractions that leads to progressive cervical dilatation and effacement resulting in delivery of baby or products of conception.

Since early days of 1950's when Oxytocin was synthesized, induction of labour has become more popular and accepted as an option in the management of PROM.

Misoprostol, a methyl ester of PGE1 is being under trial for past few years in induction of labour. Misoprostol is receiving attention as a cervical modifier and labour induction agent.

This study compares the safety and efficacy of Misoprostol with Oxytocin in labour induction in Term Prelabour rupture of membranes.

AIM OF THE STUDY

The present study is undertaken to compare the safety and efficacy of Misoprostol with that of Oxytocin in labour induction in TERM PROM.

The effects were compared between Primipara and Multipara in a selected sample.

OBJECTIVES: -

1) To study the effect on labour induction and compare the induction – delivery interval between 2 drugs.

2) To compare the mode of delivery between 2 groups.

3) To compare the foetal and maternal adverse effects between 2 drug groups.

4) To compare the maternal and foetal outcome between 2 drug groups.

5) To assess the cost effectiveness between 2 drugs.

REVIEW OF LITERATURE

ANATOMY

The human foetal membranes is composed of inner amnion and outer chorion (Bourne 1962)

Amnion is an avascular structure of thickness 0.2 – 0.5mm. It provides almost all of the tensile strength of the membranes. The Amnion at term is a tough and tenacious but pliable membrane. The development of the components of the amnion that protects against rupture or tearing is vitally important to successful pregnancy outcome.

Borne (1962) described five separate layers of amniotic tissues. They are

1) Single layer of cuboidal epithelial cells.
2) Basement membrane.
3) Acellular compact layer composed of I, III, V interstitial collagens.
4) Row of fibroblast like mesenchymal cells.
5) Acellular zona spongiosa.

Chorion is a thick opaque friable avascular structure of thickness varying from 0.02 – 0.2mm.

Intact membranes prevents ascending infection as it forms an effective barrier. They maintain a fluid environment on which foetus depends upon for its survival. They facilitate cervical dilatation and effacement. Membranes are rich source of glycerophospholipids containing Arachidonic acid, which are precursors of prostaglandins like PGE2 and PGF2α

AMNIOTIC FLUID

Speculative theories about the origin of amniotic fluid: -

1) Initially the fluid is formed from the primitive cells around the amniotic vesicle.
2) Later there is transudate of fetal extra cellular fluid through the skin and umbilical cord.
3) Diffusion to some extent occurs through the amniotic membrane.
4) In second trimester when the skin becomes keratinised fetal urine and secretions from tracheobronchial tree contributes to major volume of amniotic fluid.
5) Amniotic fluid volume is about 50ml at 12 weeks, 400ml at 20 weeks, 1000ml at 36 weeks and 800ml at 40 weeks.

FUNCTIONS

1) Amniotic fluid cushions and protects the fetus from physical trauma.
2) It distends the amniotic sac and allows further growth and free movement of the fetus.
3) It serves to maintain an even temperature.
4) When appropriately tested, it provides information about fetal maturity.

5) It promotes surfactant synthesis.

During labour

6) It forms a hydrostatic wedge, which helps in dilation of the cervix.
7) When the membranes are intact, it prevents interference with placental circulation during uterine contractions.
8) It prevents ascending infection to the uterine cavity at the end of first stage of labour by flushing and bactericidal action.

RISK FACTORS FOR PROM

1.REMEDIABLE RISK FACTORS

1.Cervico vaginitis

2.Incompetent cervix

3.Cigarette smoking

4.prenatal Diagnostic procedures like amniocentesis etc

5. * Coitus, Mineral and vitamins deficiencies, cervical examinations

* Lacks conclusive confirmation

2. NONREMEDIABLE RISK FACTORS

1. Prior PROM or preterm delivery
2. Prior cervical surgical procedure
3. Vaginal bleeding –abruptioplacentae, placenta previa etc
4. Ehlers Danlos syndrome
5. * Fetal gender (Male)

* Lacks conclusive confirmation

PROSTAGLANDINS

The existence of this group of very interesting substances has been known for many years and more than a dozen of prostaglandins have been identified. Levels of prostaglandins and their metabolites are increased during labor.

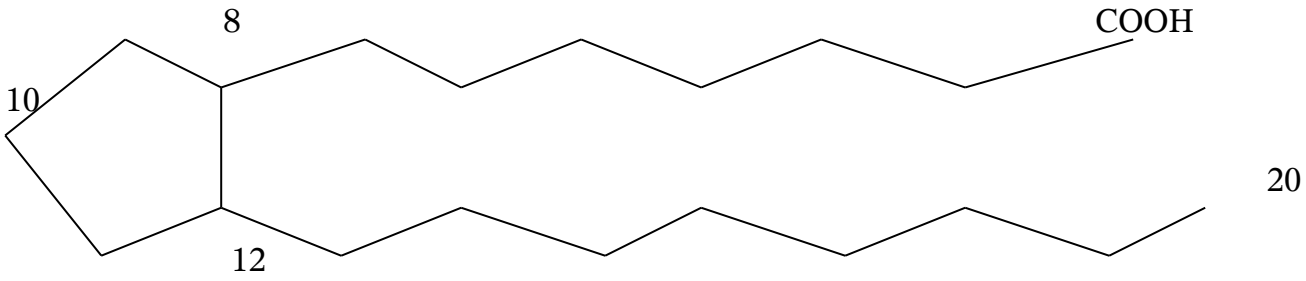
The treatment of pregnant women with prostaglandins by any of several routes of administration causes abortion or labour at all stages of pregnancy.

