A STUDY ON

"ISOSORBIDE MONONITRATE VERSUS DINOPROSTONE GEL FOR CERVICAL RIPENING AT TERM – MATERNAL AND FETAL OUTCOME"

DISSERTATION SUBMITTED FOR

M.S (BRANCH – II)

(OBSTETRICS & GYNAECOLOGY)

MAY 2018

THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled "**A STUDY ON ISOSORBIDE MONONITRATE VERSUS DINOPROSTONE GEL FOR CERVICAL RIPENING AT TERM – MATERNAL AND FETAL OUTCOME**" is a bonafide record work done by **Dr.J.RAJAM** under my direct supervision and guidance, submitted to the Tamil Nadu Dr. M.G.R. Medical University in partial fulfilment of University regulation for M.S. Branch II – Obstetrics & Gynaecology.

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This is to certify that the dissertation entitled "**A STUDY ON ISOSORBIDE MONONITRATE VERSUS DINOPROSTONE GEL FOR CERVICAL RIPENING AT TERM – MATERNAL AND FETAL OUTCOME**" is a bonafide and genuine research work done by **Dr.J.RAJAM,** in partial fulfilment of the requirement for the degree in M.S. (Obstetrics & Gynaecology), under guidance of **Prof. Dr. C.SHANTHI, MD., DGO., FICOG** HOD and Professor, Department of Obstetrics & Gynaecology.

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DECLARATION

I, **Dr.J.RAJAM** solemnly declare that the dissertation titled "**A STUDY ON ISOSORBIDE MONONITRATE VERSUS DINOPROSTONE GEL FOR CERVICAL RIPENING AT TERM – MATERNAL AND FETAL OUTCOME**" has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other University board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of M.S degree Branch – II (Obstetrics & Gynecology) to be held in May 2018.

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ACKNOWLEDGEMENT

My profound thanks to **Dr.S. MARUTHUPANDIAN MS, Dean**, Madurai Medical College, Madurai for permitting me to utilize the clinical materials of the Hospital.

I am extremely thankful to **Prof.Dr.C.Shanthi MD.,DGO.,** Head of the Department of Obstetrics &Gynaecology, Madurai Medical College, Madurai for her expert guidance and support for the completion of the study.

I am immensely thankful to my Guide **Prof.Dr.N.K.Mahalakshmi MD.,DGO.,**for her immense help and guidance in completion of the study.

I am sincerely thankful to Prof.Dr.K.S.Chithra M.D.,DGO,Prof Dr.N.SumathiM.D.,DGO, Prof.Dr.Jothi Sundaram M.D.,DGO,Prof Dr.M.Gayathri MD.,DGO,for their support,valuable advice and guidance in the analysis and successful completion of the study.

I am extremely thankful to Assistant Professor , Dr.Usha M.D O&G ., Department of Obstetrics &Gynaecology.,Govt . Rajaji Hospital,Madurai.

I thank all the assistant professors of the department of Obstetrics & Gynaecology for their guidance and kind help.

I acknowledge with thanks the cooperation of the patients without whom this study would not have been possible.

CONTENTS

INTRODUCTION

Human labour is a complex process and is characterised by the onset of effective uterine contractions leading to progressive effacement and dilatation of the cervix that result in expulsion of fetus, placenta and membranes.

Although most of the patients have a spontaneous onset of labour at term, on some occasions the labour has to be induced for several reasons. The aim of induction is to achieve a successful vaginal delivery. Maternal side effects should be minimal. Baby should be born in good condition.

AIM OF THE STUDY

To evaluate the efficacy of isosorbide mononitrate versus Dinoprostone gel in cervical ripening at term and compare the maternal and fetal outcome.

REVIEW OF LITERATURE

Pallavi R K, Lynsel D' Souza, S.R Nayak ,Bharathi Rao, Shameem V P. Isosorbide mononitrate versus Dinoprostone gel in cervical ripening at term, maternal and fetal outcome.Isosorbide mononitrate can be used as a cervical ripening agent at term in normal pregnancies without any other complicating factors with minimal maternal and neonatal side effects.

Ayesha mukhiar , Frzana Kasmi ,Farzana Rehana .Comparasion of vaginal Isosorbide mononitrate with Prostaglandin E2 for Preinduction cervical Ripening at Term. Isosorbide mononitrate is effective and cheaper alternative to PGE2 gel for cervical Ripening and induction of labour at term. Isosorbide mononitrate does not cause maternal hyperstimulation.It is convenient to use and well tolerated.

Kavitha Agarwal , Achla Batra ,Aruna Batra , and Abha Aggarwal. Randomized Comparision of Isosorbide Mnonitrate and PGE2 Gel for cervical Ripening at Term including High Risk pregnancy.PGE2 is associated with higher incidence of Uterine Hyperstimulation , Tachysystole and Nonreassuring foetal heart rate pattern.Nonreassuring foetal heart rate in PGE2 group is higher in high risk group compared to low risk women.Isosorbide Mononitrate can be safely used in such high risk cases.

PHYSIOPHARMACOLOGY OF LABOUR

The stages and Physiology of Normal Labour

The stages and physiology of normal labour Definition of labour

1. Labour is defined as the onset of painful, regular contractions, more than one every ten minute, with progressive cervical effacement and dilatation accompanied by descent of the presenting part.

2. Another definition is the process by which the fetus is expelled from the uterus

The physiology of labour

- The mechanism responsible for initiating human parturition is still unknown.

- Although much is understood about the physiology of labour in humans , the initiating biological event is still unclear

- It is certainly true however that the uterine body and cervix undergo a number of changes in preparation for labour which start a number of weeks before its onset.

- The onset of labour occurs when those factors which inhibit contractions and maintain a closed cervix diminish and are succeeded by the actions of factors which do the opposite.

- Both mother and fetus make contribution to this.

the myometrium

- Myometrial cells contain filaments of actin and myosin, which are the two key proteins for contraction.

- The interaction of myosin and actin brings about contraction, while their separation brings about relaxation, under the influence of intracellular free calcium

- An increase in intracellular free calcium brings about contraction. Prostaglandins and oxytocin increase intracellular free calcium (so they stimulate uterine contraction).

- Beta- adrenergic compounds and calcium channel blockers decrease intracellular calcium (they inhibit uterine contraction).

The uterine segments:

During labour the uterus may be divided into two functional segments.

1. The upper segment (upper part of the uterus or body of the uterus)

- This contract strongly, and with each successive contraction the smooth muscle fibers become shorter and thicker,

- This powerful segment draws the weaker, thinner and more passive lower part of the uterus up over it's contents and so will pull up and then dilate the cervix.

2. The lower uterine segment:

- This consist of the lower part of the body of the uterus and the cervix,

- It can contract but is relatively passive compared with the upper segment.

Uterine contraction and retraction

Retraction is the progressive shortening of the uterine smooth muscle cells in the upper portion of the uterus as labour progresses.

- It is a major feature of uterine contractility during labour.

- After the cells contract they relax but they do not return to their original length.

- This result in the development of the thicker, active, contracting segment in the upper portion of the uterus.

- At the same time the lower segment of the uterus becomes thinner and more stretched.

- Eventually this results in the cervix being taken up into the lower segment of the uterus and forming a continuum with the upper uterine segment.

- This retraction has the advantage that with each contraction and retraction the uterine cavity becomes progressively smaller and the fetus pushed down

- If contraction was followed by complete relaxation no progress would happened

- In the third stage of labour after the placenta is expelled, retraction enables to close the blood sinuses at the placental bed and prevent excessive blood loss.

- The cervix effaces and then dilates and the fetus descends in response to this directional force.

- It is essential that the myocytes of the uterus contract together in a coordinated fashion.

- There is cell-to-cell communications by means of gap junctions, which facilitate the passage of electrical current between cells.

- These gap junctions are absent for most of the pregnancy but appear in significant numbers at term.

- These gap junctions increase in size and number with the progress of labour and allow greater coordination of myocyte activity.

- Prostaglandins stimulate their formation, while b- adrenergic compounds possibly do the opposite.

- A uterine pacemaker from which contractions originate probably does exist but has not been demonstrated histologically.

- In labour, the lower uterine segment, cervix, vagina, pelvic floor and vulval outlet are dilated until there is one continuous birth canal.

- Uterine contractions are involuntary in nature and there is relatively minimal extra-uterine neuronal control.

- The frequency of contractions may vary during labour and with parity.

- They occur at intervals of 2-4 minutes.

- Their duration also varies during labour, from30-60 seconds or occasionally longer.

The cervix:

- The cervix contains muscle cells and fibroblasts separated by a ground substance made up of extracellular matrix molecules.

- Interaction between collagen, fibronectin and dermatin sulphate during the earlier stages of pregnancy keep the cervix closed.

- Contractions at this point do not bring about effacement and dilatation.

- Under the influence of prostaglandins there is certain changes in the cervix which brings about softening and effacement which happened near the onset of labour.

Softening of the cervix occurs by:

1. Destruction of collagen fibers.

2. A decrease in dermatine sulphate, which has strong affinity for collagen.

3. An increase in hyaluronic acid.

All these changes happened within the cervical tissues.

Hormonal factors:

- Progesterone maintain uterine quiescence by suppressing prostaglandin production, inhibiting communication between myometrial cells and preventing oxytocin release.

- Oestrogen opposes the action of progesterone.

- Prior to labour, there is a reduction in progesterone receptors and an increase in the concentration of oestrogen relative to the progesterone.

- Prostaglandin synthesis by the chorion and the decidua is enhanced, leading to an increase in calcium influx into the myometrial cells.

- This change in the hormonal milieu also increases gap junction formation between individual myometrial cells, creating a functional syncytium, which is necessary for coordinated uterine activity.

- The production of ACTH by the placenta increases in concentration towards term and potentiates the action of prostaglandins and oxytocin on myometrial contractility

- The fetal pituitary secretes oxytocin and the fetal adrenal gland produces cortisol, which stimulates the conversion of progesterone to oestrogen.

Which of these hormonal steps initiates labour is unclear.

As labour becomes established, the out put of oxytocin increases.

The stages of labour

Labour is divided into ***three stages.***

The first stage (stage of dilatation):

From the onset of true labour until the cervix is fully dilated.it is divided into ***two phases***:

1. The latent phase:

- Starts from onset of labour until the cervix reaches 3cm dilatation.

- Lasts between 3- 8 hours, shorter in multiparous women.

- Contractions occurs at least twice every 10 minutes with each lasting > 20 seconds, not more than moderately strong and are quite well tolerated without analgesia.

2. The active phase:

From 3cm- full cervical dilatation (10cm), here the contractions becomes more frequent and stronger.

- Contractions occurs 3 times every 10 minutes, with each lasting > 40 seconds.

- The cervix should dilate at a rate of 1cm / hour or faster.

- Last between 2-6 hours.

The duration of the 1st stage of labour in primipara patient range from 6-18 hours (average= 12 hours).

In multiparous women about 2-10 hours (average 5hours)-

The second stage: from full dilatation of the cervix until the fetus is born. *It is also devided into* ***two phases:*** *1.the passive phase :* the time between full dilatation and the onset of involuntary expulsive contractions. There is no maternal urge to push and the fetal head is still relatively high in the pelvis.

