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Review Article

Mifepristone as pre-induction cervical ripening agent: a review article

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ABSTRACT

Induction of labour after the period of viability by any methods medical, surgical or combined, for the purpose of vaginal delivery. The success of induction, to a great extent, depend upon pre-induction cervical status i.e. cervical ripening. So, ripening of cervix prior to induction i.e. pre-induction cervical ripening is one of the important steps for successful induction of labour. There are different methods for cervical ripening like prostaglandins (PGE). However, use of prostaglandins (PGE) and oxytocin as labour inducing agent has its own adverse effects on maternal and perinatal outcome. So, constant efforts are made for the less use of uterotonins. The present review aims to study the efficacy of oral Mifepristone for improvement in Bishop's score, requirement of additional uterotonics, induction delivery interval, mode of delivery and neonatal outcome. Electronic databases were searched by using keywords 'Mifepristone, RU486, PGE2 gel, Cervical ripening, Bishop's score and Induction of labour' and eleven articles were found from 2009 to 2018 which fulfils our study criteria and thus they were taken for review. Based on all the studies, Mifepristone appears to be effective cervical ripening in comparison to other agents with significant improvement in Bishop's score, higher vaginal delivery rate, shorter induction delivery interval and good neonatal outcome.

Keywords: Bishop's score, Cervical ripening, Induction of labour, Mifepristone, PGE2 gel, RU486

INTRODUCTION

Induction of labour is defined as initiation of uterine contractions after the period of viability by any methods medical, surgical or combined, for the purpose of vaginal delivery. It is required when the risk of continuation of pregnancy is more either to the mother or to the fetus. The incidence being over 10-20% in developed countries.^{1,2} The success of induction, to a great extent, depend upon pre-induction cervical status i.e cervical ripening which is a series of complex biochemical changes in the cervix, mediated by hormones altering both cervical collagen and ground substance. Thus, the

cervix softens, relaxes and opens in response to uterine contractions.¹ Many times induction before ripening of the cervix ends in a condition known as failed induction. The consequence of failed induction is caesarean section. So, ripening of cervix prior to induction i.e pre-induction cervical ripening is one of the important steps for successful induction of labour.

Pre-induction cervical status is assessed by Bishop's score. If the Bishop's score is less than 6, agent like PGE2 gel and Foleys catheter is used for cervical ripening which is followed by induction of labour using PGE1 tablets vaginally and orally or oxytocin infusion.^{3,4}

However, use of prostaglandins (PGE) and oxytocin as labour inducing agent has its own adverse effects on maternal and perinatal outcome. The maternal effects are hyperstimulated uterine contraction leading to increase operative interference. The perinatal effects are meconium stained liquor, foetal distress, meconium aspiration syndrome, early neonatal hyperbilirubinemia and increased NICU admission with prolonged stay. So, constant efforts are made for the less use of uterotonins. This can be achieved with the use of pre-induction cervical ripening agent like PGE2 gel and Mifepristone (RU486).

Mifepristone (RU486), is a pharmacological agent (anti-progestins) have been developed to antagonize the action of progesterone by blocking at the cellular level and initiating the labour process. Although, the use of RU486 is there for termination of pregnancy in early trimester, its use in term pregnancy as pre-induction cervical ripening agent is not a routine practice. Moreover, conflicting results on use of Mifepristone (RU486) are available regarding its use as cervical ripening.

So, in this study we planned to compare the pre-induction cervical ripening effect of Mifepristone (RU486) and commonly used PGE2 gel.

METHODS

Authors reviewed various research article obtained by using the search terms

‘Mifepristone, RU486, PGE2 gel, Cervical ripening, Bishop’s score and induction of labour’. The search engines used were google scholar, PUBMED. The filter used were English language, human study, last ten years studies. Using above criteria, we found eleven articles from 2009 to 2018 which fulfills our study criteria and thus they were taken for review.

History of induction labour

Induction of labour has been practiced for centuries from the era of Hippocrates (460-370BC). Methods of induction used in ancient era were herbs, tonics, remedies and physical exercise, administration of powdered snakes rattle, bear claw scrapings in potions, teas from the blossom of Indian corns, barriers of ground cedar brushes, ingestion of inner bark of the pine tree and fir tree.^{5,6} Digital separation of membranes from the lower uterine segment and then rupturing it above the fetal head-high for induction of labour was described in 1810 by James Hamilton. Other methods were tepid water which would separate the membranes from uterine wall and sponge tents were used to stretch the cervix were abandoned later.⁷ Amniotomy known as artificial rupture of membranes was the first reliable technique used in obstetric practice and was employed in 1756 by Thomas Denman of London.⁸ A technique including emptying of full urinary bladder, administering an enema containing a