Prostaglandin treatment of myometrial smooth muscle tissues in vitro causes contractions depending upon the prostanoid tested and physiological status of the tissues treated**.**

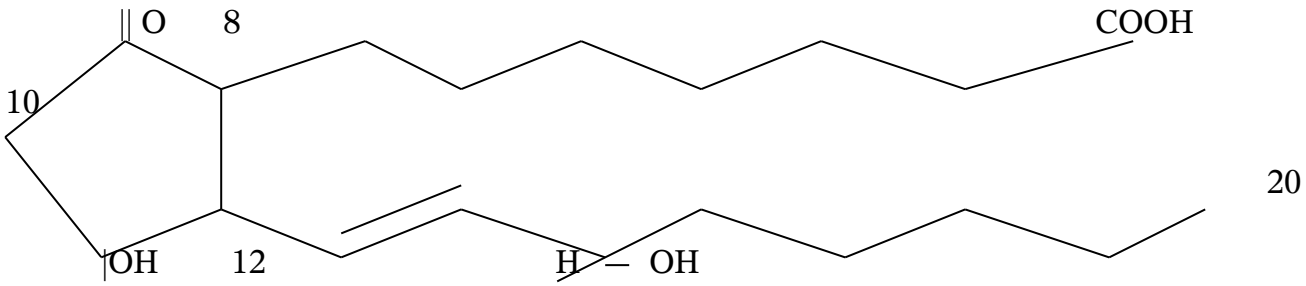
CHEMISTRY

The Prostaglandins are derivatives of prostanoic acid. They are family of highly active 20 carbon fatty acids containing a cyclopentane ring and 2 aliphatic side chains. Depending upon the configuration of the 5-carbon ring each belongs to one of the groups A to I. For each group a suffix numeral (1,2,or 3) describes the degree of unsaturation (Number of double bonds of the side chain).

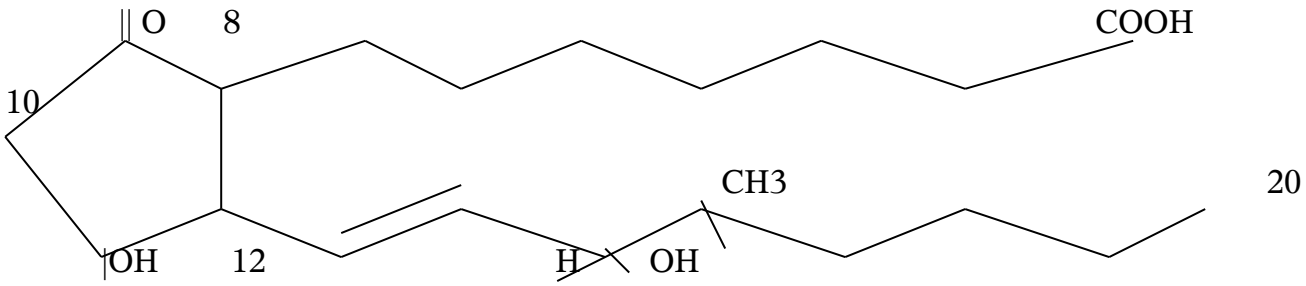
Prostanoic Acid



PGE1



Misoprostol



Caution is needed when using any prostaglandin preparation in patients with glaucoma, asthma, severe hepatic / renal impairment. No teratogenesis or fetotoxic effects have been observed in animal studies.

MISOPROSTOL: -

It is a Methyl ester of PGE1 additionally methylated at C16. It is orally active synthetic ProstaglandinE1 analogue. It is extensively absorbed and undergoes rapid de-esterification to

its free acid, which is responsible for clinical activity. T-max of Misoprostol acid is 12(+or-) 3 minutes and terminal half-life of 20-40 minutes. Misoprostol is stable at room temperature.

Systemic bioavailablity of vaginally administered Misoprostol is 3 times greater than the oral administration. It stimulates the uterine contraction probably by increasing formation of gap junctions in myometrium.

Side effects of Misoprostol are vomiting diarrhoea, dyspepsia, abdominal pain, fever, hyperstimulation syndrome, uterine rupture, cervical laceration and rarely anaphylactic reactions.

OXYTOCIN: -

It is an octapeptide secreted by posterior pituitary along with ADH.

Pituitary extract was first used in labour in 1909. Vigneaud in 1963 separated Oxytocin and ADH. Both are synthesized in supra optic and Para ventricular nuclei of hypothalamus and stored in nerve endings in neurohypophysis. Oxytocin was the first polypeptide hormone synthesized and the 1955 Nobel Prize in chemistry was awarded for this (Vigneaud and co-workers).

Oxytocin is inactive orally. Plasma half-life is 10 minutes in in-vivo studies. It is rapidly

degraded in liver and kidney.

Continuous intravenous infusion of Oxytocin shows first order kinetics with a progressive stepwise increase with every increase in infusion rate, a steady plasma concentration is reached 40-60 minutes after the alteration of an infusion. Uterine response occurs within 3 to 5 minutes of beginning infusion.

Side effects are water intoxication due to injudicious use, hyper stimulation, uterine rupture, cervical lacerations etc can occur. Sometimes hyperbilirubinemias seen in neonates. If aqueous fluids are infused in appreciable amounts along with Oxytocin water intoxication can lead to convulsions, coma and even death.

Oxytocin regimens for stimulation of labour.

Regimen	Starting Dose (mU/Min)	Incremental Dose (mU/min)	Dosage interval (min)	Maximum Dose (mU/min)
Low dose	0.5-1 1- 2	1 2	30-40 15	20 40
High dose	6	6[a], 3,1	15-40	42

a-The incremental increase is reduced to 3mU/min in presence of recurrent Hyper stimulation.