2. The second phase is called the active phase, there is a maternal urge to push because the fetal head is low, causing a reflex need to bear down. Duration should last no longer than 2 hours in a primiparous and 1 hour in multiparous.

The third stage: from the birth of the fetus or fetuses until the placenta and membranes are delivered and the uterus has retracted firmly to compress the uterine blood sinuses.

- The placenta usually delivered within few minutes of the birth of the baby.

- A 3rd stage lasting more than 30 minutes considered abnormal.

Premonitory symptoms of labour:

1.Lightening:

In most primigravidae the presenting part sinks into the pelvis during the last 3-4 weeks of pregnancy which cause the uterine fundus to descend down and reduce the upper abdominal distension, making the woman more comfortable.

2.False pain:

Many women experience uterine contractions which are strong enough to cause pain, some days before labour starts.

Such false pains differ from labour pain only in that they are less regular and are ineffective in dilating the cervix.

Symptoms and signs of labour

1. Painful uterine contractions.

2. Shortening and dilatation of the cervix.

3. Show

4. Rupture of membranes.

Uterine contractions:

Throughout pregnancy there are painless irregular uterine contractions called ***Braxton Hicks*** *contractions.*

The contractions of labour characterized by:

1. Comes at regular interval.

2. Increase gradually in frequency, intensity and duration. At the onset of labour the interval between contractions may be variable and can be as long as 20 minutes.

- Contractions are often preceded by backache and tend to increase in frequency and duration, becoming gradually more painful.

- Throughout the majority of labour they occur at intervals of 2-4 minutes.

- Their duration also varies during labour from 30-60 seconds.

- The intensity of uterine contractions is assessed by the amplitude of the intrauterine pressure generated with each contraction

- In normal labour this intrauterine pressure averages between 30 and 60mmHg.

- The pain of labour has the same character as that of spasmodic dysmenorrhoea and the same cause which is *ischemia of the uterine muscles from compression of the blood vessels in the wall of the uterus.*

- The intermittent nature of the contractions is of great importance to both the fetus and the mother

- During a contraction the circulation to the placental bed through the uterine wall is stopped.

- If the uterus contracted continuously the fetus would die from lack of oxygen.

- The interval between contractions allow the placental circulation to be re-established and

- Give the mother time to recover from the fatiguing effect of the contraction to avoid maternal exhaustion.

Shortening and dilatation of the cervix:

- At the beginning of labour the cervix of a nulliparous woman is thick-walled canal, of at least 2cm in length.

- When labour begins the contraction and retraction of the upper uterine segment stretches the lower uterine segment and the upper part of the cervix.

- As the internal os is pulled open, the cervix will dilate from above downwards, becoming shorter, until no projection into the vagina is felt but only a thick rim at the external os.

- So the whole cervix being taken up and its cavity made one with that of the body of the uterus.

Evaluation of progress in labour:

The progress in 1st stage of labour is evaluated by:

1. The rate of cervical effacement and dilatation.

2. The descent of the fetal head.

The frequency and duration of uterine contractions alone is not an adequate measure of labour progress.

-In the second stage of labour the cervix is fully dilated and progress is measured by the descent and rotation of the presenting part.

Features of phase I of labour

Unresponsive myometrium

Cervical softening

Changes in the matrix

Changes in the collagen

FEATURES OF PHASE II OF LABOUR

Changes in the myometrium

Increase in contractility

Increase in uterine responsiveness

Increase in gap junctions

Changes in the cervix

Cervical Ripening

Changes in collagen structure

Increase in collagen solubility

Infiltration by inflammatory cells

MEDIATORS OF PHASE I OF LABOUR

Progesterone

Relaxin

Prostaglandin I2

Nitric oxide

PTH-RP(Parathyroid hormone related peptide)

MEDIATORS OF PHASE II OF LABOUR

Estrogen

Progesterone

CAPs (Contraction associated proteinsGlycosaminoglycans

Proteoglycans

Prostaglandins

Cortisol

Interleukin-8

MMP (matrix metalloprotease)

CERVICAL RIPENING

The process by which the cervix becomes soft, compliant and partially dilated is termed as 'cervical ripening'. This is a fundamental process that must occur, if parturition is to progress smoothly.

Cervical ripening is thought to be due to a combination of biochemical, endocrine, mechanical and possibly inflammatory events. Structurally, the cervix is mainly composed of collagen, myometrium is predominantly consist of smooth muscle.

The cervix is composed of Type I collagen -66 %,Type II collagen- 33 %. These collagen bundles are embedded in ground substance consisting of proteoglycan.

In the cervix, The main glycosaminoglycans are dermatan sulphate and chondroitin sulphate.They both are negatively charged and hydrophobic. This is responsible for mechanical strength of cervix.

Towards term dermatan sulphate and chondroitin sulphate are replaced by Hyaluronic acid. This is hydrophilic and imbibes water.

Indeed it has been shown that the water content of the human cervix increases from 80 % in the nonpregnant state to 86 % in late pregnancy (Liggins 1978, Uldbjerg et al 1983)

Collagenase – Enzyme produced by fibroblast and leukocytes.It breaks down TYPE I,II,III collagen.

Elastase - Enzyme produced by macrophages,neutrophils and eosinophils.It breaks down elastin,collagen and proteoglycans.

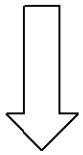
The levels of both these enzymes increases with advancing gestation with progressive decline in the cervical collagen concentration. (Uldbjerg et al 1983)

Prostaglandins have been shown to have a direct effect on the production of procollagenase , which is a precursor of collagenase (Goshowaki et al 1988).

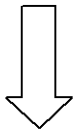
Fetal signals act through amnion and maternal signal acts through deciduas to increase the synthesis of prostaglandins.

Granstrom et al (1991) have shown that the insufficient remodelling of collagen during pregnancy will result in prolonged labour.

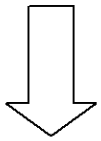
DERMATAN/CHONDROITIN SULPHATE (HYDROPHOBIC)



REPLACED BY HYALURONIC ACID (HYDROPHILIC)

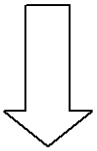


IMBIBES WATER – SOFT



DESTABILISES COLLAGEN FIBRILS

(DECREASES MECHANICAL STRENGTH)



SOFT COMPLAINT CERVIX

'CERVICAL RIPENING '

FACTOR	MECHANISM OF ACTION
CHANGES IN GROUND SUBSTANCE(GLYCOSAMINOGLYCANS)	INCREASE WATER CONTENT OF CERVIX ANDCAUSE 'SCATTERING AND DISPERSON 'OF COLLAGEN .INCREASE IN FORMATION OF IMMATURE COLLAGEN.
ENZYMES AND INFLAMMATORY MEDIATORS (ELASTASE , COLLAGENASE)	INCREASE IN COLLAGEN BREAKDOWN AND REMODELLING.

INDUCTION OF LABOUR

Unfavourable cervix is one of the main cause of failed induction. To achieve good result the cervix needs to be ripened. Induction of labour in an unripe cervix is associated with maternal complications, induction failure, higher incidence of instrumental delivery, and birth asphyxia.

BISHOP SCORE FOR ASSESSMENT OF CERVIX

The most important predictor of the success of induction of labour is the status of the cervix. Bishop score is used to assess the cervix is favourable (ripe) or unfavourable (unripe).

It was first described by Bishop in 1964.

Modified Bishop score was described by Calder in 1974.

BISHOP SCORE (BISHOP ,1964)

	0	1	2	3
DILATATION (CM)	0	1-2	3-4	5-6
EFFACEMENT (%)	0-30	40-60	60-70	80+
STATION (CM)	-3	-2	-1/0	+1/+2
CONSISTENCY	FIRM	MEDIUM	SOFT	
POSITION	POSTERIOR	MID POSITION	ANTERIOR	

MODIFIED BISHOP SCORE (CALDER , 1974)

	0	1	2	3
DILATATION (CM)	<1	1-2	2-4	>4
LENGTH (CM)	>4	2-4	1-2	<1
STATION (CM)	-3	-2	-1/0	+1/+2
CONSISTENCY	FIRM	AVERAGE	SOFT	
POSITION	POSTERIOR	MIDDLE/ANTERIOR		

SCORE 0-5 → Unfavorable

SCORE 6-12 → Favorable

Bishop score of 6 or above as favourable and predictive of high likelihood of successful induction.

Bishop score below 6 warrent an attempt at ripening the cervix.

METHODS OF CERVICAL RIPENING

1.SWEEPING OF MEMBRANES

2.PHARMACOLOGICAL

- PROSTAGLANDIN E2 {INTRACERVICAL, INTRAVAGINAL }
- PROSTAGLANDIN E1 {VAGINAL ,ORAL }

3.MECHANICAL

- TRANSCERVICAL BALLOON CATHETER
- FOLEY CATHETER
- DOUBLE BALLOON CATHETER
- TRANSCERVICAL CATHETERS WITH EXTRA-AMNIOTIC SALINE INFUSION {EASI
- LAMINARIA

4.OTHERS

- RELAXIN
- NITRIC OXIDE DONARS

SWEEPING OF THE MEMBRANES

Sweeping of the fetal membranes is also called as stripping of the membranes. The sweeping is done by gently inserting a finger through the open external os into the space between the membranes and lower uterine segment. The finger is then swept in a circular motion through 360 degrees.

The procedure strips the amniotic membrane off the lower uterine segment.

Sweeping the membranes from the uterine wall causes increased local production and release of prostaglandins PGF2 alpha from the deciduas and adjacent membranes.

This leads to onset of labour.

PHARMACOLOGICAL METHODS

Prostaglandins are commonly used for cervical ripening and induction of labour. Prostaglandins are discovered in 1970.

Prostaglandins are important mediators of uterine activity and have vital role in the contraction of the smooth muscle of the uterus and the biophysical changes associated with cervical ripening.

Prostaglandins are produced by almost every tissue in the body.

Administration of prostaglandins for inducing or ripening the unfavourable cervix has to be balanced against the effects of these agents on other systems,including the gastrointestinal tract and brain (O'Brien et al 1995).

Prostaglandin receptors are always present in myometrial tissue.

Prostaglandins can be used throught the pregnancy.

Both Prostaglandin E and F series result in uterine contractions

Prostaglandin E series more relatively uteroselective and they are more effective in producing cervical ripening.

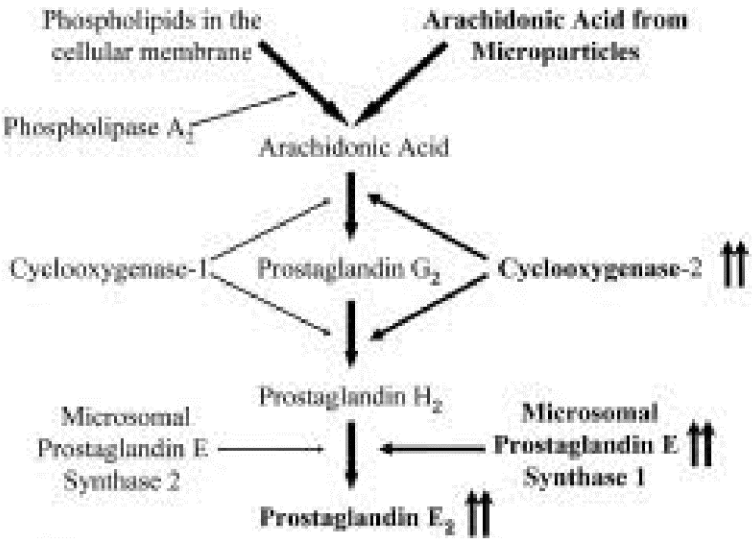
Endometrium and myometrium have substantial Prostaglandin synthesising capacity.

