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ORIGINAL RESEARCH

Unintentional uterine hyperactivity and perinatal outcomes following labor induction with intravaginal administration of sustained-release dinoprostone insert

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ABSTRACT

Objective: To evaluate the perinatal outcomes of pregnant women who underwent labor induction with intravaginal administration of controlled-release dinoprostone who involuntarily progressed to uterine hyperstimulation. **Methods:** In a retrospective cohort study design, the perinatal outcomes of 388 pregnant women who received intravaginal administration of controlled-release dinoprostone for cervix ripening at a community hospital were analyzed. Uterine hyperactivity was considered as present if the cardio-tocogram registered more than 5 uterine contractions within 10 minutes at any time post-induction. Women were grouped according to the presence or absence of uterine hyperactivity. **Results:** 26.3% (n= 102) developed uterine hyperactivity and 73.7% (n= 286) did not. In the former group, the incidence of vaginal deliveries within 12 hours post-induction and cesarean sections was marginally higher than among women who did not progress to uterine hyperactivity. However, the indications of cesarean sections were not different between both groups. The incidence of postpartum hemorrhage and of babies admitted to the neonatal intensive care unit was similar between groups (P >0.05). **Conclusions:** Uterine hyperactivity induced by intravaginal administration of controlled-release dinoprostone may increase the rate of cesarean sections without increasing the frequency of neonatal adverse outcomes.

Key words

Cervical ripening; Labor induction; Uterine hyperactivity

RÉSUMÉ

Objectif: Évaluation des effets périnataux de l'administration intra-vaginale de dinoprostone à libération contrôlée pour l'induction du travail ayant par ailleurs entraîné une hyperstimulation utérine. **Méthodes:** Cette étude rétrospective a été effectuée sur 388 femmes ayant reçu une administration intra-vaginale de dinoprostone à libération contrôlée pour accélérer la maturation du col utérin au cours du troisième trimestre de la grossesse dans un hôpital de ville. Une hyperstimulation utérine a été considérée présente lorsque la cardiotocographie avait enregistré plus de 5 contractions utérines par 10 minutes à tout moment après l'induction du travail. Les femmes ont été groupées d'après la survenue ou non d'une hyperstimulation utérine. **Résultats:** 26,3% (n= 102) des femmes ont présenté une hyperstimulation utérine et

73,7% (n= 286) n'en ont pas présenté. Dans le premier groupe l'incidence des naissances par voie vaginales durant les premières 12 heures après l'induction du travail et des césariennes était marginalement plus élevée que dans le groupe qui n'avait pas présenté d'hyperstimulation utérine. Les indications des césariennes n'étaient cependant pas différentes entre les deux groupes. L'incidence des hémorragies du postpartum et des nouveau-nés adressés à l'unité de soins intensifs néonataux était similaire (P >0,05). **Conclusions:** Une hyperstimulation utérine faisant suite à l'administration intra-vaginale de dinoprostone à libération contrôlée est susceptible d'augmenter la fréquence des césariennes sans par ailleurs accroître l'incidence des effets défavorables chez les nouveau-nés.

Mots clés

Maturation du col utérin; Induction du travail; Hyperstimulation utérin

RESUMEN

Objetivo: Evaluar los resultados perinatales de las mujeres embarazadas que recibieron dinoprostona de liberación controlada para inducción del parto y que involuntariamente progresaron a hiperestimulación uterina. **Métodos:** En una cohorte retrospectiva, el estudio analizó los resultados perinatales de 388 mujeres embarazadas que recibieron dinorpostona de liberación controlada por vía intravaginal para inducir la apertura del cérvix, en un hospital comunitario. Se consideró la presencia de hiperactividad uterina si el cardio-tocograma mostraba, en cualquier momento posterior a la inducción del parto, más de 5 contracciones uterinas en 10 minutos. El análisis de los resultados consideró dos grupos de mujeres: las que tuvieron hiperestimulación uterina y los de las que no la presentaron. **Resultados:** 26.3% (n= 102) desarrollaron hiperactividad uterina y 73.7% (n= 286) no la presentaron. En el primer grupo, la incidencia de partos vaginales dentro de las primeras 12 horas post-inducción así como de cesáreas debido a intolerancia fetal incrementaron marginalmente en comparación al segundo grupo. Sin embargo, las indicaciones de cesárea fueron similares. La incidencia de hemorragia postparto y la frecuencia de bebés que requirieron cuidados intensivos también fueron semejantes (P >0.05). **Conclusiones:** La hiperactividad uterina secundaria a la administración de dinoprostona de liberación controlada puede incrementar el número de cesáreas sin incrementar la frecuencia de efectos neonatales adversos.

