THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (January–February 2012) 62(1):47–51
DOI 10.1007/s13224-012-0156-6

ORIGINAL ARTICLE

Vaginal Misoprostol vs Vaginal Misoprostol With Estradiol for Labor Induction: A Prospective Double Blind Study

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Received: 29 April 2009 / Accepted: 15 February 2011 / Published online: 20 April 2012

Abstract
Objective To compare the safety and effectiveness of vaginal misoprostol with combined vaginal misoprostol and estradiol for induction of labor in unfavorable cervix.
Method A prospective study was carried out from Jan 2008 to Jul 2008 on total of 90 women with unfavorable cervix (Bishop's score was <5) and gestation >36 weeks with clinical indication for induction of labor. They were randomly assigned to receive either vaginal misoprostol 25 μg alone or vaginal misoprostol 25 μg with vaginal estradiol 50 μg. Misoprostol alone was repeated every 3 h in both groups till ripening of cervix (Bishop's score was = 8) and establishment of active labor.
Results Main indications were post dated pregnancies (period of gestation >41 weeks) and pregnancy induced hypertension. Age, parity and mode of delivery were not significantly different. No significant difference was found in pre induction Bishop's score, fetal outcome and maternal complications. However, doses of misoprostol required for cervical ripening ($p = 0.017$), time required for cervical ripening ($p = 0.042$), time required for starting of active labor ($p = 0.017$) and time required for delivery in vaginal delivery cases ($p = 0.047$) were found significantly less in combined estradiol and misoprostol group.
Conclusion Estradiol acts synergistically with misoprostol vaginally and significantly hastens the process of cervical ripening, initiation of active labor and vaginal delivery.

Keywords Misoprostol · Estradiol · Bishop's score · Induction · Labor

Introduction

The need to time delivery has been recognized and practiced for centuries. Cervical 'ripening' is a physiological process occurring throughout the later weeks of pregnancy and is completed with the onset of labor. When delivery is necessary and ripening has not occurred, or has failed to be initiated, this natural process has to be accelerated.

Labor induction is not without its risks for the mother and particularly for the fetus. The problems of fluid and electrolyte imbalance that sometimes accompanied prolonged syntocinon infusions in unfavorable cases are not seen now. Failed attempts at induction are more common now than 20 years ago probably because of the belief that any attempt at inducing labor should not persist beyond a

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few hours. Uterine hyperstimulation remains an infrequent but serious complication and can occur using any oxytocic agent; the consequences of this, if unrecognized, can be very serious for the fetus. The search for an induction method that changes the unfavorable to favorable cervix without stimulating uterine contractions and improves the ultimate outcome of labor without risk to the fetus remains the Holy Grail.

By the mid-1980s prostaglandins had become established as the most effective pharmacological agents for inducing labor when the cervix was unripe. The vaginal route was found to be the most acceptable, providing good efficacy and acceptability for the parturient and is now the preferred choice. During the past 15 years the introduction of misoprostol, the PGE_1 which, unlike PGE_2, is stable at room temperature and is effective if taken orally, has been the major focus of attention for labor induction. It is also considerably cheaper than the alternative prostaglandin.

With the ever-increasing concentrations of estrogen in the maternal circulation leading to term pregnancy, the belief that this could be a trigger for the onset of spontaneous labor led to studies exploring estrogens for the induction of labor. Estradiol gel given extra-amniotically, endocervically or vaginally or estradiol intramuscularly and oestriol gel extra-amniotically have been shown to produce some improved cervical favorability with minimal myometrial stimulation.

Human cervical ripening is characterized by: edema; leukocyte infiltration; dispersion of the collagen network, mainly resulting from collagen degradation by leukocyte-released matrix metalloproteinases; and an increase in total glycosaminoglycans (GAGs). The changes in the composition of the cervical connective tissue after PGE_2-induced cervical ripening are similar to those occurring in spontaneous cervical ripening [1]. Indeed, PGE_2 increases human cervical collagenolytic activity and GAG synthesis in rat cervix, induces vasodilatation of human cervical arteries and thus promotes subsequent edema and leukocyte infiltration [1]. PGE_2 transduces its signal via seven-transmembrane domain, G protein-coupled receptors, called EP receptors [2]. Ligand-binding studies have demonstrated the presence of these receptors in pregnant human cervical tissues. The EP receptor family has been further classified into four subtypes (EP_1, EP_2, EP_3 and EP_4) [2], differing in their structure, ligand-binding affinities and signal transduction pathways [2]. EP_1 and EP_3 receptors cause smooth muscle contraction, while EP_2 and EP_4 induce relaxation of smooth muscle [2].

Up-regulation of contractile EP_3 and/or down-regulation of relaxant EP_2 receptor mRNA have been reported in the myometrium of women [3] at parturition. These EP receptor labor-associated alterations suggest that EP receptor expression is hormonally regulated at the time of labor, by the changes in progesterone and estrogens associated with parturition [4].