NSAID interfere with cyclooxygenase (involved in prostaglandin production).

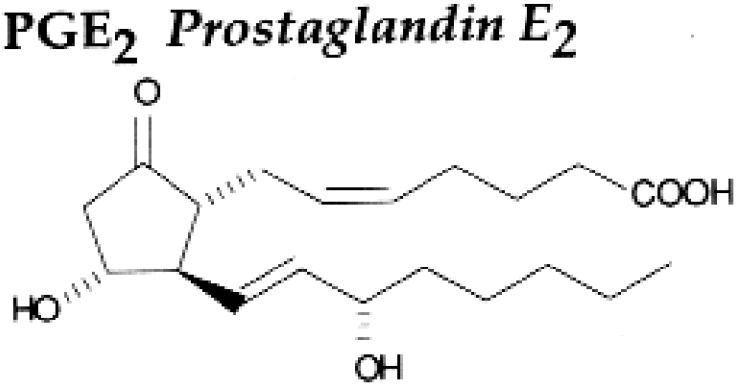
EP1 & EP2 receptors contraction promoting, abundant in fundus. EP3 & EP4 receptors relaxation promoting ,found in lower uterine segment.

Varying expression of receptors may be responsible for differing sensitivity of myometrium throughout the gestation and delivery.

PROSTAGLANDIN SYNTHETIC PATHWAY



STRUCTURE AND CLASSIFICATION



Prostaglandins are members of eicosanoid family.

They are synthesised from arachidonic acid.

Each molecule has 20 carbon atoms and cyclopentane ring and 2 side chains.

The position of side chains and number of multiple bonds determine the group identity and its action.

Prostaglandins were designed PG1,PG2,PG3, based on the number of double bonds in the polyunsaturated fatty acid from which they are formed.

PG E is soluble in ether.PG F is soluble in phosphate buffer.

The release of arachidonic acid from glycerophospholipids in the plasma membrane is the rate limiting step.

Prostaglandis act through G- Protein coupled receptors.

The final pathways involve intracellular cyclic AMP and intracellular calcium.

Prostaglandins are catabolised by the enzyme 15-OH PG dehydrogenase.

It has been shown that prostaglandin concentrations in amniotic fluid increases early in labour,before the active stage of labour is started.

Embrey pioneered the use of Prostaglandin E2 for induction of labour(Embrey1969) and cervical ripening (Calder and Embrey 1971)

Many biochemical and functional changes occur in the cervix during pregnancy (Leppert 1995).

Prostaglandins soften the cervix ,induces gap junctions .

Prostaglandins sensitise the myometrium to oxytocin,leading to progressive cervical dilatation.

DOSAGE REGIMENS AND PROSTAGLANDIN PREPARATIONS

PREPARATION	DOSAGE AND REGIMENS
PGE2 Vaginal tablet	3mg , can be repeated after 6-8 hrs if required
PGE2 Vaginal gel	Nulliparous-2mg; multiparous -1mg;can be repeated after 6 hrs if required.
PGE2 Vaginal insert	10mg,released at 0.3mg/hr for 12 hrs.
PGE2 intracervical gel	0.5mg,can be repeated after 6 hrs if required ,maximum dose 1.5mg
Vaginal misoprostal	25microgram 4-6 hrly;maximum 6 doses
Oral misoprostal	20-25microgram 2 hrly;maximum 12 doses

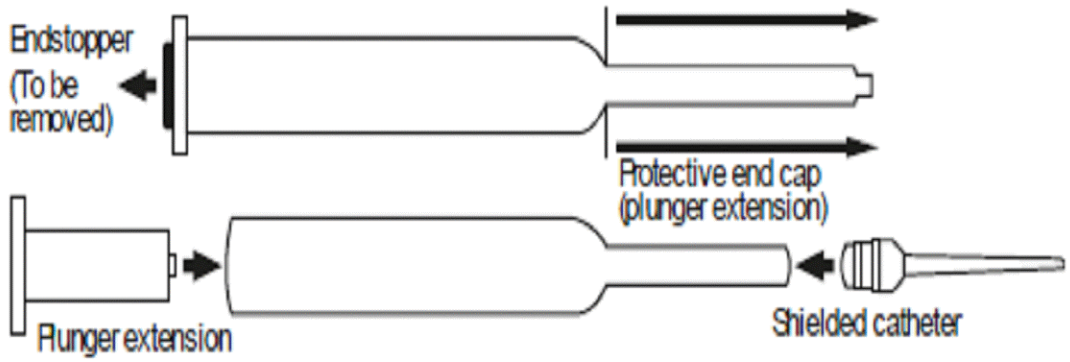
Dinoprostone Gel

DESCRIPTION :

Translucent gel containing 0.5 mg Dinoprostone BP per 3.0 g gel. For Endocervical Application.

COMPOSITION : Each syringe contains :

Dinoprostone BP ..... 0.5 mg



PHARMACOLOGY :

Dinoprostone gel contains Dinoprostone, the naturally occurring form of prostaglandin E2 (PGE2),

Dinoprostone (PGE2) is a naturally-occurring biomolecule. It is found in low concentrations in most tissues of the body and functions as a local hormone. As with any local hormone, it is very rapidly

metabolized in the tissues of synthesis (the half-life estimated to be 2.5-5 minutes). Dinoprostone Gel administered endocervically may stimulate the myometrium of the gravid uterus to contract in a manner similar to contractions seen in the term uterus during labor.

In pregnancy, PGE2 is secreted continuously by the fetal membranes and placenta and plays an important role in the final events leading to the initiation of labor. It is known that PGE2 stimulates the production of PGF2 which in turn sensitizes the myometrium to endogenous or exogenously administrated oxytocin.

Dinoprostone is also capable of stimulating smooth muscle of the gastrointestinal tract in humans. This activity may be responsible for the vomiting and / or diarrhoea that is occasionally seen when Dinoprostone is used for preinduction cervical ripening.

PGE2 plays an important role in the complex set of biochemical and structural alterations involved in cervical ripening. PGE2 is completely metabolized in humans. PGE2 is extensively metabolized in the lungs, and the resulting metabolites are further metabolized in the liver and kidney. The major route of elimination of the products of PGE2 metabolism is the kidneys.

INDICATION :

Dinoprostone gel is indicated for ripening and dilatation of an unfavorable cervix in pregnant women for labour induction.

CONTRAINDICATIONS :

There are no absolute contraindications for the use of Dinoprostone gel. However, its use in the following circumstances is not recommended.

1. Patients who are hypersensitive to prostaglandins.

2. Patients in whom oxytocics are generally contraindicated like;

a) Cases with a history of cesarean section or major uterine surgery.

b) Cases in which cephalopelvic disproportion is present.

c) Cases in which there is a history of difficult labor and/or traumatic delivery.

d) Grand multiparae with six or more previous term pregnancies cases with non-vertex presentation.

e) Cases with hyperactive or hypertonic uterine patterns.

f) Cases of fetal distress where delivery is not imminent.

g) In obstetric emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention.

3. Situations where vaginal delivery is not indicated as in herpes genitalis and patients with vasa previa, placenta previa or unexplained vaginal bleeding during this pregnancy. Contraindicated in Early, Mid-trimester Pregnancy and Breast feeding. (Except for Women undergoing an MTP or a therapeutic abortion).

It is found that prostglandins potentiate the action of oxytocin on gravid uterus. When oxytocin is used subsequently for induction of labour, the uterine activity should be carefully monitored.

PRECAUTIONS :

Certain precautions should be exercised in using Dinoprostone gel in the following cases :

1. Patients with glaucoma or raised intraocular pressure.
2. Asthma or history of asthma.
3. Pelvic infections.
4. Cardiac disease.
5. Renal impairment.
6. Hepatic impairment.
7. Lung disease.

During the use of Dinoprostone gel, uterine activity, foetal status, cervical dilatation and effacement should be carefully monitored to detect any undesirable effects like hypertonic myometrial contractions or foetal distress. In the event where high tone of myometrial contractions are sustained, the possibility of uterine rupture should be borne in mind.

ADVERSE REACTIONS :

No life threatening adverse reactions are reported with the use of Dinoprostone gel. Occasional nausea / vomiting or diarrhoea, Vaginal irritations, Abdominal & Back pain, Headache & Dizziness are reported. Uterine contractile abnormalities with or without foetal distress have also been reported. Intrapartum foetal bradycardia are reported.

Dinoprostone gel contains 0.5 mg Dinoprostone BP per 3.0 g gel in a syringe with a catheter for endocervical application.

DOSAGE AND ADMINISTRATION :

The entire contents of the syringe should be administered into the cervical canal just below the level of internal os using the catheter which is enclosed. The patient should be instructed to remain recumbent or lying down on one side for at least 30 minutes.

DIRECTION FOR USE :

Dinoprostone gel is supplied in a specially designed ready to use disposable syringe. The syringe comprises of three main components : (1) The catheter, (2) The plunger, (3) The barrel. When packed, the plunger is attached to the nozzle of the barrel. To administer the drug it is necessary to remove the endstopper & assemble the syringe.

The 3 components :

1) Catheter

2) Plunger

3) Barrel

Unscrew the plunger from nozzle of the barrel. Screw on the catheter, which is packed separately on to the nozzle. Push the plunger to expel the gel through the catheter.

An overage is added to compensate the gel that remains in the catheter.

OVERDOSAGE :

Overdosage with Dinoprostone gel may be expressed by uterine hypercontractility and uterine hypertonus.

Because of the transient nature of PGE2 -induced myometrial hyperstimulation, nonspecific, conservative management was found to be effective in the vast majority of the cases; ie, maternal position change and administration of oxygen to the mother. β-adrenergic drugs may be used as a treatment of hyperstimulation following the administration of PGE2 for cervical ripening.

STORAGE :

Dinoprostone gel should be stored in the refrigerator between 2°C to 8°C. Do not freeze. The contents of the syringe should be used for one patient only. The syringe and remaining gel, if any, should be discarded after use.

MECHANICAL METHODS

TRANSCERVICAL FOLEY CATHETER

A 16 Foley catheter with a 30 ml bulb and with tip cut off is used.

It is passed through the cervical canal, past the internal os and into extraamniotic space. The bulb is then filled with 30 ml of saline and the foley bulb is rests against the internal os. The catheter is taped to the women's thigh. Cervical ripening is achieved by this method.

ISOSORBIDE MONONITRATE

Isosorbide mononitrate is a nitric oxide donar.

Nitric oxide (NO) is a small, highly reactive, free radical gas with a half-life time of a few seconds, expressed in three isoforms; all of these isoforms are present in various cells of the uterine cervix . Cervical nitric oxide production is very low in post term pregnancy. Thus, it has been suggested that reduced cervical nitric oxide release may contribute to prolonged pregnancy.

In cervical ripening, immunological mediators play a crucial role in this process. NO is involved in the acute inflammatory response and amplifies the cytokine cascade stimulated during this response , via interactions either with prostaglandin biosynthesis or with lytic enzymes. It stimulates cyclooxygenase to increase the production of pro-inflammatory prostaglandins. Its action is accomplished by effects on connective tissue and smooth muscle cell.