Palabras clave

Apertura cervical; Inducción del parto; Hiperestimulación uterina

INTRODUCTION

Intravaginal administration of prostaglandin E2 (PGE2) is a standard method of labor induction, and different formulations containing PGE2 have been developed [1]. Dinoprostone administered as a controlled-release formulation of 5 mg is released over a period of 12 hours at a slow and constant rate [2]. Uterine hyperactivity, however, may appear after the vaginal administration of dinoprostone, potentially increasing the rate of adverse perinatal outcomes. Slow-release dinoprostone has been in Korea for several years and has been administered to a large number of women even in non-specialized centers. However, the incidence of adverse maternal and fetal outcomes is yet unknown. We therefore designed the present study in order to estimate the incidence of adverse perinatal outcomes in women who underwent labor induction with dinoprostone.

METHODS

Patients

With previous approval by the Institutional Research Board, the study was performed at a community hospital, Cheil Hospital & Women's Healthcare Center, Seoul, Korea. In a retrospective cohort study design, the clinical records of women who delivered over a period of 1 year were reviewed.

Selection criteria

The inclusion and exclusion criteria were similar to those previously reported elsewhere [3]: patients admitted to the labor room for dinoprostone induction with a singleton, cephalic fetus of at least 36 weeks gestation with an initial Bishop score less than 6. The files of 388 women who were physically examined on admission to the labor room and underwent continuous fetal monitoring by cardiotocography until delivery contained sufficient information satisfying the inclusion criteria. There were no cases of women induced with dinoprotone who had a greater than 2 cm cervix dilation, a history of prior cesarean delivery or hysterotomy, ruptured membranes, intrauterine growth restriction, known fetal anomalies, evidence of chorioamnioitis, placenta previa, suspected abruption, or a non-reassuring fetal heart pattern. Therefore, no cases were excluded from the study.

Procedures

Slow-release dinoprostone was only intravaginally administered if there was a cervical dilatation up to 2 cm, the baby was in cephalic position and vertex was well applied to the cervix, and a stable fetal hear and regular fetal movements registered respectively by means of a tocograph and

abdominal palpation were ascertained for at least 30 minutes before drug administration. The vaginal insert of dinoprostone released the drug at a rate of 0.3 mg h^{-1} over a period of 12 hours and could be retrieved at any time. Uterine hyperactivity was diagnosed when there was a tachysystole (more than five contractions per ten minute period) [4]. If uterine hyperactivity occurred, the slow-release tablet was removed within the next 30 minutes. A similar action was performed if regular uterine contractions, membrane rupture, fetal tachysystole, maternal systemic adverse effects or no reassuring fetal heart rate pattern was developed during labor induction. All cases of uterine hyperactivity were included in the data analysis of pregnancy outcomes, regardless of whether the slow-release tablet of dinoprostone was removed. In some cases, oxytocin was co-administered for labor augmentation after 1 hour of removal of the vaginal slow-release tablet of dinoprostone. However, if labor was not successfully induced or the cervix was still unfavorable after the first day of a single administration of dinoprostone alone or in combination with oxytocin, women underwent either a new course of induction with dinoprostone or cesarean section, as judged by the treating obstetrician.

Statistical analysis

Maternal age, gestational age, and fetal weigh were compared between groups by a Student t test, the number of previous pregnancies by a Mann-Whitney test, and categorical variables (number of NICU admission and of cases receiving blood volume replacement) by means of either a Chi-square test or the Fisher's exact test. The statistical analyses were performed by means of SPSS v. 10.0.7 (SPSS Inc., Chicago, ILL, USA), and the significant level was set at a two-tailed $P < 0.05$.

RESULTS

Labor induction with intravaginal administration of slow-release tablets of dinoprostone was mainly indicated in women with oligohydramnios followed by women with a prolonged pregnancy (Table 1). The maximum number of doses of dinoprostone given to the women in the study was three. Of 388 women, 261 (67.3%) delivered vaginally. There were 26.3% (102/388) of women who developed uterine hyperactivity. Of them, 61 delivered vaginally within the next 12 hours of starting labor induction and 41 underwent cesarean delivery. Within 30 minutes after detection of uterine tachysystole, the insert was removed and most of tachysystole subsided to normal or no activity except in 2/102. The incidence of vaginal deliveries within 12 hours post-induction and cesarean sections was marginally higher In the group with uterine hyperactivity ($P = 0.06$). However, the indications of cesarean section did not differ between both groups. In addition, the incidence of postpartum hemorrhage and of babies admitted to the neonatal intensive care unit was similar between groups ($P > 0.05$) (Table 2).

Table 1 Obstetric characteristics of women who used controlled-release PGE2 vaginal insert for pregnancy induction

	Uterine hyperactivity		
	Positive (n= 102)	Negative (n= 286)	P value
Maternal age (mean ± SD)	31.0 ± 3.3	30.6 ± 3.1	0.33
Gravida [median (ranges)]	1 (1-4)	1 (1-5)	0.23
Gestational age (mean ± SD)	39.8 ± 1.2	40.0 ± 1.1	0.14
Indication of labor induction: [n (%)]			
Oligohydrmanios*	46 (55.1)	116 (40.6)	0.43
Prolonged pregnancy**	34 (33.3)	115 (40.2)	0.22
Others***	22 (21.6)	55 (19.2)	0.61
Fetal weight (g) (mean ± SD)	3,330 ± 512	3,340 ± 451	0.83

*Amniotic fluid index <5 cm; **Gestational age ≥ 41 weeks; ***Maternal hypertension, intrauterine growth retardation, large for gestational age, or polyhydroamnios.