The woman should have direct nursing supervision while Oxytocin is being infused. The goal is to effect uterine activity that is sufficient to produce cervical change and fetal descent while

avoiding uterine hyper stimulation. Contractions must be evaluated continuously and oxytocin discontinued if they persist as greater than 5 in 10 minutes or 7 in 15 minutes period; If they last longer than 60 to 90 seconds or if the fetal heart rate pattern becomes non reassuring when oxytocin is stopped, its concentration in plasma rapidly falls because the mean half life is approximately 5 minutes. Either low dose or high dose regimen can be used employing flexible dosing schedule based on hyper stimulation.

Cervical Scoring systems

Bishops's score (Bishop 1964)

	0	1	2	3
Dilatation (cm)	0	1-2	3-4	5-6
Effacement (percent)	0-30	40-60	60-70	80+
Station	-3	-2	-1/0	+1/+2
Consistency	Firm	Medium	Soft	-
Position	Posterior	Mid-position	Anterior	-

Modified Bishops's score (Calder 1974)

	0	1	2	3
Dilatation (cm)	<1	1-2	2-4	>4
Effacement(cm)	>4	2-4	1-2	<1
Station	-3	-2	-1/0	+1/+2
Consistency	Firm	Average	Soft	-
Position	Posterior	Mid-anterior	-	-

Expected problems in Induction

1. Failure to labour induction.
2. Unforeseen disproportion.
3. Prematurity.
4. Sepsis.
5. Cord compression and
6. Accidental hemorrhage.

Diagnosis of PROM

1. History of leak or sudden gush of fluid from the vagina and a sterile speculum examination may reveal the leakage of liquor.

2.The nitrazine Test

It has an accuracy of 90 to 95 percent. It differentiates the alkaline pH of amniotic fluid (7 to 7.5) and acid pH of vaginal fluid (4-4.5)

3**. The fern Test**

The fluid is dried on a slide and observed under microscope. Fern pattern is seen due to crystallization of sodium chloride in amniotic fluid

4**.The Nile blue Sulphate Test**

The presence of desquamated cells from the fetal skin, which stains orange, indicates ruptured membrane.

5.**Intra amniotic dye instillation**

Instillation of indigo carmine, Evans blue, sodium flourescein and examination of vaginal fluid on pad for the presence of dye after the few hours is useful.

6**.AMNIOSCOPY**

It may reveal the absence of membranes. This is not done routinely.

7**.DIAMINE OXIDASE TEST**

Diamine oxidase is produced by decidual cells, enters amniotic fluid and can be detected by paper strips.

8**. Heat Test**

Endo cervical material is heated on a glass slide and the color of the residue is noted. A white residue indicates the presence of amniotic fluid and a brown one indicates its absence.

9.Measurement of alpha feto protein in vaginal fluid is a recent test.

10.Monoclonal antibodies to fetal fibronectin or used to detect the presence of amniotic fluid in vaginal secretions.

11.ULTRA SOUND

To know the amount of liquor left behind and for fetal maturity, USG is done.

Management

Spontaneous rupture of membranes occurs relatively frequently. Reported incidence of PROM Varies between 2-18%. (Lebterz 1964, Sanyal it al) Overall about 10% of the pregnancies are complicated by PROM. Of these 60% occur in term pregnancies.

Early and increase in rise in perinatal morbidity with an increase in latent period makes early decision mandatory. There should be no delay in immediate induction if foetus is judged to have good chance of extra uterine survival.

There are two problems in term PROM with unfavourable cervix – 1. Risk of infection when induction is postponed. 2. Failed induction resulting in increased caesarean section rate.

Algorithm for management of a term patient with PROM.

