Review article

Use of Misoprostol in Pregnancy- A Review Article

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Abstract

Prostaglandins are the pharmacological agents used for induction of labour and augmentation of labour. Prostaglandin E_2 gel is used for cervical ripening and induction of labour. These are however, costly and need to be stored in a refrigerator at a temperature of 2 - 8^oC, half life 18 months. The Tablet form of prostaglandin E_2 is not available in Bangladesh. Misoprostol, a synthetic prostaglandin (PG) E_1 analogue is used orally for the treatment of gastric and duodenal ulcer and used as a cytoprotective agent. It was first used for labour induction in 1987.

Prostaglandin can be used in several gynaecological and obstetric conditions. It can be given through several routes. This article will elaborately delinate the role of misoprostol, a prostaglandin in obstetrics and gynaecological conditions.

Introduction

History & Background:

While several natural substances such as histamine, 5-Hydroxy tryptamine & bradykinine have the capacity to stimulate the smooth muscle of the uterus, only a few agents have been sufficiently evaluated for their safe use as oxytocic agents. These Includes oxytocin, some prostaglandin's (PG) and ergot alkaloids. In several areas of Obstetrics and Gynecology, prostaglandins and their analogues have established clinical applications[1].

The first recorded biological effects of prostaglandins were by Kurzok and Lieb in 1930 when they observed the expulsion of human semen that have been introduced into the uterine cavity[2]. A few years later, the smooth muscle stimulating and blood pressure lowering activity of extracts of human seminal fluid was established independently by Gold blatt (1934, 1935) and von Euler (1934, 1935). Believing that the active principle originated in the prostate, von Euler coined the name prostaglandin[3,4,5,6]. Eliasson (1959) showed that the seminal prostaglandins originate from the seminal vesicles and from the prostate gland. However, this did not defer the term prostaglandin from being firmly established[7].

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It was the elucidation of the structure and the isolation of several prostaglandin three decades ago by Bergstrom and Sjovall (1960) that resulted in intensive research around the world in this field[8,9].

Research on the role of prostaglandin in the reproductive system (Pickles 1967, Karim 1979) and identification of specific inhibitors of PG synthesis (Vane 1971) further contributes to the understanding of the physio-pharmacology and pathological involvement of the prostaglandin in the reproductive area[10,11,12].

Pharmacology & metabolism:

Prostaglandins are a family of polyunsaturated 20-carbon fatty acids containing a cyclopentene ring and two aliphatic side chains; chemically derivatives of the prostanoic acid.

Prostaglandin is divided into groups (A, B, C, D, E, F, G, H, I) according to the differences in the structure of the five membered cyclopentene ring.

All PGs are hydroxylated in the 15 position & posses a 13, 15 trans double bond in lower side chain. The main classes are subdivided according to the degree of unsaturation of the side chains and a suffix denotes the number of double bonds (PGE_1, PGE_2, PGE_3) when stero isomerism exists, its nature is shown by addition of alpha or beta (for example $PGF_2\alpha$ or $PGF_2\beta$). The prostaglandins E_2 & $F_2\alpha$ are the oldest known member of this family. On its release from membrane phospholipids; arachinonic acid is metabolized by two types of enzymes. The enzymes cyclo-oxygenase converts it to an unstable prostaglandin endoperoxide, PGG_2. This is converted immediately to PG endoperoxide H_2. The latter is converted enzymatically (in some cases non-enzymatically) into stable substances PGE_2, $PGF_2\alpha$ and PGD_2.[1]

Sub division:

According to degree of unsaturation of the side-chains and number of double bonds these are subdivided as PGE_1, PGE_2, PGE_3, PGF_1, PGF_2 etc. PGE_2 and PGF_2 oldest & commonest involved in pathophysiology of reproduction.[1]

Function of PG in the body:

Prostaglandins have got an oxytocic effect on the pregnant

uterus. Oxytocic effect caused by a change in myometrial cell membrane permeability to calcium ion leading to alteration in cell membrane - bound calcium ion.

Smooth muscle contraction

Collagenolysis- Ripening of cervix

Side effect of natural PG:

PGE_1 and PGE_2 have similar side effect and risk profiles including uterine hyper tonicity, fetal heart rate deceleration, fetal distress, nausea, vomiting, fever, and peripartum infection.[13]

Synthetic Analogues:

During last two decades a lot of studies have been done. PGE_2 & PGE_1 analogues show high success rates and lower side effect than natural PG[1].

Contraindication of prostaglandin:

Absolute: PGE analogue should not be used in patients with a history of Asthma, glaucoma or myocardial infraction.

Relative: unexplained vaginal bleeding, chorioamnionitis, ruptured membranes or previous cesarean section are all relative contraindications the use of prostaglandins for cervical ripening[13].