In the uterus both NO production and 1 NOS expression are increased during pregnancy to assist uterine quiescence , and decreased during both term labour and antiprogestin induced preterm labour.

NDC 0143-1333-01

Isosorbide Mononitrate Tablets

20 mg
WHITE

℞ Only

100 TABLETS

Manufactured by:
West-ward Pharmaceutical Corp.
Eatontown, N.J. 07724

Each tablet contains:
Isosorbide Mononitrate ..... 20 mg

USUAL ADULT DOSAGE:
See accompanying product literature for complete information.

C-3

Store at 20-25°C (68-77°F). [See USP Controlled Room Temperature].
Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

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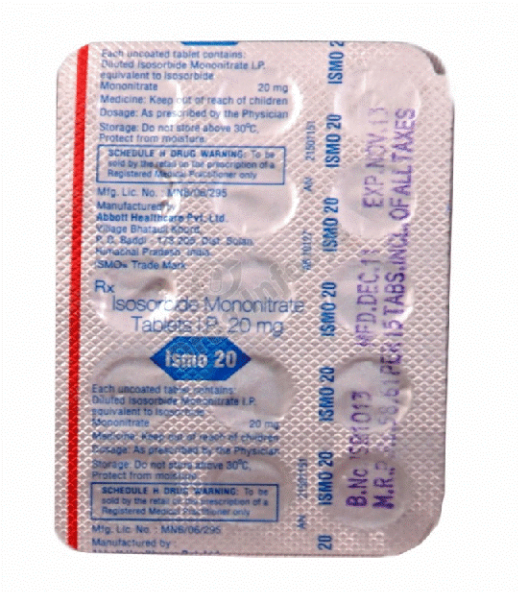
Exp. Date:

Control No.:



ISOSORBIDE MONONITRATE TABLET

Proinflammatory cytokines IL-1,TNF afpha,IL-8 are involved in cervical ripening.These cytokines induce the transcription of the inducible isoform of cyclooxygenase (COX2) at the site of inflammation. Nitric oxide is a powerful inducer of COX II and elevates local PGE2 concentrations .

- Isosorbide mononitrate (IMN)is a drug used principally in the treatment of angina pectoris.

- Vaginal administration IMN reduces the cervical resistance without inducing uterine hyperstimulation or abnormal fetal heart rate.

The serum concentration reaches 337micro gram following Isosorbide mononitrate 40 mg vaginal dose.

The half life is approximately 5 hrs. The volume of distribution is 0.62litre/kg,Systemic clearance is 115ml/mt.

ISOSORBIDE MONONITRATE

DESCRIPTION

Isosorbide mononitrate (ISMN), an organic nitrate and the major biologically active metabolite of isosorbide dinitrate (ISDN), is a vasodilator with effects on both arteries and veins. Each tablet, for oral administration, contains 10 mg, 20 mg or 30 mg of isosorbide mononitrate in an extended-release formulation. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, diethyl phthalate, hydrogenated castor oil, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, talc and titanium dioxide.

The molecular formula of ISMN is C H NO and the molecular weight is 191.14. The chemical name for ISMN is 1,4:3,6-dianhydro-,D-glucitol 5-nitrate; the compound has the following structural formula:

ISMN is a white, crystalline, odorless compound which is stable in air and in solution, has a melting point of about 90°C, and an optical rotation of +144° (2% in water, 20°C). Isosorbide mononitrate is freely soluble in water, ethanol, methanol, chloroform, ethyl acetate, and dichloromethane.

CLINICAL PHARMACOLOGY

Mechanism of Action at Cervix :

Although locally administered prostaglandins are effective in inducing cervical changes and the results of many experimental and clinical studies suggest that endogenous prostaglandins are involved in cervical ripening, there are also studies which question their role in this process. Firstly, physiological cervical ripening (i.e. mainly softening and effacement) largely occurs independent of uterine contractions. However, uterine contractions are essential for dilatation.

The cervix is still able to ripen despite being surgically isolated from the uterine corpus during pregnancy Fourthly, cervical incompetence is an extreme example of contraction-independent cervical ripening in humans. Fifthly, cyclooxygenase (COX) inhibitors (neither non-selective nor specific COX-II inhibitors) do not block antiprogestin-induced cervical ripening in humans.

The discovery that the nitric oxide generating system is present the cervix and plays a pivotal role in the ripening process seems not only to answer, at least in part, these puzzling questions, but may also have therapeutic implications. Meanwhile, there is ample evidence from experiments and clinical studies to postulate that nitric oxide, acting

synergistically with progesterone, plays an important role in the maintenance of uterine quiescence and placental perfusion during pregnancy by inducing smooth muscle relaxation (Chwalisz *et al.*, 1996; Rosselli, 1997). In rats, the uterine nitric oxide production [mainly by the inducible NO synthase (iNOS) and to lesser extent by endothelial nitric oxide synthase (eNOS)], is gestationally-regulated and progesterone-dependent (Buhimschi *et al.*, 1996). The placenta represents another important source of nitric oxide during pregnancy. Recent studies in rats using immunoblotting and immunohistochemistry indicate that iNOS (i) is highly expressed in rat placenta, (ii) is strictly located in the peripheral placental layer and (iii) exhibits a major down-regulation which starts before term.

Recent immuno-histochemical studies in human uterus and placenta suggest that there is no change in uterine and placental nitric oxide synthase expression and activity before and after the onset of labour at term (Thomson et al ., 1997a). However, this study was performed at term (37 weeks gestation), i.e. at the time point in which the NOS expression level in the uterus and placenta might be already at the minimum. In the cervix there is low nitric oxide production during pregnancy and high nitric oxide production during term and preterm labour. During pregnancy both the myometrium and placenta seem to be the major sources of nitric

oxide, whereas the migratory and resident inflammatory cells are most likely to be responsible for increased nitric oxide production in the cervix.

iNOS-derived nitric oxide possesses profound proinflammatory properties and it has been implicated in host defence, acute and chronic inflammation, cytotoxicity, tissue damage and apoptosis. The same inflammatory stimuli are known to induce the transcription of the inducible isoform of cyclooxygenase (COX-II) at the site of inflammation, More interestingly, both iNOS and COX-II seem to be also progesterone-dependent and can be up-regulated in cervix of pregnant rats and guinea pigs. In addition, it was recently found in various models of inflammation that nitric oxide is a powerful inducer of COX-II and elevates local PGE 2 concentrations in inflamed tissues.

Nitric oxide represents the final metabolic mediator of cervical ripening acting at the end of the ripening cascade. nitric oxide may activate further steps of cervical ripening, but it may also cooperate with the prostaglandin pathway by inducing COX-II as it does in chronic arthritic joint disease. This interaction may in turn amplify the proinflammatory effects of nitric oxide. This model would explain why COX inhibitors have little if any effects on cervical ripening.

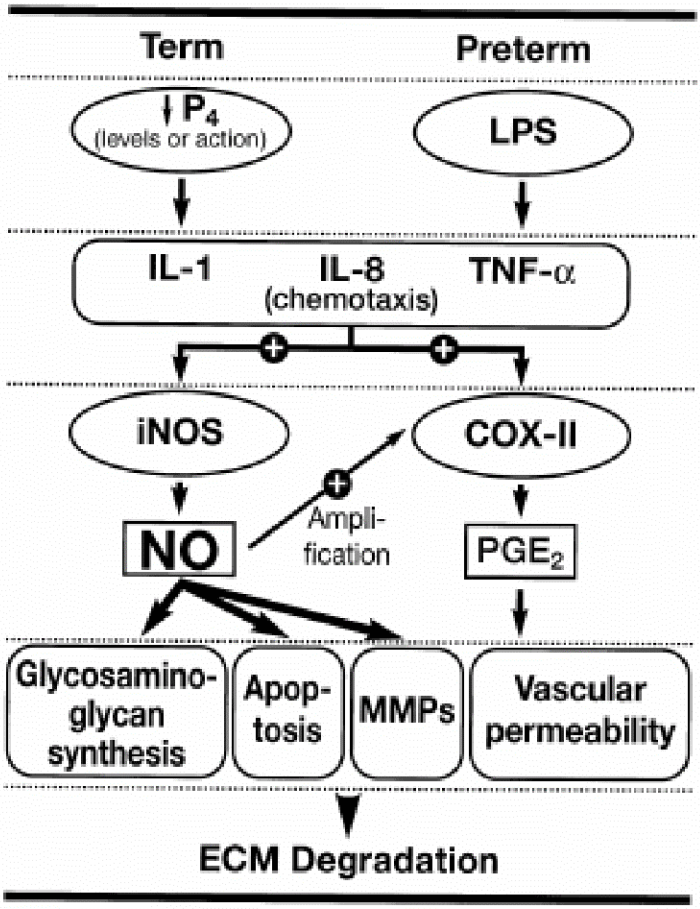


Figure 1. Proposed model of cervical ripening.
LPS = lipopolysaccarides; iNOS = inducible NO synthase; TNFα = tumour necrosis factor α; PGE_2 = prostaglandin E_2; P_4 = progesterone; NO = nitric oxide; MMPs = metalloproteinases; IL = interleukin; COX II = inducible isoform cyclooxygenase.

Mechanism of Action at Heart

The isosorbide mononitrate is the major active metabolite of isosorbide dinitrate; most of the clinical activity of the dinitrate is Attributable to the mononitrate.

The principal pharmacological action of ISMN and all organic nitrates in general is relaxation of vascular smooth muscle, producing dilatation of peripheral arteries and veins, especially the latter.

Dilatation of the veins promotes peripheral pooling of blood, decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure and mean arterial pressure (afterload). Dilatation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilatation remains undefined.

Pharmacodynamics

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored. Isosorbide mononitrate extended-release tablets, during long-term use over 42 days dosed at 120 mg once daily, continued to improve exercise performance at 4 hours and at 12 hours after dosing but its effects (although better than placebo) are less than or at best equal to the effects of the first dose of 60 mg.

Pharmacokinetics and Metabolism

After oral administration of ISMN as a solution or immediate-release tablets, maximum plasma concentrations of ISMN are achieved in 30 to 60 minutes, with an absolute bioavailability of approximately 100%. After intravenous administration, ISMN is distributed into total body water

in about 9 minutes with a volume of distribution of approximately 0.6-0.7 L/kg. Isosorbide mononitrate is approximately 5% bound to human plasma proteins and is distributed into blood cells and saliva. Isosorbide mononitrate is primarily metabolized by the liver, but unlike oral isosorbide dinitrate, it is not subject to first-pass metabolism. Isosorbide mononitrate is cleared by denitration to isosorbide and glucuronidation as the mononitrate, with 96% of the administered dose excreted in the urine within 5 days and only about 1% eliminated in the feces. At least six different compounds have been detected in urine, with about 2% of the dose excreted as the unchanged drug and at least five metabolites. The metabolites are not pharmacologically active. Renal clearance accounts for only about 4% of total body clearance. The mean plasma elimination half-life of ISMN is approximately 5 hours.

CONTRAINDICATIONS

Isosorbide mononitrate extended-release tablets are contraindicated in patients who have shown hypersensitivity or idiosyncratic reactions to other nitrates or nitrites.

