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A literature review on misoprostol versus dinoprostone for induction of labor

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Article History	Abstract
Received on: 26-11-2021 Revised On : 11-12-2021 Accepted on : 19-01-2022	In recent decades, the proportion of women undergoing induction of labor has increased accordingly within countries, industrialized areas, and various hospitals. The main aim of the article is to review most of the literature in order to provide safety and efficacy to obstetrical care providers on induction of labor. Systematic reviews/meta-analyses, cohort studies, and case-controlled studies that compared safety and efficacy during labor induction. Searches were updated on a regular basis using modified bishop scores. Some of the literature was retrieved from the websites of health technology-related agencies clinical trial agencies and clinical practice guidelines. This review mainly summarizes the controversies concerning the indications, methods for induction of labor, medical uses, and contra-indications. This emphasizes the evidence of the safety and effectiveness of misoprostol when compared to dinoprostone during induction of labor.
Keywords: Induction of Labor, misoprostol, dinoprostone, normal vaginal delivery.	
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Introduction

Induction of labor is defined as the artificial initiation of uterine contractions in a pregnant woman before labor begins to achieve a vaginal birth within 24 to 48 hours. Major role of conducting labor induction is to achieve a successful vaginal delivery that is as naturally as possible [1].

Normal vaginal delivery (NVD) occurs between weeks 37 and 42 of pregnancy and its time is calculated from the first day of the last menstrual period [2].

In countries with high levels of economic development, it is used in about 1 in 5 pregnant women after the 37th week of pregnancy [3].

In more situations in which induction of labor is usually preferred over non-operative procedures [4]. Induction of labor is a common obstetric intervention, employed in broad range of conditions in which prompt delivery may be perceived to reduce the risk of maternal or neonatal morbidity and mortality [5].

A multi-centre randomized study published in 2018 indicates that induction of a low-risk pregnancy at 39th week of pregnancy may reduce the percentage of caesarean sections, hypertension-related pregnancy complications, improve patient satisfaction and through the reduction of pain without compromising neonatal outcomes [6].

In pregnancy, cervix serves mainly two major functions there are (1) maintains its firmness (i.e. physical integrity) and enlargement of uterus gradually until the time for delivery (2) cervical ripening. Presence of cervical ripening is one of the fundamental importance for a successful labor induction [7]. Cervical ripening is a procedure that is frequently used because of some

medical or obstetric complications requiring interruption of the pregnancy. When induction of labor is necessary and the cervix is unripe, the obstetrician is faced with a management experience that frequently ends in cesarean delivery. For these reasons, a great amount of research has been directed in the last few years for the development of efficient cervical ripening agents [8].

According to a recent Cochrane review, when used for IOL, PGs increase the incidence of uterine hyperstimulation with fetal heart rate (FHR) changes, but either have no effect on caesarean section rates, or may reduce them by up to 10% [9].

While Cervical ripeness is a major factor in estimating successful labor induction. Prostaglandins, specifically PGE, are known as the most effective drugs to provide adequate cervical ripening. Dinoprostone, the analogue of PGE2 which is an effective drug for cervical ripening and labor induction, is available as a gel, tablet, pessary or suppository [10].

Two commonly used cervical-ripening agents, dinoprostone (prostaglandin E2) and misoprostol (prostaglandin E1), are commercially available [12]. Post-term pregnancy is one of the most common indications for induction of labor. . One of the pre-induction methods used in patients with an unripe cervix is MVI. It is a therapeutic system applied to the posterior vaginal vault releasing misoprostol (prostaglandin E1 analogue – PGE1) at a dose of about 7 µg per hour for a period of 24 hours [11].

Indications for Induction of Labor –

- mother’s age;
- gestational age at admission;
- amniotic fluid index;
- estimated fetal weight;
- parity;
- Bishop score

Methods for Induction of Labor [13]

Pharmacologic methods: a) Intravaginal prostaglandins (PGE2 and PGF2) b) Cervical PGE2 c) Oxytocin d) Amniotomy e) Oxytocin with amniotomy f) Vaginal Misoprostol g) Oral Misoprostol h) Buccal or sublingual misoprostol

Non pharmacologic methods

Membrane Sweeping

Complementary and alternative medicine methods

Castor Oil Acupuncture Breast Stimulation

Investigational method: Mifepristone Oestrogens Corticosteroids Relaxin Hyaluronidase Isosorbide Mononitrate

Mechanical methods laminaria tents, synthetic equivalents such as Dilapan, Foley catheters, and other types of balloon catheter for induction of labor

Medical Uses for Induction of Labor [14]

- post-term pregnancy,
- pregnancy induced hypertension,
- pre-eclampsia,
- eclampsia,
- premature rupture of membranes,
- intrauterine fetal growth retardation,
- Chorioamnionitis,
- fetal death, and maternal diabetes

Contraindications for Induction of Labor

- Placenta or vasa previa
- Umbilical cord presentation
- Transverse lie or footling breech
- Prior classical or inverted T uterine incision
- Significant prior uterine surgery (e.g. full thickness myomectomy, transfundal uterine surgery)
- Active genital herpes
- Pelvic structural deformities associated with cephalopelvic disproportion
- invasive cervical carcinoma
- Previous uterine rupture
- Previous pelvic surgeries like vesicovaginal fistula/rectovaginal fistula/pelvic floor repair (third or fourth degree perineal tears repair), trachelorrhaphy.