Therapeutic use:

The successful first time use of natural prostaglandins for induction of labour at term (Karim 1968; Karim 1970) and for the termination of early pregnancy (Karim and Filshie 1970; Roth Brandel 1970) but the effect generalised & no selective function[14,15,16,17]. It have short lived function & unwanted gastrointestinal side effects such as nausea, vomiting & diarrhea more[1].

Misoprostol a Synthetic prostaglandin (PG) E_1 analogue, available in the market for prevention and treatment of gastric ulcers resulting form long term use of non-steriodal anti inflammatory drugs (NSAIDS) and used as a cytoprotective agents. It was first used for labour induction in 1987 in Brazil by Mariani Neto[18].

Two forms of Prostaglandin are commonly used for cervical ripening prior to induction of labour at term: Misoprostol (PGE_1analogue) and dinoprostone (PGE_2). Misoprostol is manufactured in 100µg unscored and 200µg scored tablets, which can be administered orally, vaginally and rectally[13].

It is now available in Bangladesh as Tab. Cytomis 200µg and 100µg and Tab. Isovent 200µg are commonly used as oxytocic drugs.

Misoprostol is effective for cervical ripening and labour induction at term[19,20].

Discussion

Several studies have evaluated misoprostol for use in interrupting first and second-trimester pregnancies[21-28]. Compared with other prostaglandin preparations misoprostol is equally effective, cheaper, and easier to use[21-24].

A comparative study of oral & vaginal misoprostol for induction of labor at term was done by Nawarat from October 2001 to May 2003 in the department of Obstetrics & Gynaecology & division of Obstetrics & Gynaecology, Mahido University, Bangkok, Thailand. This study includes 153 pregnant women at term and Bishop score ≤ 6 were randomly assigned to receive misoprostol either 100mg orally or 50mg vaginally every 6 hours for 48 hours. Repeated dose was given until Bishop score ≥ 8 was achieved or spontaneous rupture of membrane occurred. Those who were not in labor after 48 hours, labour induced with amniotomy and oxytocin. The main out come measure was induction to delivery time. It was stated that the median induction to vaginal delivery time in oral group (14.3 h) was not significantly different form those of the vaginal group (15.8 h). There was a significant higher incidence of uterine tachysystole in the vaginal group compared to oral group (17.1% vs 5.3, $P = 0.032$). There was no hyper stimulation in either group & no significant differences with respect to oxytocin augmentation, cesarean section rate, analgesic requirement and neonatal outcomes. This study showed that oral 100mg misoprostol has similar efficacy to intravaginal 50mg misoprostol for labor induction with less frequent abnormal uterine contractility. So 100mg of misoprostol orally can be used as an alternative to the vaginal route for labor induction[29].

Various regimens of oral & vaginal route are studied, such as 50mg every 4 hours orally and 6 hours orally 100-200mg every 3 hours, orally and 100mg vaginally followed by 100mg orally 2 hourly. All these studies show that vaginal route is more effective than oral route in terms of interval from induction to delivery. But uterine hyperstimulation and abnormal fetal heart rate pattern occurred more commonly in the vaginal route. So oral misoprostol is safer and better accepted by pregnant women[30,31,32,33].

Another comparative study was done by Saipin Pongsatha at department of Obstetrics & Gynaecology, Faculty of medicine Chiang University, Chiang Mai, Thailand to compare the efficacy & safety of 100mg oral misoprostol for induction of labor between the regimen of 3 hour and 6 hour internal administration. 100mg oral misoprostol 3 hourly is more effective than 6 hourly but there was no difference in mode of delivery, analgesic requirement, maternal complications and neonatal out come. A dose of 100mg misoprostol orally 3 hourly seems to be optimum regimen and the new option for labor induction[34].

A comparative study of oral and vaginal misoprostol for

induction of labour at term was done by Janice at Kingerten General Hospital, Ontario, Canada. Including 167 patients from July 1997 to May 1998 showed that vaginal misoprostol compared with oral misoprostol, vaginal misoprostol for induction of labour at term results in a shorter induction-to-delivery time, with fewer doses required per patient. Vaginal misoprostol may be associated with higher rates of caesarean section than oral misoprostol[35].

Misoprostol is administered orally and effective in inducing of abortion in both the 1st and 2nd trimester of pregnancy and are also used to promote the expulsion of a missed abortion[36].