WARNINGS

Amplification of the vasodilatory effects of isosorbide mononitrate by sildenafil can result in severe hypotension. The time course and dose dependence of this interaction have not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.

The benefits of ISMN in patients with acute myocardial infarction or congestive heart failure have not been established; because the effects of isosorbide mononitrate are difficult to terminate rapidly, this drug is not recommended in these settings. If isosorbide mononitrate is used in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

PRECAUTIONS

General

Severe hypotension, particularly with upright posture, may occur with even small doses of isosorbide mononitrate. This drug should, therefore, be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by isosorbide mononitrate may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy. In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence. The importance of these observations to the routine, clinical use of oral isosorbide mononitrate is not known.

Information for Patients

Patients should be told that the antianginal efficacy of isosorbide mononitrate extended-release tablets can be maintained by carefully following the prescribed schedule of dosing. For most patients, this can be

accomplished by taking the dose on arising. As with other nitrates, daily headaches sometimes accompany treatment with isosorbide mononitrate. In patients who get these headaches, the headaches are a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with isosorbide mononitrate, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Aspirin or acetaminophen often successfully relieves isosorbide mononitrate-induced headaches with no deleterious effect on isosorbide mononitrate's antianginal efficacy. Treatment with isosorbide mononitrate may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

Drug Interactions

The vasodilating effects of isosorbide mononitrate may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety. Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Drug/Laboratory Test Interactions

Nitrates and nitrites may interfere with the Zlatkis-Zak color reaction, causing falsely low readings in serum cholesterol determinations.

Carcinogenes is , Mutagenes is , Impairment of Fertility

No evidence of carcinogenicity was observed in rats exposed to isosorbide mononitrate in their diets at doses of up to 900 mg/kg/day for the first 6 months and 500 mg/kg/day for the remaining duration of a study in which males were dosed for up to 121 weeks and females were dosed for up to 137 weeks. No evidence of carcinogenicity was observed in mice exposed to isosorbide mononitrate in their diets for up to 104 weeks at doses of up to 900 mg/kg/day. Isosorbide mononitrate did not produce gene mutations (Ames test, mouse lymphoma test) or chromosome aberrations (human lymphocyte and mouse micronucleus tests) at biologically relevant concentrations. No effects on fertility were observed in a study in which male and female rats were administered doses of up to 750 mg/kg/day beginning, in males, 9 weeks prior to mating, and in females, 2 weeks prior to mating.

Hemodynamic Effects

The ill effects of isosorbide mononitrate overdose are generally the result of isosorbide mononitrate's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo, palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death. Laboratory determinations of serum levels of isosorbide mononitrate and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of isosorbide mononitrate overdose. There are no data suggesting what dose of isosorbide mononitrate is likely to be life threatening in humans. In rats and mice, there is significant lethality at doses of 2000 mg/kg and 3000 mg/kg, respectively.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of isosorbide mononitrate. In particular, dialysis is known to be ineffective

in removing isosorbide mononitrate from the body. No specific antagonist to the vasodilator effects of isosorbide mononitrate is known, and no intervention has been subject to controlled study as a therapy of isosorbide mononitrate overdose. Because the hypotension associated with isosorbide mononitrate overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good. In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of isosorbide mononitrate overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia

Methemoglobinemia has been reported in patients receiving other organic nitrates, and it probably could also occur as a side effect of isosorbide mononitrate. Certainly nitrate ions liberated during metabolism of isosorbide mononitrate can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b reductase activity, however,

and even assuming that the nitrate moiety of isosorbide mononitrate is quantitatively applied to oxidation of hemoglobin, about 2 mg/kg of isosorbide mononitrate should be required before any of these patients manifest clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of isosorbide mononitrate. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr (equivalent, in total administered dose of nitrate ions, to 7.8 to 11.1 mg of isosorbide mononitrate per hour), the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO. Classically, methemoglobinemic blood is described as chocolate brown without color change on exposure to air. When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1 to 2 mg/kg intravenously.

MATERIALS AND METHODS

Source of data

Term cases with obstetric indications for induction, in Department of Obstetrics and Gynaecology, attached to Madurai Medical College, Madurai.

Methods of collection of data:

- Study design: Randomized Comparative study, Prospective Study.
- Study period: 6months
- Sample design: Simple Random Sampling
- Sample size: 60
- Inclusion Criteria

1. Low risk group GA 37 weeks or more of pregnancy
2. High risk group DM/HTN/IUGR
3. Single gestation
4. Cephalic presentation
5. Reactive fetal heart rate pattern
6. Obstetric indications for induction

   Post dated pregnancy

Preterm PROM

Term PROM

Hypertensive disorder- Preeclampsia

Eclampsia

Chronic Hypertension

Oligohydramnios

RH Isoimmunisation

- Exclusion Criteria:

1. Cervical dilatation > 3cm
2. Bishop score >5
3. Contraindication for induction

   Fetal malpresentation

   Multiple pregnancy

   Placenta praevia

   Previous Uterine incision

   Polyhydramnios

   Pregnancy with APH

   Known allergy to drugs

   Bronchial asthma

Methodology

This study was conducted at labour ward in Department of Obstetrics and Gynaecology, attached to Madurai Medical College, Madurai for a period of 6 months.

Proper informed consent was taken from each woman. Initial evaluation was done by taking complete history, general physical examination, systemic and obstetric examination. Fetal assessment was done by Cardiotocography and Biophysical profile

The study subjects was randomly assigned into 2 groups of 30 cases each.

- ✓ Group 'A' – received T.Isosorbide mononitrate 40 mg intravaginally repeated every 6^{th} hrly according to Bishop score.
- ✓ Group 'B'- received Dinoprostone Gel 0.5 mg Intracervically repeated every 6^{th} hrly according to Bishop score maximum of 3 doses.

STUDY GROUP

An informed consent was obtained from eligible mothers of inclusion criteria.

T.Isosorbide mononitrate 40 mg was administered in the posterior fornix.The Bishop score was reviewed at 6,12 and 24 hrs.If the Bishop score was <6 at 6 and 12 hrs then the 2nd and 3rd dose was administered.Careful fetal heart rate monitoring was done every 30 minutes.Vitals monitoring was done every 2 nd hrly.Time of first and second dose of induction noted and time at which patient delivers was also noted to know induction delivery interval.No further dose was given if patient went into labour spontaneously or signs of fetal distress like tachycardia and bradycardia or moderate to severe decelerations in CTG or uterine hyperstimulations noted.If bishop score improved more than 6 then amniotomy followed by augmentation ,if necessary was performed.If bishop score did not improve after 3 doses it was considered as induction failure.Possible side effects were also noted.

CONTROL GROUP

Women attending antenatal op department at GRH,those who met inclusion criteria were examined.Bishop score was noted.If the BIishop score was < 6 , dinoprotone gel 0.5mg was administered into the cervical canal.The Bishop score was reviewed at 6 , 12, 24 hrs.If

the Bishop score was <6 at 6 and 12 hrs then the 2nd and 3rd dose was administered. Careful fetal heart rate monitoring was done every 30 minutes. Vitals monitoring was done every 2nd hrly. Time of first and second dose of induction noted and time at which patient delivers was also noted to know induction delivery interval. No further dose was given if patient went into labour spontaneously or signs of fetal distress like tachycardia and bradycardia or moderate to severe decelerations in CTG or uterine hyperstimulations noted. If bishop score improved more than 6 then amniotomy followed by augmentation ,if necessary was performed. If bishop score did not improve after 3 doses it was considered as induction failure. Possible side effects were also noted.

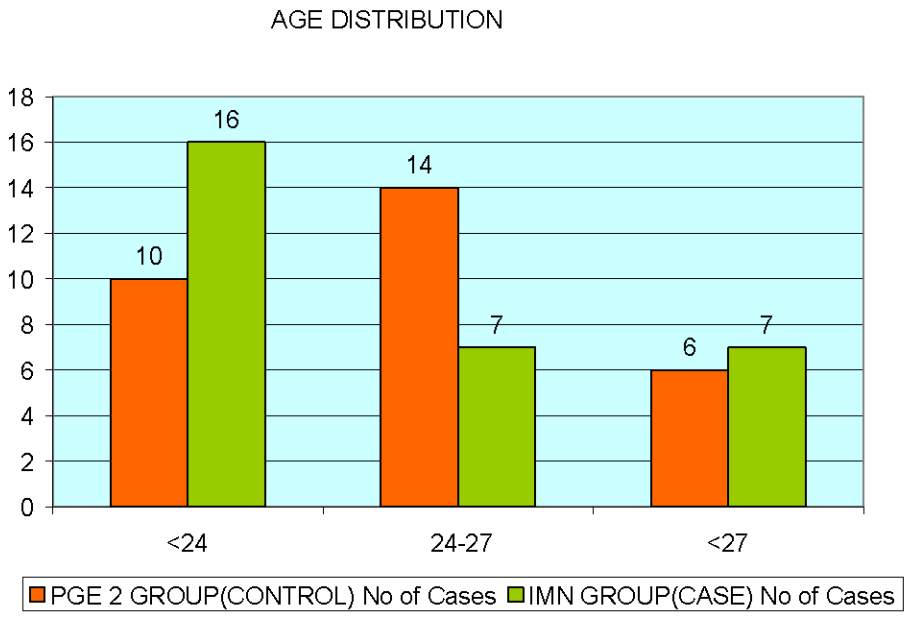
Tests Carried Out In the Study

- ✓ HB
- ✓ PLATELETS
- ✓ RBS
- ✓ BLOOD UREA
- ✓ S.CREATININE
- ✓ URINE ALBUMIN

OBSERVATION AND RESULTS

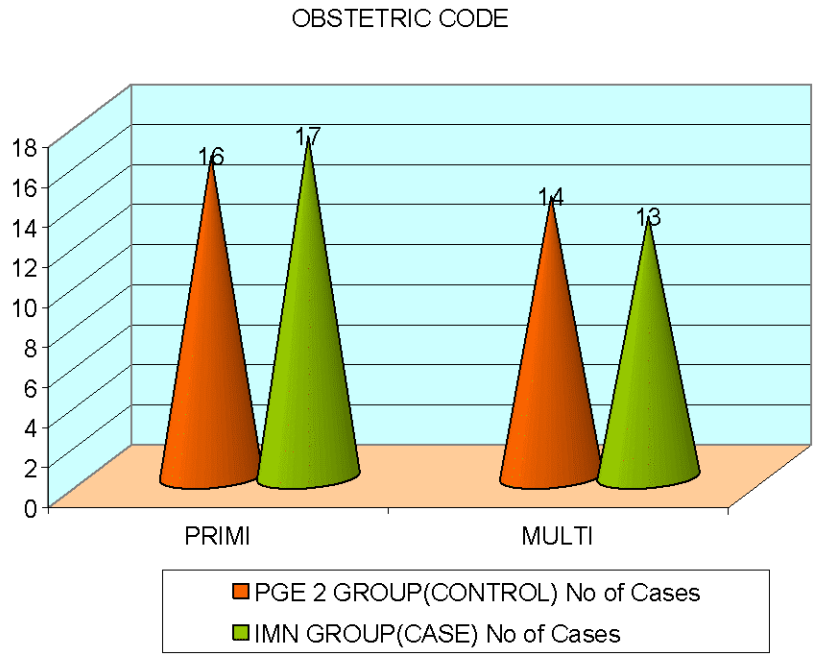
AGE	PGE 2 GROUP (CONTROL)		IMN GROUP(CASE)	
	No of Cases	%	No of Cases	%
<24	10	33.33	16	53.33
24-27	14	46.67	7	23.33
<27	6	20.00	7	23.33
Total	30	100.00	30	100.00
Mean	24.87		24.13	
SD	3.026		3.319	
P'value	0.375 - Not Significant			

Mean age are similar in both groups (24.87 in PGE2 group and 24.13 in study group) p value 0.375 statistically not significant.