Clinical Practice Guidelines

In 2013, Clinical practice guidelines released by The Society of Obstetricians and Gynaecologists of Canada (SOGC) are:

Intracervical Foley catheters are acceptable agents are safe both in VBAC and in the outpatient setting. Double lumen catheters considered as a second line alternative.

Neither PGE2 (cervical and vaginal) nor misoprostol should be used in VBAC because of an increased risk of uterine rupture.

Vaginal PGE2 may be considered with ruptured membranes at term and can be used in this setting. Misoprostol can be considered a safe and effective agent for labor induction in women with intact membranes, and on an inpatient basis [15].

Bishop Score

The Bishop score was developed in 1964 as a predictor of success for an elective induction. The initial scoring system used 5 determinants (dilatation, effacement, station, position, and consistency) that attributed a value of 0 to 2 or 3 points each (for a maximum score of 13).

Bishop showed that women with a score of > 9 were equally likely to deliver vaginally whether induced or allowed to labor spontaneously (16). The Bishop score remains the most commonly used system to assess for pre-induction readiness (17). The Bishop scoring system was used for cervical evaluation. It is commonly utilized to predict the induction success [18]. The score was modified in 1974 to become the 'Calder score', or modified Bishop Score (with minor changes in emphasis), and is now the most commonly used scoring method [19].

Misoprostol

Misoprostol is a synthetic 15-deoxy-16-hydroxy-16-methyl analog of PGE1 and is water soluble (20). It has been approved by the Food and Drug Administration (FDA) to be taken orally for the prevention and treatment of gastric ulcers associated with the use of non-steroidal anti-inflammatory drugs. It also became an important drug in obstetrical and gynecological practice due to its uterotonic and cervical-ripening actions. This drug may also be used to treat and even prevent postpartum hemorrhage [21]. It is also used to prevent and treat stomach ulcers, start labor, cause an abortion, and treat postpartum bleeding due to poor contraction of the uterus. Misoprostol is commonly used for labor induction. It causes uterine contractions and the ripening (effacement or thinning) of the cervix. It can be less expensive than the other commonly used ripening agent, dinoprostone. Misoprostol binds to myometrial cells to cause strong myometrial contractions leading to expulsion of tissue. This agent also causes cervical ripening with softening and dilation of the cervix. Misoprostol binds to and stimulates prostaglandin EP2 receptors, prostaglandin EP3 receptor and prostaglandin EP4 receptor but not Prostaglandin EP1 receptor and therefore is expected to have a more restricted range of physiological and potentially toxic actions than prostaglandin E2 or other analogs which activate all four prostaglandin receptors (22). Misoprostol (Cytotec, Orthotec) has been extensively investigated in the past few years for use in cervical ripening and induction of labor (23). Prostaglandins (misoprostol) may be administered in various ways (IV, oral, sublingual, vaginal or intracervical channels). It was stated that misoprostol may be beneficial in cases where competent obstetricians are not sufficiently available [24]. After many years of research into misoprostol for PPH prophylaxis, it appears that it reduces postpartum blood loss, but that it is not as effective as oxytocin. Misoprostol, 400 µg given

vaginally every 3–6 hours, is probably the optimal regimen for second-trimester abortion. More than 800 µg of misoprostol is likely to have more side effects, especially diarrhea [20]. Misoprostol Tablet: 200 micrograms is used for the management of incomplete abortion and miscarriage, and also for the prevention of postpartum hemorrhage where oxytocin is not available or cannot be safely used. Vaginal tablet: 25 micrograms, used only for induction of labor where appropriate facilities are available. A review of 45 randomized studies concluded that vaginal misoprostol (25–100 µg) was more effective than oxytocin or dinoprostone at the usual recommended doses used for induction, but was associated with increased rates of uterine hyper stimulation, both with and without associated fetal heart rate changes, as well as with meconium stained fluid.

Misoprostol has a higher rate of vaginal delivery within 12h of starting induction than with dinoprostone [25]. Misoprostol has the advantages of lower cost, no need for refrigeration, and potentially higher efficacy (26). Vaginal deliveries were more in the misoprostol group as compared to dinoprostone (27).

The use of lower doses of misoprostol may decrease the incidence of complications without diminishing the efficacy of the drug [28].

Dinoprostone

Prostaglandin E2 (PGE2) also known as dinoprostone, is a naturally occurring prostaglandin with oxytocic properties that is used as a medication. The most commonly used preparations of prostaglandin E2 are 'Prostin' vaginal gel and 'Prostin' vaginal tablets (Pharmacia UK). The gel is available in 1- and 2-mg formulations. The tablets are available in a 3-mg formulation only [29].