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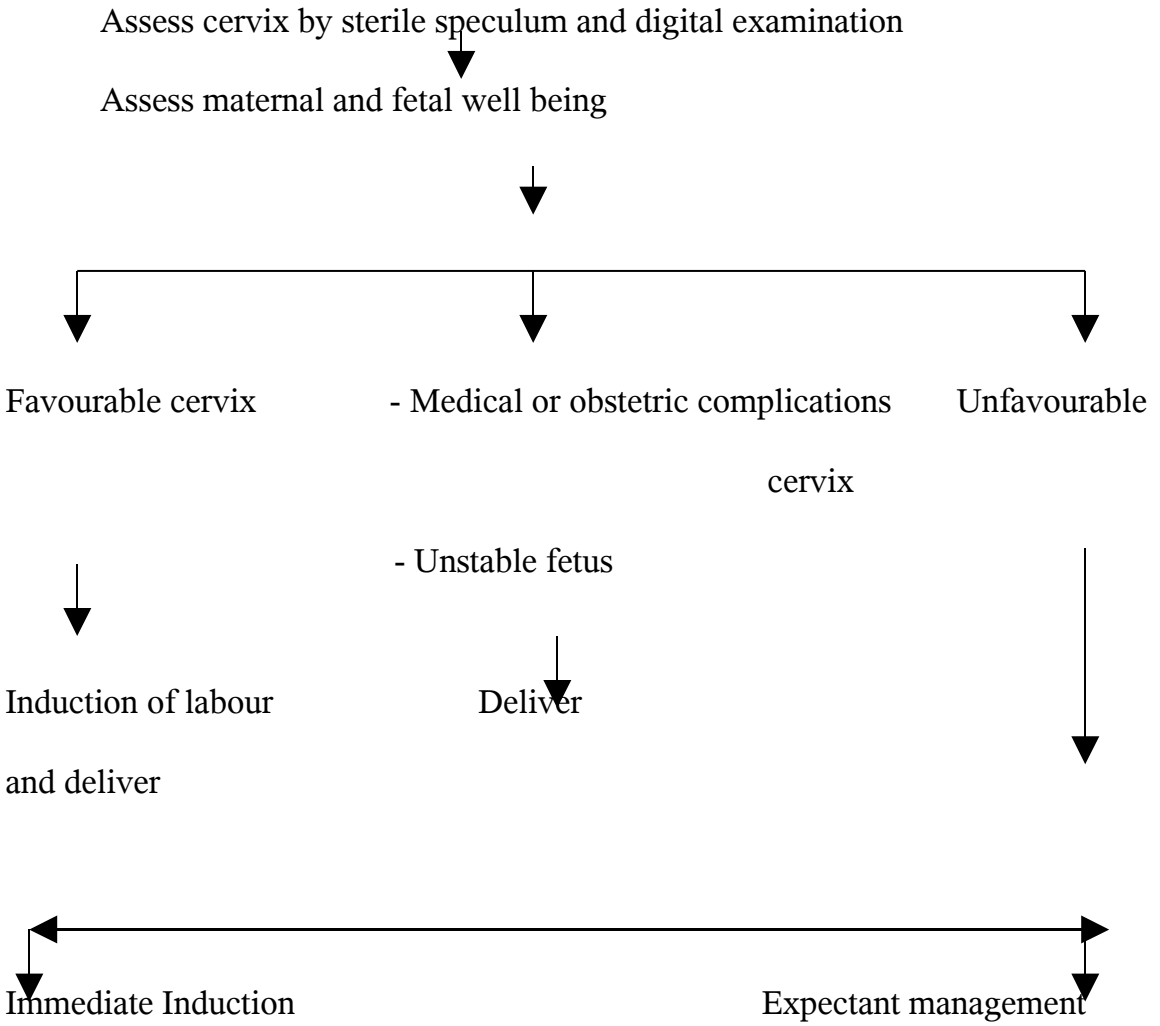
Confirm diagnosis by direct visualization of pooling of amniotic fluid, ultra sound

↓



Evaldson et al 1980 found that patients delivered 24 hours after PROM had significant risk of infection. Infection is related to PROM, number of vaginal examinations, time taken between first PV and delivery and Caesarean section.

Unless the mother is grossly neglected mortality due to PROM should not occur. Even morbidity is almost negligible. But still development of chorioamnionitis or overt infection is associated with higher maternal morbidity and rarely death.

In the presence of infection abnormal labour pattern are common and the chances of operative delivery are increased. Rarely uncontrolled infection may lead to septicemia, shock, DIC, ARDS and ultimately maternal death.

Neonatal risks are due to infection, complications during labour and delivery. Higher incidence of LSCS for foetal distress is found in patients with PROM 7-9%. Analysis of electronic foetal heart rate patterns in patients with foetal distress revealed that these patterns are consistent with umbilical cord compression.

Though the problem of PROM was identified centuries ago the cause is yet unknown,

management is controversial and the outcome is equivocal.

Karim et al 1972 was the first one to use prostaglandins for induction of labour. They used prostaglandins intravenously. In 1973 various local preparations of PGE2 have been applied to the vagina and the cervix in the form of gels, tablets and pessaries. Misprostol is available as 100 μg, 200μg tablets for treatment of peptic ulcer. It was first reported in 1987 for induction of labour in case of intra uterine death in third trimester. It has been extensively investigated in past few years for use in cervical ripening and labour induction.

Luis Sanchez – Ramos, Anita H – Chen and Colleagues 1997 found that Misoprostol usage significantly reduces Induction – delivery interval in labour Induction in term PROM patients and concluded that vaginal Misoprostol is effective, cheap and safe.

Wing and collaborators reported 50 μg oral Misprostol was less effective than 25 μg vaginal Misoprostol for labour induction and 100 μg oral tablet was as effective as 25 μg of vaginal Misoprostol.

Luis Sanchez – Ramos and associates 1993 compared safety and efficacy of intravaginal Misoprostol vs intravenous Oxytocin infusion for labour induction and they reported shorter induction delivery interval with Misoprostol in Vaginal delivery group – 11 hrs Vs 18hrs. In 74% of patients only one 50µg dose of Misoprostol resulted in successful labour induction.

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Miriam Zieman and associates in 1997 studied the absorption kinetics of oral Vs Vaginal Misoprostol and found that system bioavailability of Vaginal administration is higher than that of oral administration.

Evita Fernandez, Suseela Varila [2001] conducted a randomized prospective study of Misoprostol (50 mcg) for term labour induction. Average induction delivery interval was 10.34 hrs. Caesarean rate was 29%. Tachysystole occurred in 21/200 women of which 15 patients were delivered by caesarean section.

In Dec 2000 ACOG reaffirmed its recommendation for the use of Misoprostol because of proven safety and efficacy. The committee on obstetrics recommends 25µg intravaginal dose. (William's obstetrics 22nd Edn.). Such usage is considered to decrease the need for Oxytocin, achieve higher rates of vaginal delivery and significantly reduce induction-delivery interval.

Kadanalis and kumtupe [1996] in their study on term labour induction with Misoprostol vs Oxytocin/PGE2 found that drug induction delivery interval was shorter in Misoprostol group 9.2± 2.4 hours P=0. 001.There was a higher prevalence of cesarean section for failed induction in the Oxytocin/PGE2group than in the Misoprostol group (13.4 vs 6.3%)P<0.001. Neonatal outcomes of both groups were also similar.