OBSTETRIC CODE	PGE 2 GROUP(CONTROL)		IMN GROUP(CASE)	
	No of Cases	%	No of Cases	%
PRIMI	16	53.33	17	56.67
MULTI	14	46.67	13	43.33
Total	30	100.00	30	100.00
P value	0.924 Not significant			

Primi gravida was 53.33% in PGE2 group, 56.67% in IMN group. Multigravida was 46.67% in PGE2 group and 43.33% in IMN group. P value 0.924 statistically not significant.



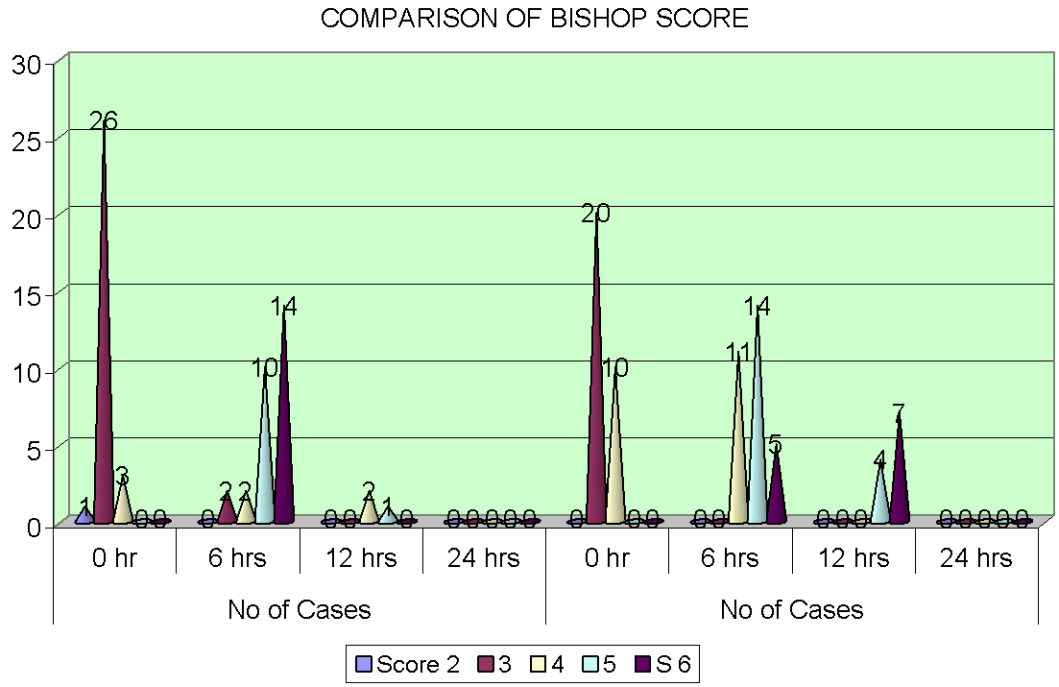
GA	PGE 2 GROUP(CONTROL)		IMN GROUP(CASE)	
	No of Cases	%	No of Cases	%
<40	16	53.33	15	50.00
>40	14	46.67	15	50.00
Total	30	100.00	30	100.00

Mean	39.067	39.233
SD	1.23	0.845
P'value	0.545 Not significant	

In PGE2 group, 16 cases were <40 weeks of gestational age and in IMN group 15 cases were <40 weeks of gestational age

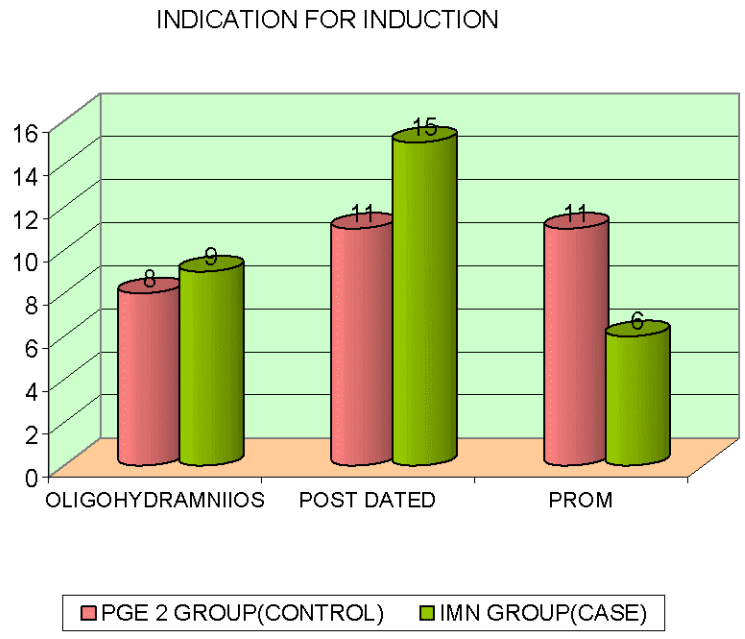
BISHOP SCORE	PGE 2 GROUP(CONTROL)				IMN GROUP(CASE)			
	No of Cases				No of Cases			
	0 hr	6 hrs	12 hrs	24 hrs	0 hr	6 hrs	12 hrs	24 hrs
2	1	-	-	-	-	-	-	-
3	26	2	-	-	20	-	-	-
4	3	2	2	-	10	11	-	-
5	-	10	1	-	-	14	4	-
6	-	14	-	-	-	5	7	-
Nil	-	2	27	30	-	-	19	30
Total	30	30	3	30	30	30	30	30
Mean	3.067	5.286	4.333		3.333	4.8	5.636	
SD	0.365	0.897	0.577		0.479	0.714	0.505	
P'value	0.019 Sig	0.026 Sig	0.002 Sig					

Mean Bishop score after 12 hrs was 4.33±0.57 in PGE2 group, and 5.63 ± 0.51 in Study group.



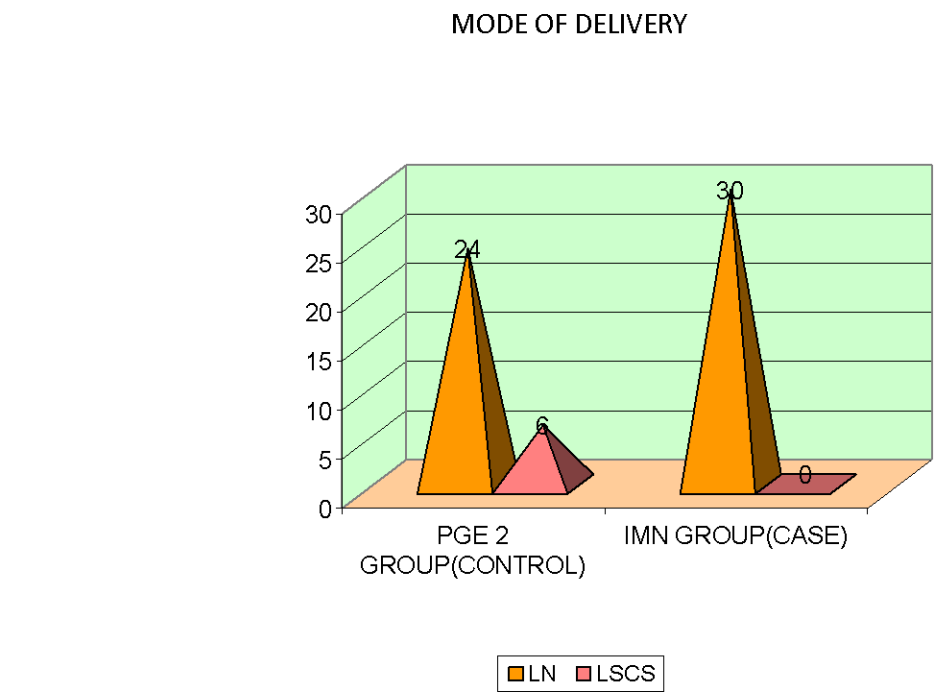
INDICATION FOR INDUCTION	PGE 2 GROUP(CONTROL)		IMN GROUP(CASE)	
	No of Cases	%	No of Cases	%
OLIGOHYDRAMNIOS	8	26.67	9	30.00
POST DATED	11	36.67	15	50.00
PROM	11	36.67	6	20.00
Total	30	100.00	30	100.00
Mean	687.867		990.000	
SD	275.720		366.715	
P'value	0.007 Sig			

Number of oligohydramnios was 8 cases in PGE2 group, 9 cases in IMN group, Postdated cases was 11 in PGE2 group, 15 cases in IMN group, No.of PROM cases was 11 in PGE2 group, 6 cases in IMN group



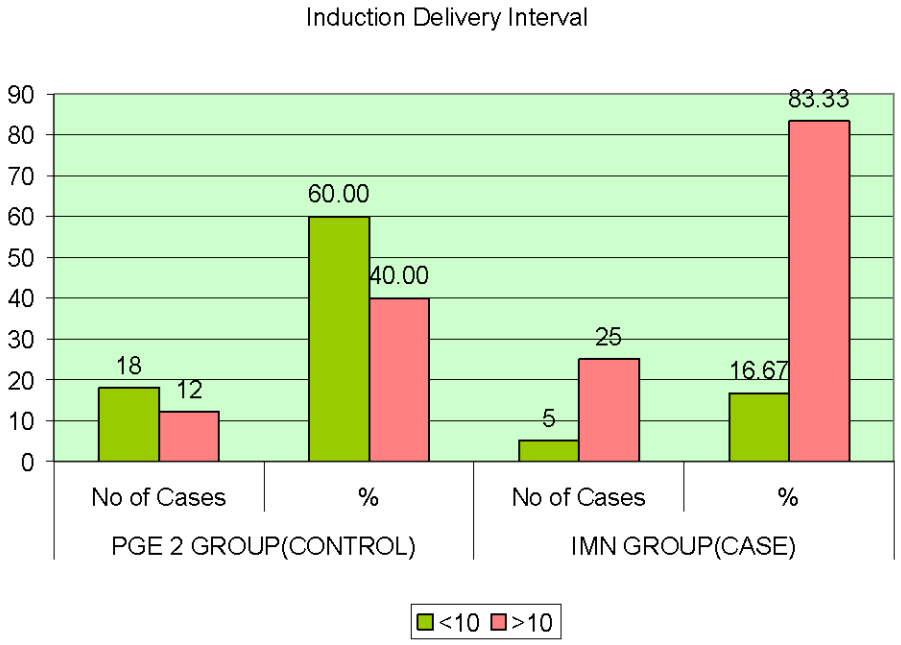
MODE OF DELIVERY	PGE 2 GROUP(CONTROL)		IMN GROUP(CASE)	
	No of Cases	%	No of Cases	%
LN	24	80.00	30	100.00
LSCS	6	20.00	0	0.00
Total	30	100.00	30	100.00
P value	0.042 Significant			

LSCS was more in PGE2 group (6 cases) but in IMN group all cases were delivered by labour natural.