Dinoprostone is used in labor induction, bleeding after delivery, termination of pregnancy, and in newborn babies to keep the ductus arteriosus open. PGE2 synthesis within the body begins with the activation of arachidonic acid (AA) by the enzyme phospholipase A2. Once activated, AA is oxygenated by cyclooxygenase (COX) enzymes to form prostaglandin endoperoxides. Specifically, prostaglandin G2 (PGG2) is modified by the peroxidase moiety of the COX enzyme to produce prostaglandin H2 (PGH2) which is then converted to PGE2. Dinoprostone is a synthetic prostaglandin E2 (PGE2) analogue with smooth muscle contraction inducing property. (30). While the exact mechanism of action is unknown, prostaglandin E2 causes contractions in the myometrium via direct stimulation. It binds to G protein-coupled receptors (GPCRs) EP1-4 that lead to a

variety of downstream events depending on the EP subtype and cell-type-specific expression patterns. For example, EP receptors in the myometrium act via cell membrane calcium channels and intracellular cyclic 3'5'-adenosine monophosphate (cAMP). As some of the known receptors for prostaglandin E2 antagonize each other, researchers have hypothesized that the expression of these receptors determines the specific effects. The efficacy of prostaglandin E2 during pregnancy may link to the expression of these receptors. Prostaglandin E2 also promotes cervical dilation, effacement, and softening similar to the natural progression of pregnancy, possibly due to increased collagenase secretion [31]. Dinoprostone is available only in vaginal form; it is expensive and needs to be kept in the refrigerator. Vaginal dinoprostone is the current gold standard drug for cervical ripening during labor induction, but misoprostol is a good alternative in low resource settings [31].

Advantages of PGE2 include patient acceptance, a lower operative rate than oxytocin, and less need for oxytocin augmentation when used with an unfavourable cervix [32].

Misoprostol Verses Dinoprostone

A RCT compared the efficacy of intravaginal misoprostol (50 micrograms) to intracervical dinoprostone gel for pre-induction cervical ripening in 61 patients whose cervixes were unfavourable (Bishop score: 4). The results within 12 hours significantly favour misoprostol (56% versus 17%; $P = 0.007$). Fewer doses of misoprostol were required to achieve cervical ripening, and the interval from induction to delivery was shorter in the misoprostol group [33].

Another comparison between 50 microg vaginal misoprostol 6 hourly and 0.5 mg intracervical dinoprostone 6 hourly for cervical ripening and induction of labor evidenced vaginal misoprostol is safer and more effective, with lesser need of oxytocin augmentation and shorter induction delivery interval [34].

In the study by Buser et al, Bishop scoring was done after 4 hours in the Misoprostol group and after 6 hours in the women receiving Dinoprostone. A mean change of 3.53 and 2.7 were noted in the Misoprostol and Dinoprostone groups, respectively, showing a significantly higher change with the use of Misoprostol ($p = 0.01$) [35].

In the present study, the mean time taken from the induction to the delivery was 12.40 hours in the

Misoprostol group and 16.42 hours in the Dinoprostone group [36].

Kolderup et al saw that Misoprostol was associated with significantly fewer hours from the start of induction to delivery (19.8 hours in the Misoprostol group vs. 28.9 hours in the Dinoprostone group; $p=0.005$) [37].

In the study by Wing et al mean induction to delivery interval was 18.35 hours in the Misoprostol group and 26.53 hours in the Dinoprostone group. This interval was significantly shorter in the Misoprostol group [38].

From these studies, we can prove that the Misoprostol has better in producing cervical changes and in inducing labor. Nearly every measure of adequacy of labor induction was significantly better with misoprostol use, including time from induction to delivery, lesser requirement of oxytocin augmentation and fewer doses of the drug used. In 2011, Silfeler et al. conducted a study comparing vaginal misoprostol (25µg every 4h up to a maximum of 8 doses), controlled-release vaginal dinoprostone (10mg over 24h) and oxytocin in women with intact membranes. They observed that misoprostol was more effective than dinoprostone or oxytocin, achieving a rate of vaginal delivery of 48.5% within 12h in the misoprostol group compared to 36.1 and 13.3% in the oxytocin and dinoprostone groups, respectively. [39].

In 2014, Abraham et al. carried out a retrospective study on the induction of women with premature rupture of membranes using 25µg vaginal misoprostol every 4h up to a maximum of 6 doses vs 10mg of dinoprostone over 12h. They concluded that vaginal misoprostol is more effective than dinoprostone for induction of labor in this population, without increasing the rate of adverse outcomes. Further, they found a caesarean section rate of 20% in the dinoprostone group compared to 11% in the misoprostol group [40].

Conclusion

The proportion of women undergoing induction of labor has increased which has led to decreased rate of women from advantageous natural process of labor which is the most efficient and comfortable way comparatively to induction. Clinicians should use best possible methods for induction of labor to optimize a safe process for achieving a successful vaginal delivery. This review evident that use of prostaglandin provide an effective method for achieving the induction of labor. Finding all possible literature it is evident that misoprostol is effective and well tolerated option for

cervical ripening and labor induction when compared to dinoprostone.

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