Mundle WR, Young DC 1996 in their study of vaginal Misoprostol in labour induction concluded that induction – delivery interval was shorter in Misoprostol group. Neonatal outcomes were similar and Misoprostol is cost effective.

Merrell DA, Koch MA 1995 in their study of Misoprostol in second and third trimester pregnancies found that Misoprostol is effective, easy to use, cheap and safe.

Kramer RL, Gilson GJ and Colleagues 1997 in their randomized trial of Misoprostol(100µg every 4 hours vaginally) and Oxytocin for induction of labour found that induction delivery interval is shorter(585minutes vs 885 minutes, P<0.001) in the Misoprostol group.Uterine tachysystole was more common and hospital charges were less with Misoprostol

group.

Orane JM in 2003, in his study found that Vaginal PGE1 results in higher rate of vaginal delivery within 24hours and increased satisfaction in mothers.

Fabiana da graca, Jose Cecatti and Colleagues in their study (Sep 2005) found that Misoprostol is associated with shorter latency period, shorter maternal hospitalization and increased occurrence of alterations of contractility without maternal, neonatal adverse outcomes.

Wing DA, Paul RH (1997) in their study found that induction – delivery interval was 1 hour longer in Misoprostol group and no difference in tachysystole/ hypertonus / hyperstimulation between two groups and concluded that Misoprostol is an effective alternative to Oxytocin in induction of labour in PROM beyond 36 weeks.

Lin MG, Ramsey PS in their Meta analysis –Misoprostol for induction of labour in women with term PROM (2005) concluded that Misoprostol is an effective and safe agent for induction of labor in Term PROM. When compared to Oxytocin, the risk of contraction abnormalities and the rate of maternal and neonatal complications were similar between 2 groups.

M.S Urala, Lavanya Roy (2001) studied the effect of single dose Misoprostol 50µg for induction of labour. In this study 86 women requiring induction of labour were enrolled, 69.7% delivered vaginally. Induction delivery internal was 9.09hours and incidence of tachysystole was 9.3%.

Peter Danielien et al (1999) studied Misoprostol for Term Labour Induction. Single blind randomized comparative trial was carried out with 50µg, 4th hourly Misoprostol and 1mg 6^{th} hourly Dinoprostone. Misoprostol group had a significant reduction in induction – delivery interval and more women were delivered vaginally. There were no adverse neonatal outcomes associated with use of Misoprostol.

Suk wai Ngai, Yik ming chan – 2000 conducted prospective randomized study on "Misoprostol (100µg orally every 4 hours) Vs Oxytocin in women at term with prelabour rupture of membranes" and concluded that oral Misoprostol caused earlier peak uterine activity compared with Oxytocin (6 – 8 hours vs. 8- 10 hours). Both Oxytocin and oral Misoprostol caused an increase in uterine activity within one hour of labor induction. Peak uterine activity was reached 6-8 hours after oral Misoprostol with persistent effects, and 8-10 hours after Oxytocin, requiring continuous titration of medication. The duration of labour was significantly reduced in nulliparouswomen, but not in those who were multiparous in the Misoprostol group. The induction-to-delivery interval, the mode of delivery, the perinatal outcome were similar for the two groups. Oral Misoprostol was not only as effective as Oxytocin in inducing labour in women at term with prelabour rupture of the membranes, but it reduced significantly the duration of labour in nulliparous women.

MATERIALS AND METHODS.

SETTING: -

This study was carried out in the Institute of Obstetrics and Gynecology, Madras Medical College, Chennai.

STUDY DESIGN: -

Prospective randomized control study

STUDY PERIOD: - July 2004 – Feb 2006

SAMPLE SIZE: - Determined by statistical analysis. Statistical analysis was done using chi square test and student 't' test used in appropriate places. About 200 women were randomized to either Misoprostol or Oxytocin.

Diagnosis of prelabour rupture of membranes made on the basis of history, clinical examination, and speculum examination and confirmed with USG.

INCLUSION CRITERIA: -

1. Singleton pregnancy
2. Cephalic presentation
3. Bishop's score ≤ 4
4. Completed 37 weeks of gestational age
5. Live fetus showing no signs of fetal compromise on admission CTG.

EXCLUSION CRITERIA: -

1. Multiple pregnancy
2. Non cephalic presentations
3. Bishop's Score > 4
4. H/o previous scar, Uterine Surgery
5. Any medical Conditions complicating Pregnancy
6. Hydramnios, IUGR, Gestational age < 37 weeks
7. Women in labour
8. Suspected chorioamnionitis

At the time of entry into study name, age, status of booking, immunization, menstrual

history, marital history, obstetrical history, medical and personal history were noted down.

General Condition is assessed by pulse rate, Blood Pressure, Height, Weight with particular attention to pedal odema, anemia. Cardiovascular and respiratory systems were examined. Obstetrics examination includes size of uterus, lie, presentation, attitude, foetal heart sound and rate, liquor adequacy and estimated foetal weight Pelvic examination was done to rule out cephalo pelvic disproportion and for Bishop's scoring. USG done for foetal maturity, Liquor status and for foetal well-being. Admission CTG done.

METHODS OF APPLICATION: -

MISOPROSTOL: -

Informed consent obtained for Misoprostol group of patients. In dorsal position 25 μg of Misoprostol inserted into posterior fornix and patient is advised to lie down in left lateral position for 30 minutes. Dose is repeated at the interval of 6hrs to the maximum of 3 doses.