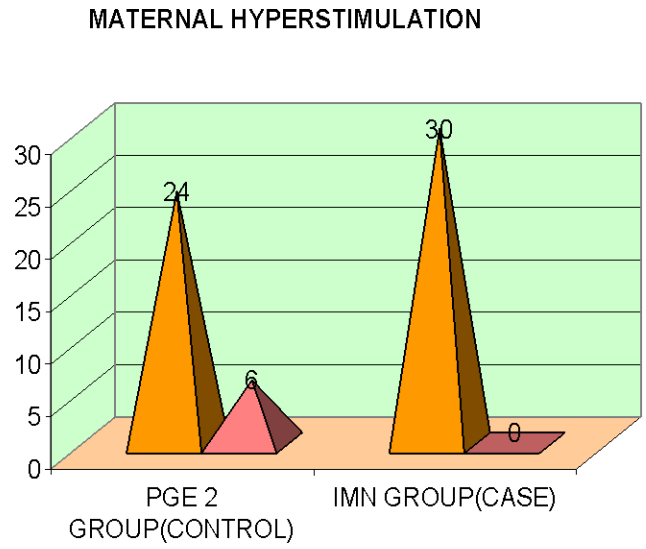
INDUCTION DELIVERY INTEREVAL	PGE 2 GROUP(CONTROL)		IMN GROUP(CASE)	
	No of Cases	%	No of Cases	%
<10	18	60.00	5	16.67
>10	12	40.00	25	83.33
Total	30	100.00	30	100.00
Mean	16.33		20.36	
SD	6.56		7.34	
P'value	<0.001 Significant			

Mean induction delivery duration is higher in IMN group (20.36 hrs) but in PGE2 group only 16.3 hours p value significant <0.001



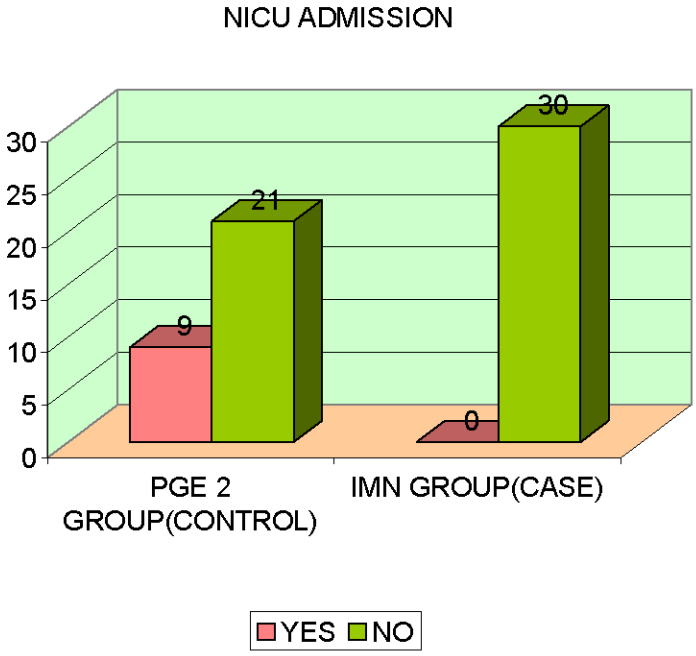
MATERNAL HYPERSTIMULATION	PGE 2 GROUP(CONTROL)		IMN GROUP(CASE)	
	No of Cases	%	No of Cases	%
YES	6	20.00	0	0.00
NO	24	80.00	30	100.00
Total	30	100.00	30	100.00

In PGE2 group, 6 cases had maternal hyperstimulation but in IMN group none of the cases had maternal hyperstimulation.

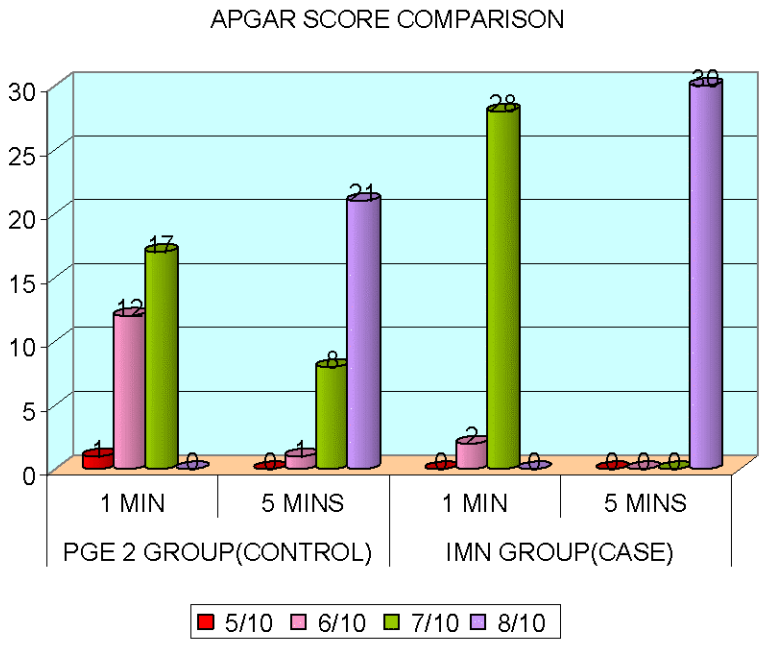


NICU ADMISSION	PGE 2 GROUP(CONTROL)		IMN GROUP(CASE)	
	No of Cases	%	No of Cases	%
YES	9	30.00	0	0.00
NO	21	70.00	30	100.00
Total	30	100.00	30	100.00
p value	0.002 Significant			

In PGE2 group, 9 cases need NICU admission but in IMN group none of the cases need NICU admission.



APGAR SCORE	PGE 2 GROUP(CONTROL)		IMN GROUP(CASE)	
	No of Cases		No of Cases	
	1 MIN	5 MINS	1 MIN	5 MINS
5/10	1	0	0	0
6/10	3	1	1	0
7/10	24	25	28	5
8/10	2	4	1	25
Total	30	30	30	30



DISCUSSION

Mean age are similar in both groups (24.87 in PGE2 group and 24.13 in study group) p value 0.375 statistically not significant.

Primi gravida was 53.33% in PGE2 group, 56.67% in IMN group. Multigravida was 46.67% in PGE2 group and 43.33% in IMN group. Parity index was comparable in both groups. P value 0.924 statistically not significant.

Mean Bishop score after 12 hrs was 4.33+0.57 in PGE2 group, and 5.63 + 0.51 in Study group.

The mean gestation in PALLAVI study was 40weeks +1day.The mean gestation in the PRIM study was 40weeks6days.The mean gestation in the present study was 40weeks 3 days which was comparable.

The mean induction delivery duration was 25.2 hrs in PALLAVI study. The mean induction delivery was 39.7hrs in PRIM study. The mean induction delivery was 20.36 hrs in present study.

In IMN group, 5 cases were delivered after single dose of tablet Isosorbide mononitrate and 20 cases were delivered after 2 doses and remaining 5 cases needed 3doses for delivery.

Vaginal delivery was occurred in 100% cases in PALLAVI study. In the PRIM study 36% of the cases had vaginal delivery. In the present study 100% of cases had vaginal delivery.

The babies with Apgar <7 for one minute score in Pallavi study was 0% , 11.7% in PRIM study. In our study apgar score for < 7 for one minute was only 1 cases (3.3%)

NICU admission in pallavi study was 0%, 6.6% in PRIM study, but in our study NICU admission was 0 %

6 cases had Maternal hyperstimulation and tachysystole in PGE2 group but in our study group no maternal hyperstimulation and tachysystole.

CONCLUSION

1. Isosorbide mononitrate is cheaper and effective to prostaglandin E2 for cervical ripening at term in normal pregnancies.

2. IMN does not cause uterine hyperstimulation and maternal tachysystole.

3. IMN does not cause non reassuring fetal heart rate pattern

4. IMN does not cause neonatal side effects.

5. Induction delivery interval prolonged in IMN group (mean 20.36 hrs) in study group mean delivery interval time was 16.32 hrs.

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PROFORMA

Date: IP No:

Name: LMP :

Age : EDD :

CONFIRM GA (BY EARLY USG):

Address:

Date of Admission: Date of Delivery :

Booked/Unbooked:

Complaints:

Past History:

Menustral History:

Marital history:

Obstetric history:

General Examination:

Systemic Examination:

P/A:

P/V:

USG:

Diagnosis:

CTG :

BISHOP SCORE :

INDICATION FOR INDUCTION :

Date and Time of Induction :

Date and Time of Delivery :

Induction Delivery Interval :

HRS	BISHOP SCORE
0	
6	
12	
24	

Baby detail:

Sex:

Birth weight:

Apgar score :1'

5'

OUTCOME :

Mode of delivery :

Induction delivery interval :

Maternal Hyperstimulation :

NICU admission :

PGE2 - CONTROL GROUP

S.NO	NAME	IP NO.	AGE	OBSTETRIC CODE		GA				BISHOP SCORE				INDICATION FOR INDUCTION
				PRIMI	MULTI	WEEKS	week to days	DAYS	Total Days	0 hr	6 hrs	12 hrs	24 hrs	
1	MANJULA	**20327**	26	PRIMI	-	38	266	**0**	**266**	3	5	-	-	PROM
2	THAVAMANI	**77973**	25	PRIMI	-	38	266	**0**	**266**	4	6	-	-	PROM
3	PANDISELVI	**20251**	28	PRIMI	-	39	273	**0**	**273**	3	5	-	-	PROM
4	SANTHYA	**19109**	23	-	MULTI	40	280	2	**282**	3	4	-	-	POST DATED
5	TAMILSELVI	**76989**	24	-	MULTI	40	280	2	**282**	3	3	4	-	POST DATED
6	NANDHINI	**75465**	22	PRIMI	-	39	273	4	**277**	3	5	-	-	PROM
7	JEYAPRATHA	**74365**	26	-	MULTI	39	273	1	**274**	3	5	-	-	OLIGOHYDRAMNIIOS
8	ALAGUDEVI	**76200**	19	PRIMI	-	37	259	4	**263**	4	5	-	-	PROM
9	ARUVUGATHAMMAL	**19675**	26	-	MULTI	41	287	1	**288**	3	6	-	-	POST DATED
10	ALAGESWARI	**19014**	24	PRIMI	-	40	280	3	**283**	3	6	-	-	POST DATED
11	PITCHAIAMMAL	**19204**	21	PRIMI	-	40	280	1	**281**	3	3	4	-	POST DATED
12	HEMALATHA	**19583**	23	PRIMI	-	39	273	2	**275**	3	6	-	-	OLIGOHYDRAMNIIOS
13	BHUVANESWARI	**77746**	23	PRIMI	-	38	266	4	**270**	3	-	-	-	PROM
14	ANITHA	**77881**	21	PRIMI	-	40	280	2	**282**	3	6	-	-	POST DATED
15	SINDHU	**19715**	24	PRIMI	-	39	273	2	**275**	3	5	-	-	PROM
16	SARANA	**20486**	20	PRIMI	-	38	266	3	**269**	3	6	-	-	OLIGOHYDRAMNIIOS
17	SATHAMMAL	**18821**	20	PRIMI	-	38	266	3	**269**	3	-	-	-	PROM
18	RAJATHI	**20197**	30	-	MULTI	38	266	4	**270**	3	6	-	-	PROM
19	INDIRA	**78336**	31	-	MULTI	37	259	4	**263**	3	6	-	-	OLIGOHYDRAMNIIOS
20	CHITRA	**79298**	27	PRIMI	-	39	273	5	**278**	3	6	-	-	PROM
21	SNEHA	**20460**	25	-	MULTI	38	266	3	**269**	3	5	-	-	OLIGOHYDRAMNIIOS