During cervical ripening, PGE_2 is generally considered to act mainly as an inducer of stromal extra cellular matrix protein and glycoprotein alteration. PGE_2 exerts its effects on blood vessels through actions on multiple counterbalanced signaling pathways in vascular smooth muscle cells. EP_1 and EP_3 receptors induce vasoconstriction whereas EP_2 and EP_4 receptors provoke vasodilatation [5]. PGE_2 can act as an important modulator of cervical vascular tone. Any modification of the contractile/relaxant EP receptor ratio will affect the ability of PGE_2 to provoke either vasoconstriction or vasodilatation.

EP_1 and EP_3 receptor protein expression were both significantly decreased in the blood vessel media of estradiol-replaced ovariectomized ewes compared with control tissues (by 23 and 31 % respectively). Estradiol concentrations rise in ovine maternal plasma at parturition and prostaglandins mediate premature delivery induced by estradiol in pregnant sheep and goats [6]. Estradiol, by decreasing EP_1 and EP_3 receptor expression, would facilitate EP_2 and EP_4 receptor-dependent vasodilator effects of PGE_2 and thus promote cervical ripening. Even modest variation in cervical EP receptor expression might be sufficient to provoke physiological alterations in the vascular response to PGE_2. Both in vitro and in vivo studies suggest an important role for EP_4 receptor in mediating PGE_2 ripening effects. PGE_2 induces GAG synthesis by human cervical fibroblasts via EP_4 receptors [7, 8]. Therefore, the significantly decreased expression of EP_1 and EP_3 receptors in the cervical stroma after estradiol replacement might play a role by altering the balance of positive and negative influences. As a result, the activation of EP_4 receptors by PGE_2 in this tissue compartment would represent a second mechanism for estradiol to promote cervical ripening.

In addition to the changes in EP_1 and EP_3 receptor tissue distribution, estradiol alters cellular EP receptor localization, demonstrated by perinuclear localization of EP receptors in porcine cerebral microvascular endothelial cells [9], in human embryonic kidney cells [9] and in human myometrium [10].

Activation of pig peri-nuclear EP receptors by PGE_2 modulates intranuclear calcium transients and transcription of genes such as inducible nitric oxide synthase (NOS) [9] and endothelial NOS [11]. Therefore, PGE_2 might increase NO synthesis and facilitate cervical dilatation during parturition in an intracrine manner via the activation of perinuclear EP_3 receptor in the longitudinal muscle layer. Finally, estradiol-dependent expression of perinuclear EP_3 receptor might represent a novel indirect pathway for estradiol to regulate gene expression.

In conclusion, EP receptors are widely distributed within cervical tissues and predominantly expressed in blood vessels.

Estradiol replacement in the ovariectomized ewes decreased EP_1 and EP_3 receptor protein expression in the blood vessel media and decreased EP_1 receptor protein expression in the longitudinal muscle layer. These changes would favor PGE_2-induced vasodilatation, subsequent edema and leukocyte infiltration during the cervical ripening process as well as facilitating smooth muscle relaxation during cervical dilatation. Furthermore, estradiol administration results in perinuclear expression of the EP_3 receptor in the longitudinal muscle layer. This finding suggests that EP receptor locations are not only regulated by estradiol at the tissue level, but also at the cellular level, and that PGE_2 may control smooth muscle contraction and regulate ovine cervical dilatation in an intracrine manner via EP_3 receptors.

Methods

A prospective double blind study was carried out from Jan 2008 to Jul 2008 on total of 90 women with unfavorable cervix and gestation >36 weeks with clinical indication for induction of labor. They were randomly assigned to receive either vaginal misoprostol 25 μg alone or vaginal misoprostol 25 μg with vaginal estradiol 50 μg. Misoprostol alone was repeated every 3 h in both groups till establishment of active labor. The repeat doses and evaluation was done by the staff. Neither the women nor the staff knew whether the woman under observation was assigned to only misoprostol or misoprostol with estradiol group.

Cervical evaluation was done using Bishop's score. A score <5 was taken as unfavorable and cervix was termed as ripe when Bishop's score was = 8. End point of the study was ripening of cervix or initiation of active labor though evaluation continued till delivery to record the duration of induction delivery interval, mode of delivery, any labor complication and fetal outcome.

Inclusion criteria were >36 weeks gestation, singleton pregnancy with vertex presentation, no contraindication to vaginal delivery, no indication of urgent delivery e.g. fetal distress etc. Statistical analysis was done using student *t* test and χ^2 test comparing doses of misoprostol required, induction to active labor interval, induction delivery interval, mode of delivery, labor complications and fetal outcome in two groups.

Results

A total of 90 women were enrolled in the study. 45 women were assigned to vaginal misoprostol and 45 to vaginal misoprostol with estradiol.

Table 1 shows indications and their distribution in both study groups. No significant difference was found between two groups on statistical analysis. Main indications were post dated pregnancies (period of gestation >41 weeks) and pregnancy induced hypertension.