OXYTOCIN :-

As Infusion pump in not available, Oxytocin infusion started intravenously in either Normal saline/Ringer lactate at dose of 8 drops/mt (5mU/mt) incremented at 30 minutes interval to the maximum of 48 drops/mt (30 mU/mt) and monitored with Oxytocin chart

For all patients progress of labour was monitored with partogram. During induction following parameters are monitored.

1. Maternal pulse rate, temperature, blood pressure, and urine output.
2. Uterine contractions for their frequency, duration and strength.
3. Fetal heart rate.
4. Onset of various stages of labour.

Duration of labour and mode of delivery were notified. Caesarean section was resorted to whenever fetal distress arises or for failed induction or for failure to progress with minor degrees of cephalo pelvic disproportion. Babies were followed up in neonatal unit, whenever they got admitted. Mother and baby were discharged in good condition and followed up to six weeks.

After delivery when mother and baby were discharged from hospital, advice was given for postpartum follow up. Clinical evaluation of mother and foetus was scheduled at 2 weeks after delivery and followed upto 6 weeks.

OBSERVATION

(I) AGE DISTRIBUTION:-

Age In Years	Misoprostol (100)		Oxytocin (100)	
	No. Of Pts.	%	No. Of Pts.	%
≤ 20	32	32%	13	13%
21 - 30	66	66%	83	83%
< 30	2	2%	4	4%

$X^2 = 10.63$, $P = 0.004$

1. Distribution of patients under the age group ≤ 20 years is significantly more in Misoprostol group (32%) compared to Oxytocin group (13%).
2. Distribution of patients in age group between 20-30 years is significantly more in Oxytocin group (83%) compared to Misoprostol group (66%.)
3. Mean age between 2 groups is not statistically significant $p = 0.2$, $t = 1.27$.

ii. Height distribution

Height In Cms	Misoprostol (100)		Oxytocin (100)	
	No.of Pts.	%	No.of Pts.	%
< 150	13	13%	14	14%
150 – 100	69	69%	71	71%
< 160	18	18%	15	15%

No statistically significant differences observed between the two groups.

$X^2 = 0.34$, $P = 0.84$

iii. Parity distribution:

Parity	Misoprostol (100)		Oxytocin (100)	
	No.of Pts.	%	No.of Pts.	%
Nullipara	76	76%	75	75%
Para 1	23	23%	22	22%
≥ Para 2	1	1%	3	3%

Parity wise no statistically significant difference observed between two groups. $X^2 = 1.34$, $P = 0.59$

iv. Gestational Age Distribution: -

GA	Misoprostol (100)		Oxytocin (100)	
	No.of Pts.	%	No.of Pts.	%
37– 40 WKS	99	99%	100	100%
40– 42 WKS	1	1%	-	-
≥ 42 WKS	-	-	-	-

Not much statistical difference observed between the two groups.

$X^2 = 0.01$, $P = 1$

v. Bishop Score distribution

Bishop Score	Misoprostol (100)		Oxytocin (100)	
	Nullipara	Multipara	Nullipara	Multipara

Mean	4	4	4	4

No Statistical difference between the two groups.

vi. No. Of doses of 2 drugs

No. Of doses	Misoprostol	Oxytocin	Total
1	64	78	142
2	36	22	58
Total	100	100	200

vii. Outcome: - Mode of delivery

Mode of delivery	Misoprostol (100)				Oxytocin (100)			
	Nulli para (76)	%	Multi para (24)	%	Nulli para (75)	%	Multi para (25)	%

LN	65	85.56	22	91.67	57	76	23	92
LSCS	9	11.84	2	8.33	16	21.4	2	8
Out let forceps	2	2.6	-	-	2	2.6	-	-
Total	76	100%	24	100%	75	100%	25	100%

1. For Primipara vaginal delivery in Mispostol group is – 85.56% LN+2.6% outlet forceps and in Oxytocin group – 76% LN +2.6% outlet forceps. But this difference is statistically not significant. P = 0.38.
2. Incidence of LSCS for primipara in Misoprostol group is (11.84%) and in Oxytocin group is (21.5%.). But this difference is statistically not significant p=0.48

For multipara no significant difference was observed between two groups either in vaginal delivery or in incidence of LSCS.

INDUCTION-DELIVERY INTERVAL:

I – D interval Duration in hours.	Misoprostol (100)				Oxytocin (100)			
	Nulli para (76)	%	Multi para (24)	%	Nulli para (75)	%	Multi para (25)	%
< 12	66	86.84	22	91.66	52	72.22	23	92%
12 – 24	1	1.31	-	-	7	9.33	-	-
> 24	-	-	-	-	-	-	-	-

Primipara → "P" = 0.001 (Significant)

Multipara → "P" = 0.63 (Non-significant)

1. Mean induction delivery interval in Misoprostol group for nullipara is 8.5 hrs. For multipara it is 6.6 hrs.
2. Mean induction delivery interval in Oxytocin group for nullipara is 10:4 hrs. In multipara it is 6.5 hrs.
3. Mean induction delivery interval for primipara is significantly reduced in Misoprostol group compared to syntocinon group. P = 0.001.
4. No statistically significant difference is observed for multipara between both the groups p = 0.63.

ix. PROM – Admission interval

PROM – Induction interval	Misoprostol (100)				Oxytocin (100)			
	Primipara (76%)		Multipara (24%)		Primipara (75%)		Multipara (25 %)	
< 6 hours	34	44.73%	6	25%	31	41.33%	11	44%
6 – 12 hours	40	52.63%	18	75%	42	56%	14	56%
> 12 hours	2	2.63%	-		2	2.66%	-	

Mean	Misoprostol (100)	Oxytocin (100)	Std. Deviation	t – test

1. PROM-Induction interval	8.6 hours	8.2 hours		
2. PROM – Delivery	11.68hours	13.11hours	2.326(M) 2.881(S)	t = 4.42 P - 0.001

1. Mean PROM –Admission interval is not statistically significant between both groups. For Misoprostol it is 8.6hrs and for Oxytocin 8.2 hrs.