mixture of oil water and honey, pouring of egg white into vagina to soften the cervix was described by Soranas of Ephesus in early 100s.^{8,9} Foley catheter was derived from the approach that was used by Robert Barnes of London in 1861 in New York. This approach used hydrostatic bag placed through the cervix with a view of labour induction.¹⁰ In the year 1807, John Stern first introduced ergot for obstetric procedures in America. Later in early 20th century, ergot, quinine and pituitary extracts became the primary medication for induction of labour.¹¹ Sir Henry Dale physiologist and pharmacist in early 20th century, made the first observation that posterior pituitary extracts caused uterine contractions. He gave samples to the obstetrician William Blair Bell who began to use it for induction of labour as these were initially given as intramuscular injection.⁷ The reliable preparations of oxytocin became available only after later half of 20th century. Geoffrey Theobald described “physiological drip” as a dilute intravenous infusion of oxytocin. Corey EJ et al, in 1969 synthesized prostaglandins at Harvard. Although, these chemicals existed since 1930’s but came into clinical practice only after 30 years. Later in 1975 PGEs added an extra dimension to labour induction as they had positive impact on cervical ripening and also had uterine contraction outcome.¹⁰ In 1980, a French pharmaceutical company Roussel-Uclaf developed RU-486 (Mifepristone) and it came into market in 1988.

Structural and biochemical remodeling in cervical ripening

The firmness of the cervix is a result of presence of collagen. In non-pregnant uterus, collagen is in irregular bundles and packed tightly. Cervical cells and neutrophils secrete collagenases enzymes throughout the pregnancy which helps in remodeling of cervix from first trimester to delivery.^{12,13} In early pregnancy, collagen is reorganized and integrated with proliferation and hyperplasia of the cellular component. As term approaches, multiple factors work together in complex interactions that cause collagen dispersion and its fibres also becomes loosely packed which promotes the cervical ripening and softening. Decorin and hyaluronic acids levels increases and physiological cell death occur which helps in remodeling process. As the collagen bundles spread and loses its strength, cytokines, hyaluronic acid, collagenase, and elastase act together to allow effacement. Then, the mechanical forces of uterine contractions expand the elastin and allow dilatation. During dilation, cytokines and hyaluronic acid levels decreases, which cause decrease in collagenolytic activity and allow the cervix to begin the process of repairing itself. During term pregnancy, there is reduction in oestrogen and progesterone receptors. Interleukins-1 β and interleukins-8 are the main cytokines which activates the inflammatory cells and intensify the activity of collagenase. Prostaglandins E2, I2, F2 α levels are increased during term and causes collagen disintegration and changes the GAG composition causing alternation in tissue hydration.¹⁴

Indications for induction of labour

'Induction of labour' is a common obstetric procedure that is indicated when the benefits to either mother or fetus are greater than that of continuing the pregnancy. Induction of labor is indicated to be advantageous for both the mother and the baby. Induction has the potential to improve neonatal outcomes when it is done between 37-41 weeks.^{15,16} Indications for induction of labour include post-term pregnancy, intrauterine fetal growth retardation, medical disorders of pregnancy like diabetes mellitus, renal disease, chronic pulmonary disease, hypertensive disorders, premature rupture of the membranes, premature termination of the pregnancy (abortion), scheduling concerns, fetal death inside uterus, twin pregnancy continuing beyond 38 weeks of gestation, fetal complications like isoimmunization, non-reassuring fetal status and fetal anomalies. Contraindications are vasa previa or complete placenta previa, transverse or oblique fetal lie, umbilical cord prolapsed, prior classical uterine incision or trans-fundal uterine surgery, active genital herpes infection, absolute cephalopelvic disproportion, malpresentation and cervical carcinoma.¹⁷⁻¹⁹

Pre-requisites of an ideal inducing agent are as follows i.e. safe, effective, non-invasive, easy to use and store.

Methods of induction of labour

Labour can be induced either by medical, mechanical, surgical or combined methods.

Pharmacological methods

Commonly used medical methods are prostaglandin, synthetic oxytocin preparations, mifepristone and relaxin. Similarly, mechanical and surgical methods are membrane sweeping and artificial rupture of the membranes respectively.

Progesterone receptor antagonists (Mifepristone)

In 1980, a French pharmaceutical company Roussel-Uclaf developed RU-486 (Mifepristone) and it came into market in 1988. It has been proved that in human beings it is an active antiprogesterone and anti-glucocorticosteroid. Mifepristone is a 19-nor steroid compound with 11β-[p-(Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. It antagonizes the action of progesterone by blocking at the cellular level and initiating the labour process.²⁰ Mifepristone is administered orally and readily absorbed. Its recommended dosage is 200 mg per orally. It is orally active compound with 70% absorption rate. Its plasma half-life is 18 hours and it is excreted by feces and urine. Bleeding, abdominal cramps, fever, vomiting and nausea are its side effects.²¹ It has been used for early pregnancy termination. Because of its action, trials had been undergoing for its applicability in cervical ripening and

labor induction as it is known as a selective progesterone receptor antagonist. The studies showed significant improvement in cervical ripening with Mifepristone and reduced the rate of caesarean section as compared to placebo.²²

Non-pharmacological methods

Commonly, used non-pharmacological methods are membrane stripping, mechanical cervical dilators (like laminaria tents, dilapan and lamichel), transcervical balloon, catheters with extra-amniotic saline infusion and with concomitant oxytocin administration and amniotomy

Limitations of induction

There are certain limitations of induction of labour for mother and fetus. Limitations for mothers are abnormal uterine activity, increased operative interference, increased morbidity, increased need of labour analgesia, induction failure leading to cesarean section creating psychological upset for mother.