Table 1 Indications for inductions

Indication	Misoprostol ($n = 45$)	Misoprostol + estradiol ($n = 45$)	p value (Fisher exact test)
Postdatism	11	20	0.075
PROM	2	2	1.000
PIH	25	16	0.090
Oligohydramnios	3	2	1.000
IUGR	4	5	1.000

Table 2 Parity and mode of delivery in the vaginal misoprostol and misoprostol + estradiol groups

	Misoprostol ($n = 45$)	Misoprostol + estradiol ($n = 45$)	p value (Fisher exact test)
Age	21.67 ± 1.15	22.33 ± 2.58	0.121$
Parity	0.89 ± 0.87	0.67 ± 0.78	0.210$
Nullipara	35	27	
Parity ≥1	10	18	
Mode of delivery			
Spontaneous vaginal	32	33	1.000
Vacuum/forceps	3	5	0.714
Caesarean	10	7	0.591

$ unpaired *t* test

Table 2 displays parity and mode of delivery among both groups. Age and parity were not significantly different. No significant difference between groups was found in mode of delivery also. The cesarean delivery rate for both (22.2 vs 15.5 %) was consistent with the institutional rate of 19 %.

Table 3 shows fetal outcome, doses of misoprostol required, induction—cervical ripening interval, induction—active labor interval, induction—delivery interval and post partum complications. No significant difference was found in pre induction Bishop's score, fetal outcome and maternal complications. However, doses of misoprostol required for cervical ripening ($p = 0.017$), time required for cervical ripening ($p = 0.042$), time required for starting of active labor ($p = 0.017$) and time required for delivery in vaginal delivery cases ($p = 0.047$) were found significantly less in combined estradiol and misoprostol group.

Discussion

Around 20 % of all deliveries are preceded by labor induction. Prolonged pregnancy and maternal hypertensive

Table 3 Outcome of labour in the vaginal misoprostol and misoprostol + esradiol groups

	Misoprostol ($n = 45$)	Misoprostol + estradiol ($n = 45$)	p value (Fisher exact test)
Pre induction bishop score	3.55 ± 2.18	2.83 ± 2.08	0.113$
No of doses till cervical ripening[a]	4.67 ± 1.53	3.73 ± 2.11	0.017**$
Induction initiation to cervical ripening[a]	12.67 ± 3.21	10.57 ± 6.03	0.042**$
Induction initiation to active labor[b]	15.33 ± 3.76	12.97 ± 5.27	0.017**$
Induction initiation to delivery[c]	18.25 ± 6.13	15.66 ± 6.09	0.047**$
Fetal distress[d]	9	8	1.000
Apgar <5 at 1 min	5	6	1.000
Apgar <7 at 5 min	3	4	1.000
Birth weight (kg)	2.67 ± 0.38	2.83 ± 0.95	0.297$
Meconium staining	7	6	1.000
Neonatal infections	7	5	0.758
NICU admissions	8	7	1.000
Post partum maternal complication	8	9	1.000

** significant

$ unpaired t test

[a] Bishop score = 8

[b] Cervix dilatation = 3 cm with uterine contractions = 3 per 10 min, duration = 30 s

[c] Excludes cesarean cases

[d] Bradycardia, late deceleration or severe variable deceleration

disorders being the major indications for the last 50–60 years. The 'other' indications are ante partum hemorrhage, diabetes mellitus, red-cell alloimmunisation, demonstrable placental failure and previous unexplained still birth at term etc. In our study also, prolonged pregnancy and maternal hypertensive disorders accounted for 34.44 % (31/90) and 45.56 % (41/90) cases respectively.

The recent analysis by Kirby et al. [12] data on induction of labor in the United States from 1990 to 2002 found the increase in inductions from around 5–10 % in 1990 to around 17–21 % in 2002. During the early part of this period, the national rate for caesarean section in the United States was relatively static at around 21–22 %, followed by a sudden increase to 26 % in 2002. In our study, 18.89 % (17/90) women underwent cesarean.

Till date, no study has compared misoprostol effect with combined effect of misoprostol and estradiol, though some studies have compared estradiol alone with misoprostol [13].

Various studies have found induction delivery interval with vaginal misoprostol 16–20 h, which is in agreement with our study (18.25 ± 6.13 h) [13–15]. On an average, 4–5 doses of misoprostol were required in our study for cervical ripening or initiation of active labor which is similar to other studies, however dose required in combined group was significantly less ($p = 0.017$).

In our study, in misoprostol group, induction initiation to cervical ripening interval, induction initiation to active labor initiation and induction initiation to delivery were 12.67 ± 3.21, 15.33 ± 3.76 and 18.25 ± 6.13 h, respectively. Other studies have also shown intervals of similar duration [13–15]. Some studies have shown effect on cesarean section rate with misoprostol; however this was not seen in this study.

There were no significant adverse effects seen with use of vaginal 25 μg misoprostol on either fetus or mother in both protocols. There was no incidence of uterine hyper stimulation in both study groups.

Though it is a small study it has shown significant differences in, induction initiation to cervical ripening interval, induction initiation to active labor initiation and induction initiation to delivery [Induction to cervical ripening ($p = 0.017$), time required for cervical ripening ($p = 0.042$), time required for starting of active labor ($p = 0.017$) and time required for delivery in vaginal delivery cases ($p = 0.047$)]. Further studies are required to validate our findings.

Conclusion

Estradiol acts synergistically with misoprostol vaginally and significantly hastens the process of cervical ripening, initiation of active labor and vaginal delivery.

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