2.But mean PROM – delivery interval is 11.08 hours in Misoprostol group as against 13.11 hours in Oxytocin group, which is statistically significant. t test – t= 4.42 , p = 0.001

x. INDICATION FOR LSCS: -

Indication for LSCS	Misoprostol				Oxytocin			
	Nulli para (76%)	%	Multi Para (24%)	%	Nulli para (75%)	%	Multi Para (25%)	%
Failed induction	3	3.95	-	-	8	10.66	-	-
Fetal Distress	4	5.26	1	4.16	4	5.33	2	8
Failure to progress $\overline{C}$ CPD I°	2	2.63	1	4.16	4	5.33	-	-
Total	9	11.84	2	8.32	16	21.22	2	8

P=0.59

1. Failed induction as an indication for LSCS, is more in Oxytocin group (10.66%) than in

Misoprostol group (3.95%). But this is statistically not significant.

2. Foetal distress incidence is not statistically different between Misoprostol group (9.42%) and Oxytocin (13.3%)

xi. Birth weight distribution: -

Birth weight (1Kg)	Misoprostol (100)		Oxytocin (100)	
	Nullipara (76)	Multipara (24)	Nullipara (75)	Multipara (25)
Mean	2.83	2.86	2.78	2.8

P = 0.28

Not statistically significant

xii. Meconium Stained Liquor: -

Presence of Meconium	Misoprostol (100)	Oxytocin (100)	Neonatal Outcome
Thick	6	8	Good
Thin	10	12	Good

P=0.52

1. In Misoprostol group, 6 patients were with thick meconium stained liquor,

   10 Patients were with thin meconium stained liquor. All are NST reactive. Of 6 thick meconium stained liquor patients, 5 were not in active phase labour and went in for LSCS and one patient in advanced labour delivered by outlet forceps. All patients with thin meconium stained liquor delivered vaginally.

2. In Oxytocin group, 8 patients were with thick meconium stained liquor, 12 patients were with thin meconium stained liquor. All are NST reactive. Of 8 thick meconium stained liquor patients, 6 were not in active phase of labour and went in for LSCS, 2 patients in advanced labour delivered by outlet forceps. All patients with thin meconium stained liquor delivered vaginally.

3. Neonatal outcomes were good in both groups.

xiii. APGAR: -

Apgar	Misoprostol				Oxytocin			
	Nulli para	%	Multi Para	%	Nulli para	%	Multi Para	%
<4 at 1mt	-	-	-	-	-	-	-	-
4-6at 1mt	8	10.52	1	4.16	9	12%	1	4
> 7 at 5mts	-	-	-	-	2	2.66	-	

$X^2 = 3.08$ "P" = 0.55 for Apgar at 1 mt

$X^2 = 4.97$ "P" = 0.29 for Apgar at 5 mts

No Statistical difference between two groups in Apgar score

xiv. NICU ADMISSION: -

	Misoprostol (100)		Oxytocin (100)	
	Nullipara	Multipara	Nullipara	Multipara
NICU Admission	1LBW 2 1 Mild Resp. Distress	1- Mild Resp. Distress	5- Mild Resp. Distress 6 1 LBW	-
Death	-	-	-	-

$X^2 = 2.25$ "P" = 0.69

No statistical difference in NICU admission between two groups.

xv. Maternal Complications: -

Maternal complications	Misoprostol	Oxytocin

	(100)	(100)
Vomiting	1	-

$X^2 = 1.01$ $P = 0.32$

1. One patient in Misoprostol group had one episode of vomiting, but no other side effects.
2. No significant difference between two groups in maternal complications.

DISCUSSION

PROM is a common indication for induction of labour. Oxytocin and prostaglandins are the most frequently used agents. Success of Oxytocin depends upon condition of cervix at beginning of induction. With Prostaglandins, the advantage is promotion of both cervical ripening and myometrial contractility. But the drawback is hyper stimulation syndrome and also frequent administration of vaginal Prostaglandins may increase the risk of ascending infection.

This study compares the safety and efficacy of Misoprostol with Oxytocin. Of 200 patients, each 100 patients were randomized to Misoprostol and Oxytocin group. Outcomes were measured in relation to Induction – delivery interval, mode of delivery, side effects, maternal and neonatal morbidity and cost effectiveness.

The latency period and time from recruitment until delivery were significantly shorter in primipara in Misoprostol group compared to Oxytocin group in the present study. Induction delivery interval for primipara in Misoprostol group is 8.5 hours and in Oxytocin group it is 10.4 hours. P= 0.001. For multipara, induction-delivery interval in Misoprostol group is 6.6 hrs and in Oxytocin group is 6.5 hrs. P=0.63. This is comparable to the following studies.

S.No	Studies	Induction Delivery Interval (hrs)	Present study: Induction Delivery Interval (hrs)

1	Fabiana de graca & colleagues (2005)	11 P=0.001	8.06 P=0.001
2	Kadanalis, Kumtupe 1996	9.2(+ or -) 2.4 P=0.001	
3	Sanchez and Ramos and colleagues. 1993.	11 P=0.004	
4	Kramer RL, Gilson GJ and Colleagues 1997	585 minutes P=0.001	
5	Chuck FJ, Huffaker- 1995	11.4 P=0.001	

Vaginal delivery incidence observed for primipara in Misoprostol group is 88% compared to Oxytocin group 78.6 %. Prevalence of LSCS in Misoprostol group for primipara is 11.84%, and for multipara is 8.34% and in Oxytocin group, for primipara it is 21.4%and for multipara it is 8%. However this difference is statistically not significant.