22	SARANYA	**77789**	23	PRIMI	-	39	273	3	**276**	4	6	-	-	OLIGOHYDRAMNIIOS
23	MUTHUSELVI	**79939**	25	PRIMI	-	38	266	**0**	**266**	3	5	-	-	OLIGOHYDRAMNIIOS
24	ABIRAMI	**77761**	27	-	MULTI	40	280	2	**282**	2	4	5	-	POST DATED
25	JEGATHESWARI	**20064**	26	-	MULTI	40	280	3	**283**	3	5	-	-	POST DATED
26	GAYATHIRI	**19801**	25	-	MULTI	38	266	4	**270**	3	6	-	-	PROM
27	KARPAGAM	**17732**	28	-	MULTI	39	273	2	**275**	3	6	-	-	OLIGOHYDRAMNIIOS
28	SELVI	**18832**	29	-	MULTI	40	280	3	**283**	3	5	-	-	POST DATED
29	MANIMEGALAI	**20312**	28	-	MULTI	40	280	2	**282**	3	6	-	-	POST DATED
30	MUTHULAKSHMI	**19682**	27	-	MULTI	40	280	2	**282**	3	6	-	-	POST DATED

MODE OF DELIVERY		**INDUCTION DELIVERY INTEREVAL**				**MATERNAL HYPERSTIMULATION**		**NICU ADMISSION**		**APGAR SCORE**	
LN	**LSCS**	**HOURS**	**Hours to Mins**	**MINUTES**	**Total mins**	**YES**	**NO**	**YES**	**NO**	**1 MIN**	**5 MIN**
-	LSCS	15	900	2	902	YES	-	YES	-	7/10	8/10
LN	-	8	480	5	485	-	NO	-	NO	6/10	8/10
-	LSCS	10	600	15	615	YES	-	YES	-	6/10	8/10
LN	-	16	960	**0**	960		NO	-	NO	6/10	7/10
-	LSCS	22	1320	10	1330	YES	-	YES	-	7/10	8/10
LN	-	10	600	20	620	-	NO	YES	-	5/10	6/10
LN	-	10	600	20	620	-	NO	-	NO	7/10	8/10
LN	-	8	480	5	485	-	NO	-	NO	6/10	7/10
LN	-	8	480	30	510	-	NO	-	NO	7/10	8/10
LN	-	8	480	30	510	-	NO	-	NO	7/10	8/10
-	LSCS	18	1080	**0**	1080	YES	-	YES	-	6/10	8/10
LN	-	7	420	**0**	420	-	NO	-	NO	7/10	8/10

LN	-	9	540	17	557	-	NO	YES	-	7/10	8/10
LN	-	7	420	50	470	-	NO	-	NO	7/10	8/10
LN	-	18	1080	15	1095	-	NO	YES	-	6/10	7/10
LN	-	10	600	**0**	600	-	NO	-	NO	6/10	8/10
LN	-	5	300	**0**	300	-	NO	-	NO	7/10	8/10
LN	-	10	600	**0**	600	-	NO	-	NO	7/10	8/10
LN	-	6	360	40	400	-	NO	-	NO	6/10	7/10
LN	-	13	780	40	820	-	NO	-	NO	6/10	7/10
LN	-	13	780	0	780	-	NO	-	NO	7/10	8/10
LN	-	7	420	25	445	-	NO	YES	-	6/10	7/10
-	LSCS	17	1020	22	1042	YES	-	-	NO	6/10	7/10
-	LSCS	21	1260	30	1290	YES	-	YES	-	6/10	7/10
LN	-	14	840	0	840	-	NO	-	NO	7/10	8/10
LN	-	9	540	0	540	-	NO	-	NO	7/10	8/10
LN	-	8	480	0	480	-	NO	-	NO	7/10	8/10
LN	-	13	780	0	780	-	NO	-	NO	7/10	8/10
LN	-	12	720	20	740	-	NO	-	NO	7/10	8/10
LN	-	5	300	20	320	-	NO	-	NO	7/10	8/10

IMN GROUP - CASE

S.NO	NAME	IP NO.	AGE	OBSTETRIC CODE		GA				BISHOP SCORE				INDICATION FOR INDUCTION
				PRIMI	MULTI	WEEKS	week to days	DAYS	Total Days	0 hr	6 hrs	12 hrs	24 hrs	
1	MANIPRIYA	**18128**	22	PRIMI	-	39	273	3	**276**	4	5	-	-	OLIGOHYDRAMNIIOS
2	SEENU	**78843**	23	PRIMI	-	38	266	2	**268**	3	4	6	-	OLIGOHYDRAMNIIOS
3	LOGESWARI	**20250**	29	-	MULTI	40	280	4	**284**	3	4	6	-	POST DATED
4	PAPPA	**20402**	25	-	MULTI	40	280	3	**283**	3	5	-	-	POST DATED
5	KARTHIGAISELVI	**20355**	21	PRIMI	-	40	280	4	**284**	3	4	5	-	POST DATED
6	NATHIYA	**78591**	22	PRIMI	-	39	273	2	**275**	4	5	6	-	PROM
7	LAKSHMI	**20622**	29	-	MULTI	40	280	2	**282**	4	6	-	-	POST DATED
8	RAJALAKSHMI	**20266**	23	-	MULTI	40	280	2	**282**	3	4	-	-	POST DATED
9	RENUGA	**18214**	21	PRIMI	-	40	280	2	**282**	3	4	5	-	POST DATED
10	SIVAJOTHI	**17214**	20	PRIMI	-	39	273	1	**274**	4	5	-	-	OLIGOHYDRAMNIIOS
11	KAMALA	**14321**	22	PRIMI	-	38	266	5	**271**	4	5	-	-	PROM
12	KAVITHA	**15350**	26	-	MULTI	40	280	2	**282**	4	6	-	-	POST DATED
13	PARAMESWARI	**16751**	28	-	MULTI	40	280	3	**283**	3	5	-	-	POST DATED
14	ILAKIYA	**76214**	27	-	MULTI	40	280	2	**282**	3	4	6	-	POST DATED
15	PETCHI	**72351**	29	-	MULTI	38	266	4	**270**	4	6	-	-	PROM
16	SUBBULAKSHMI	**79757**	30	PRIMI	-	38	266	6	**272**	4	6	-	-	OLIGOHYDRAMNIIOS
17	ISHWARIYA	**79662**	26	-	MULTI	39	273	5	**278**	3	6	-	-	OLIGOHYDRAMNIIOS
18	SARASWATHI	**20426**	29	PRIMI	-	40	280	2	**282**	3	4	6	-	POST DATED
19	RANJITHA	**20485**	24	PRIMI	-	39	273	6	**279**	3	4	5	-	OLIGOHYDRAMNIIOS
20	SATHYA	**20579**	23	PRIMI	-	40	280	3	**283**	3	4	5	-	POST DATED
21	SONIYA	**78861**	29	-	MULTI	39	273	4	**277**	3	5	-	-	PROM
22	SWATHY	**19577**	25	-	MULTI	38	266	3	**269**	3	5	-	-	OLIGOHYDRAMNIIOS

23	GOWRI	**20507**	22	-	MULTI	40	280	4	**284**	3	5	-	-	POST DATED
24	MUTHULAKSHMI	**20514**	20	PRIMI	-	40	280	2	**282**	3	5	-	-	POST DATED
25	PANDEESWARI	**20515**	20	-	MULTI	38	266	3	**269**	3	5	-	-	OLIGOHYDRAMNIIOS
26	SANGEETHA	**79341**	24	PRIMI	-	38	266	1	**267**	3	4	6	-	PROM
27	HEMA	**79324**	23	PRIMI	-	40	280	2	**282**	4	5	-	-	POST DATED
28	SUMITHRA	**78846**	19	PRIMI	-	38	266	4	**270**	3	5	-	-	PROM
29	RAJATHI	**72910**	21	PRIMI	-	40	280	2	**282**	4	5	-	-	POST DATED
30	AMUTHA	**20485**	22	PRIMI	-	39	273	1	**274**	3	4	6	-	OLIGOHYDRAMNIIOS

MODE OF DELIVERY		**INDUCTION DELIVERY INTEREVAL**				**MATERNAL HYPERSTIMULATION**		**NICU ADMISSION**		**APGAR SCORE**	
LN	**LSCS**	**HOURS**	**Hours to Mins**	**MINUTES**	**Total mins**	**YES**	**NO**	**YES**	**NO**	**1 MIN**	**5 MIN**
LN	-	10	600	0	600	-	NO	-	NO	6/10	8/10
LN	-	15	900	30	930	-	NO	-	NO	7/10	8/10
LN	-	20	1200	0	1200	-	NO	-	NO	7/10	8/10
LN	-	9	540	**0**	540	-	NO	-	NO	7/10	8/10
LN	-	23	1380	20	1400	-	NO	-	NO	7/10	8/10
LN	-	22	1320	0	1320	-	NO	-	NO	7/10	8/10
LN	-	6	360	30	390	-	NO	-	NO	7/10	8/10
LN	-	21	1260	0	1260	-	NO	-	NO	7/10	8/10
LN	-	22	1320	10	1330	-	NO	-	NO	6/10	8/10
LN	-	12	720	0	720	-	NO	-	NO	7/10	8/10
LN	-	20	1200	**0**	1200	-	**NO**	-	NO	7/10	8/10
LN	-		0		0	-	NO	-	NO	7/10	8/10
LN	-		0		0	-	NO	-	NO	7/10	8/10
LN	-		0		0	-	NO	-	NO	7/10	8/10

LN	-		0		0	-	NO	-	NO	7/10	8/10
LN	-		0		0	-	NO	-	NO	7/10	8/10
LN	-		0		0	-	NO	-	NO	7/10	8/10
LN	-		0		0	-	NO	-	NO	7/10	8/10
LN	-		0		0	-	NO	-	NO	7/10	8/10
LN	-		0		0	-	NO	-	NO	7/10	8/10
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LN	-		0		0	-	NO	-	NO	7/10	8/10

MADURAI MEDICAL COLLEGE

MADURAI, TAMILNADU, INDIA -625 020

(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.J.Rajam
Course	:	PG in MS., Obstetrics & Gynaecology
Period of Study	:	2015 - 2018
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	A study on Isosorbide Mononitrate versus Dinoprostone Gel for Cervical Ripening at term – Maternal and Fetal outcome.
Ethical Committee as on	:	11.09.2017

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.,(Neuro), Dsc (Hon)
CHAIRMAN-
IEC - Madurai Medical College
Madurai

Dean
Madurai Medical College
Madurai-20

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