A comparative study out come of 2nd trimester pregnancy terminations with misoprostol was done by Rodney and Shireen at Shands Hospital at the university of Florida form June 1996 to February 2004 on 147 women undergoing medical termination of pregnancy at 13 to 27 weeks. For low dose 200mg intravaginally 12 hourly (h=100) and high dose intravaginal 400µg every 6 hour (h 47) group respectively, median times to delivery were 22.5 VS 13.25 hours (p .001). More patients in the high dose group were delivered vaginally within 24 (81% VS 54%; P = .002) and 48 hours (98% VS 27%; P = .014). Clinical chorioamnitis was more common on high dose group (p = .03). Side effects were uncommon in both groups. One patient experience of uterine rupture & include in the analysis, this study shows that high dose (400µg every 6 hour) regimen for termination of pregnancy effects delivery more rapidly without an appreciable increase in side effects or complications[37].

Another study showed that women carrying dead fetus deliver more rapidly when undergoing medical termination of pregnancy in 2nd trimester[27,28].

A prospective study on 63 pregnant women (14-28 weeks) IUD with 400µg of oral Misoprostol with unfavorable cervix (Bishop score<4) was done by Saipin at Chang Mai university, Thailand.The success rates of temination within 12, 24, 36, 48 hours were 50.8%, 84.1%, 88.9% and 92.1% respectively mean induction to delivery time in case of delivery within 48 hours was 13.2 ± 8.4 hrs. There was no serious maternal complication and most common is chill (33.3%). So, this study showed that 400µg oral misoprostol every 4 hour is effective for pregnancy termination in case of IUD and is convenient & safe[38].

Misoprostol either by intravaginal and/or intracervical route is also highly effective for pregnancy terminatio in case of IUD[27,39].

A Study was done by Nguyen et al Showed that medical abortion (1st trimester of Pregnancy with the option of home administration of misoprostol is safe and feasible into Vietnamese healthcare system. This study should that the complete abortion rate 89.2%[40].

A Randomized Controlled study comparing oral and vaginal misoprostol for cervical priming before surgical termination of 2nd trimester of pregnancy was done by premila. Showed that cervical priming to abortion interval was significantly longer with oral misoprostol when compared with vaginal group (p<0.0001). Oral group more likely to complain nausea and vaginal group more to complain tiredness. Majority of the nursing staff (83%) admitting women preferred the Oral route of administration. So, Cervical Priming with 400µg Oral misoprostol at home is effective with high patient and staff acceptibility[41].

Some studies have suggested the vaginal route of misoprostol administration to be superior to Oral administration[42,43].

A Prospective Study was done by Shamsunnahar in 153 severe Preeclampsia & Eclampsia patients at Gyne dept of Khulna Hospital, Bangladesh Showed that Intravaginal misoprostol is well tolerated and very effective for the induction of labor in severe preeclampsia and eclampsia with unripe cervix[44].

A study to compare the safety and efficacy of conservative management of PROM at term in patients with unfavorable cervix, with active management with misoprostol was done by Aqueela Ayaz showed that oral misoprostol (50µg) is safe and effective for Cervical ripening and labor induction. In patients with PROM and an unfavorable Cervix with low rates of cesarean sections and Maternal Complications[45].

A Randomized placebo controlled trial of oral misoprostol in the 3rd Stage of labour was done by Hofmeyr at Hospital & University of Withatersrand South Africa. Showed that Oral misoprostol promise as a method of Preventing Post partum Hemorrhage. Because of the potential benefits for childbearing women, particularly those in developing Countries. No serious side effects were noted. Further research to determine its effects with greater certainty should be expedited[46].

A double blind placebo controlled randomized trial of oral misoprostol (400µg) and oxytocin 10.u. I/M in the management of the third stage of labor showed that in low risk women oral misoprostol appears to be as effective in minimizing blood loss in the third stage of labor as intramuscular oxytocin. Shivering was noted more frequently with misoprostol use, but no other side effects were noted. Misoprostol has great Potential for use in the third stage of labor especially in developing Countries[47].

Postpartum hemorrhage is an important cause of maternal mortality and morbidity. In the developing world, it is estimated to account for 28% of maternal deaths. Evidence suggests that active management of the third stage of labor using Oxytocics, significantly reduces the risk of PPH. Oxytocics are not always used in the developing world, due

to storage problems, mode of administration and associated side-effects. Research using misoprostol, a prostaglandin, suggests that it may be effective in the prevention of PPH. It is given orally, does not require refrigeration and has few side-effects further research is planned, if misoprostol is found to be acceptable alternative to other oxytocic agents, and then it may be instrumental in reducing world wide death from PPH[48].

Misoprostol has been the drug of choice for induction of labor & cervical priming in developing countries during almost a decade, because it is cheap, stable at room temperatures, does not require refrigeration prior to use, easy to prepare and the route of administration is convenient. It is used in 3rd stage of labour for the prevention of postpartum Hemorrhage. It is also a common drug for termination of early pregnancy and expulsion of missed abortion.

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