This is comparable to the following studies.

S.NO	Studies	Caesarean Rate	Present study
1.	Fabiana de graca Collegues(2005)	20% P=0.22	20.17% P=0.27

2.	Kadanalis,kumtepe 1996	30%	
3.	Kramer RL, Gilson GJ and Colleagues (1997)	8% P=0.2	
4.	Wing DA;Paul RH (1996)	20.8%	

In the present study neonatal outcomes were similar.

In Misoprostol group, six patients were with thick meconium stained liquor.

A 20 year old primi / 39 weeks of gestational age/ on admission with clear liquor, had thick meconium stained liquor on 2nd dose of Misoprostol and in early phase of labour (NST reactive) went in for LSCS.

Similarly three primipara with term gestation on admission with clear liquor,had thick meconium stained liquor on 2nd dose of Misoprostol and in early phase of labour (NST reactive) went in for LSCS.

A 25 year old second gravida (G2P1L1), previous full term normal delivery with 40 weeks gestational age had thick meconium liquor on 2nd dose of Misoprostol and in latent phase of labour (NST reactive) went in for LSCS.

A 29year old primi with term gestation had thick meconium with 1st dose of Misoprostol

and in active phase of labour delivered by outlet forceps.

In Oxytocin group eight patients were with thick meconium stained liquor.

Four primi para with term gestation on admission with clear liquor had thick meconium stained liquor with Oxytocin. Infusion and latent phase of labour (NST reactive) went in for LSCS.

Two-second gravida with term gestation on admission with clear liquor had thick meconium liquor after Oxytocin. Infusion and in latent phase of labour (NST reactive) went in for LSCS.

Two primipara with thick meconium liquor in active phase of labour were delivered by outlet forceps.

Two babies got admitted in NICU in Misoprostol group-one for low birth weight (2.1kg) and other baby for mild respiratory distress (APGAR7/10,8/10) for observation. In Oxytocin six babies got admitted-one for low birth weight (2kg) and five babies for mild respiratory distress for observation. All babies were discharged in good condition.

Following studies supports this.

1. Fabiana da graca, Jose Cecatti and colleagues Sep 2005. BJ OG vol 112, 1284 – 1290, Sep 2005.
2. Sanchez and Ramos and colleagues 1993 & 1997 Int J Gynaecology obstet 1993 Mar 81:3, 332-6 1997 April obstet Gynaecol 89:4, 133-42
3. Kadanalis, Kumtupe 1996 Int I obstet Gynaecol 1996, 55:2, 99-104
4. Windrim R. Bennett K and Colleagues 1997 Obstet Gynaecol 1997 March 89:3, 392 –7.
5. Sukwai ngai, Yikming chan 2000 BJ OG 107 – 222 – 227

In this study, one patient had vomiting of one episode, which resolved spontaneously. No other side effects were observed. And there is no statistically significant difference was observed in adverse effects between two drug groups.

This is supported by the following studies.

1. Fabiana da graca, Jose Cecatti and Colleagues – Sep 2005 BJ OG Vol 112, 1284 – 1290 Sep 2005.
2. Sanchez and Ramos and Colleagues – 1993 & 1997 Int J Gynaecol Obstet 1993 March 81:3, 332-6 .1997 April obstet Gynaecol 89:4, 133-42.
3. Kadanalis, Kumtupe 1996 Int J Gynaecol Obslet 1996, 55:2, 99-104
4. Sukwai ngai, Yik ming chan 2000 BJ OG 107 – 222 - 227

Misoprostol is cost effective. 25 µg of Misoprostol costs about 3.81 – 4.25 Rupees.

Supportive studies are

1. Mundle WR, Young DC 1996 Gynaecol Obstet 1996 Oct.88:4 521-5
2. Chuck FJ, Huffaker BJ 1998 AMJ Obstet Gynaecol 1998 Oct 173:4 1137-42

No significant differences observed in terms of tachysystole / Hyper tonus / Hyper stimulation between two drug groups.

Supportive studies are as follows.

1. Wing DA, Paul RH 1999 AMJ Obstet Gynaecol 1999 Jan 180, 253-4.
2. Lin MG, Ramsey PS and Colleagues in their metaanalysis of Misoprostol for labour induction in women with term PROM.
3. Sanchez and Ramos and Colleagues 1993 & 1997 Int J Obstet Gynaecol 89:4, 133-42.

This powerful little tablet (Misoprostol) can work wonder and save time, energy and money for many but has to be used with caution and respect.

SUMMARY:-

1. Misoprostol at 25µg dose repeated 6th hourly is an effective, cheap, safe and easy to use labour induction agent.
2. Induction – delivery internal is shorter in primipara in Misoprostol group compared to Oxytocin group.
3. For multipara, no significant difference in Induction – delivery interval is observed between both the groups.
4. No statistically significant difference was observed in caesarean section rate between two drug groups.
5. Neonatal outcomes were comparable between both groups.
6. Maternal complications were not significantly different between both groups.
7. No increased incidence of tachysystole / Hyper tonus / Hyper stimulation observed.
8. Misoprostol is cost effective, easy to use and stable at room temperature.

CONCLUSION

Misoprostol is an effective, cheap, safe, stable at room temperature and easy to use if it is used in appropriate dosage for induction of labour in prelabour rupture of membranes at term.

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