For fetus induction of labour can lead to iatrogenic prematurity, prolonged labor and hypoxia due to uterine dysfunction.

DISCUSSION

Bishop's score

Comparative studies conducted by Sah MK et al, Arumugaselvi B et al, Gaikwad V et al and Fathima S et al compare the efficacy, safety and feto-maternal outcome of oral Mifepristone and endocervical PGE2 gel showed improvement in Bishop's score ranges from 66% to 94% in Mifepristone group and 56% to 80% in PGE2gel group.^{4,23-25}

There was significant improvement noted in the studies done to compare Mifepristone and placebo by Ramesh B et al, Kanan Y et al, Athawale R et al, Hapangama D et al and Berkane N et al.^{3,22,26-28}

Similar, results were seen in comparative studies of Mifepristone and Misoprostol for pre-induction cervical ripening done by Archana A et al, Mandade K et al.^{29,30} In all the studies mentioned above there was significant improvement in Bishop's score with Mifepristone.

Requirement of uterotonics

Requirement of Misoprostol in a study done by Mandade K et al and Archana A et al to study the efficacy of Mifepristone ranges from 54% to 68%.^{29,30} There is no significant difference within the above-mentioned studies.

In comparative studies of Mifepristone and PGE2 gel for pre-induction cervical ripening by Sah MK et al, Arumugaselvi B et al, Gaikwad V et al, Fathima S et al, oxytocin requirement was higher in PGE2 gel group as compared Mifepristone group because there was significant improvement with Mifepristone.^{4,23-25}

Mode of delivery

In comparative studies conducted by Sah MK et al, Arumugaselvi B et al, Gaikwad V et al, Fathima S et al and to compare the efficacy of Mifepristone and PGE2 gel, rate of vaginal delivery was higher in Mifepristone as compared to PGE2gel ranging from 70% to 84% in all the studies.^{4,23-25}

Comparative studies of Mifepristone and Misoprostol for pre-induction cervical ripening by Archana A et al and Mandade K et al, vaginal delivery rate was higher in Misoprostol group as compared to Mifepristone plus Misoprostol group in both the studies.^{29,30}

Studies done by Ramesh B et al, Kanan Y et al, Athawale R et al, Hapangama D et al to study the role of Mifepristone as a pre-induction cervical ripening agent over placebo, the rate of vaginal delivery was higher in Mifepristone group ranging from 70.8% to 96%.^{3,22,26,27} Over all, vaginal delivery rate was higher in Mifepristone group.

In the studies by Archana A et al, Sah MK et al and Gaikwad V et al, major indication for LSCS was fetal distress.^{4,23,29}

Induction delivery interval

In comparative studies conducted by Sah MK et al, Arumugaselvi B et al, and Fathima S et al compare the efficacy, safety and fetomaternal outcome of oral mifepristone and endocervical PGE2 gel, induction delivery interval was not significant with both groups but in Gaikwad V et al study, induction delivery interval was higher (29 hours) in mifepristone group as compared to (21 hours) in PGE2 gel group.^{4,23-25} In comparative studies of mifepristone and misoprostol for pre-induction cervical ripening done by Archana A et al, and Mandade K et al, induction delivery interval was shorter in mifepristone plus misoprostol group than misoprostol group in both the studies.^{29,30}

In comparative studies of mifepristone and placebo for pre-induction cervical ripening done by Ramesh B et al, Kanan Y et al, Athawale R et al and Hapangama D et al, induction to delivery interval was shorter in mifepristone group ranging from 28.6 hours to 31 hours as compared to placebo group (35.44 hours).^{3,22,23,26,27}

A randomized controlled trial was done by Baev O et al in 2017 to evaluate the efficacy and safety of mifepristone for cervical ripening and induction of labour

versus expectant management in full term pregnancy, induction-delivery interval was shorter in mifepristone group than expectant group.³¹

In above mentioned all the studies, induction delivery interval was shorter in Mifepristone group except Gaikwad V et al study in which induction delivery interval was higher.⁴ There was no significant effect of Mifepristone seen in neonatal outcome.

CONCLUSION

Based on above mentioned studies, Mifepristone is more efficient cervical ripening agent than other methods with significant improvement in Bishop's score, less requirement of additional uterotonics, shorter mean induction delivery interval, high vaginal delivery rate and good neonatal outcome. Thus, mifepristone may be considered efficient cervical ripening agent in term pregnancy.

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