Table 2 Perinatal outcomes according to uterine hyperactivity

	Uterine hyperactivity		
	Positive (n= 102)	Negative (n= 286)	P value
Vaginal delivery ≤12 h post-treatment	25 (41.0)	57 (29.5)	0.06
Cesarean sections	41 (40.2)	86 (30.1)	0.06
Labor failing to progress	30 (73.2)	73 (84.9)	0.54
Fetal distress	11 (26.8)	13 (15.1)	0.10
NICU admissions	1 (1.0)	12 (4.2)	0.19
Patients who required blood transfusion or colloid infusion	2 (2.0)	2 (0.7)	0.28

NICU: neonatal intensive care unit. Data are n (%)

DISCUSSION

Prostaglandin E2 is used on a large scale for cervical ripening and labor induction. However, its administration has been associated with an increased rate of adverse maternal and fetal events [5] [6]. The administration of PGE2 may result in uterine hyperactivity and insufficient uteroplacental oxygenation, resulting in fetal distress [7]. In addition, prostaglandins cross the placenta and may stimulate the fetal ileum, favoring the passage of meconium [8]. In the present study, one fourth of the women who underwent uterine stimulation with dinoprostone had uterine hyperactivity. However, we did not observe any increased risk of adverse maternal or fetal events.

Sustained-release preparations are designed to produce relatively slow and uniform absorption of the drug for 8 hours or longer. The advantage of such preparations are seen in the reduction in frequency of dose administration, maintenance of therapeutic effect overtime, and a decreased incidence or intensity of undesired effects by elimination of high peaks in drug concentration (C_{max}) that often occur after administration of immediate-release dosage forms [9].

Lower C_{max} and longer times to reach it are observed in the vaginal insert of sustained-release dinoprostone in comparison with the regular formulation of immediate release [2] [10]. The estimated plasma half-life of PGE2 is very short, less than 15 seconds [11]. These characteristics are expected to induce cervical ripening with a lower rate of adverse effects. In our study, the high incidence of uterine hyperactivity was not associated with an increased incidence of adverse maternal and fetal outcomes. This was most likely due to the fact that the insert was removed at an appropriate time which limited the extent of uterine hyperstimulation.

In experimental animal models, the uteroplacental hypoxia secondary to induced uterine hyperactivity is one of the most common causes of late deceleration and other adverse fetal outcomes [12] [13]. The risks of uterine hyperstimulation and systemic adverse effects are known to be related to the dose and plasma concentration of PG [11] [14]. Furthermore, increasing uterine activity with an unripe cervix or labor induction with poor preparation of labor is known to increase the incidence of cesarean deliveries especially in nulliparas [15] [16].

In our study we used a stringent definition of uterine hyperstimulation and included frequent mild contractions irrespective of pain. That may partially explain the higher number of cases with uterine hyperactivity observed in our study in comparison to the approximately 18% reported in previous studies using a similar PGE2 vaginal insert [17]. In relation to pregnancy outcomes, although the difference between groups was not statistically significant, there was a higher rate of cesarean sections among women who progresses to uterine hyperactivity in comparison to those who did not. This difference was probably secondary to

the higher rate of cases of fetal distress in the former group. Interestingly, the proportion of babies referred to the NICU was low in spite of the elevated number of fetuses with non-reassuring heart rates. It is possible that uterine hyperactivity or fetal distress were overestimated, resulting in some cases of unnecessary cesarean sections.

There were several limitations that deserve to be mentioned. The criteria of digital examination for judging cervical ripening probably exhibited large variations due to the shifts of staff and residents in the labor ward during the study period. The protocol of labor induction was not consistent in terms of dosage of dinoprostone. We were unable to objectively judge the decision in taking a patient for cesarean section since it was determined by the attending physician during or after the first attempt for uterine stimulation. However, despite such limitations, our results were consistent to other reports stating that slow-release dinoprostone has been associated with a low rate of adverse prenatal outcomes.

In conclusion, our study suggests that intravaginal administration of a slow-release tablet of dinoprostone is associated with a high incidence of uterine hyperactivity that can be easily reverted by extracting the vaginal insert. No increased risk of adverse perinatal maternal and fetal outcomes was observed.

AUTHORS' PARTICIPATION

JY H conceived the idea of the study, JY H & SI C designed the study, H P retrieved the information, JS C analyzed data; all the authors participated in the discussing the findings and drafting the manuscript.

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None to declare.

CONFLICT OF INTERESTS/DISCLAIMERS

JY H, EY V-A, & AA N-O are members of the Editorial Board of the journal.

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