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ORIGINAL ARTICLE

Oral versus vaginal prostaglandin for labor induction

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Abstract

Objective: To compare the efficacy and safety of oral prostaglandin (PG) in solution versus vaginal PG gel for labor induction.
Design: A retrospective study.
Methods: Data from original obstetric records at a university hospital in Sweden 2012–2013.
Results: In all women, oral PG resulted in vaginal birth (VB) < 24 h in 66% compared to 80% with vaginal PG ($p < 0.001$), and cesarean section (CS) in 19% versus 32% ($p = 0.02$). In primiparous women, oral PG was followed by VB <24 h in 54% compared to 71% ($p = 0.01$), and CS in 25% versus 41% ($p = 0.03$). In women with an unripe cervix, oral PG lead to VB <24 h in 66% compared to 79% ($p = 0.01$), and CS in 21% versus 33% ($p = 0.04$). Despite a longer induction to vaginal delivery interval with oral PG, the rates of obstetric bleeding, chorioamnionitis, and neonatal asphyxia were not increased.
Conclusions: Oral PG in solution was less effective than vaginal PG gel in achieving VB <24 h. However, oral PG was safer, since it resulted in fewer CSs without increasing maternal morbidity or neonatal asphyxia.

Keywords

Cesarean section, dinoprostone, misoprostol, vaginal birth

History

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Introduction

Prostaglandins (PGs) are the key mediators of cervical ripening, acting via membrane bound G-coupled receptors. PGs alter the progesterone receptor isoform A and B expressions, leading to a functional progesterone withdrawal, promote leukocyte extravasation and collagenase enzyme activity. These biochemical events result in a changed proteoglycan composition and dispersed collagen fibrils, allowing for cervical effacement and dilatation [1–3]. Vaginal PG gel has been used for labor induction since the 1980s. Oral PG was avoided because of presumed less efficacy and gastrointestinal side effects and was not used for labor induction until the 1990s [4,5].

Induction of labor has become more frequent over the latest decades [4,5]. It has increased in Sweden from 7% of all childbirths in 1992 to 16% in 2012–2013 [6]. Induced labor involves increased risks for prolonged labor and cesarean section (CS), particularly in primiparous women and women with an unripe cervix [7]. Among these women, preinduction cervical ripening is important for a successful vaginal birth (VB). The rising CS rates worldwide coincide with increasing reports on maternal complications such as life-threatening obstetric bleeding and peripartal hysterectomy, as well as neonatal and infant complications such as breathing disturbances and altered intestinal microbiota [7–9]. Most CSs are carried out in women with a previous CS. Therefore, if a woman achieves a non-operative first delivery, she has a greater probability to avoid a later CS [7].

The objective of this study was to compare the efficacy and safety of oral PG in solution versus vaginal PG gel for labor induction. Our hypothesis was that oral PG would be safer and at least as effective as vaginal PG. To our knowledge, there are no previous reports on labor induction comparing these methods in primiparous women and women with an unripe cervix [4].

Methods

The study was approved by the Ethics Board for Medical Sciences in Stockholm on 9 April 2015, Dnr 2014/255–31. It was initiated as a quality control project. The World Health Organization (WHO) International Classification of Diseases (ICD)-10 and the obstetric records of all women who had labor induced with PG at the Department of Women's and Children's Health, Karolinska University Hospital, Solna, Sweden in 2012–2013 were examined. Inclusion criterion was gestational age $\geq 34 + 0$ weeks. Between 1 January 2012 and 31 December 2013, there were 7868 deliveries in the unit. Labor was induced in 1658 women (21%). Of these, 542 women (33%) had labor induced with PGs. Women ($n = 25$) suffering from intrauterine fetal death were excluded from the calculations. Vaginal PG gel was the only available PG

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method in 2012. A total of 252 women had labor induced with this method, 207 women in 2012 and 45 in 2013, due to the individual physician's choice. Endogenous PGE gel dinoprostone (Minprostin®, Pfizer, CD Pharma, SE-191 90 Sollentuna, Sweden) 2 mg was inserted in the posterior vaginal fornix every 6–8 h up to a maximum of three doses. The fetal heart activity was monitored with cardiotocography (CTG) 20 min before and after each dose and at labor onset. Oral PG in solution was introduced for labor induction in 2013, and 265 women had labor induced with this method. Oral PG treatment was carried out using the smallest available synthetic, esterified PGE analog misoprostol tablet (Cytotec®, Pfizer) 200 μg dissolved in 20 mL of water resulting in a concentration of 10 μg/mL. An adequate concentration of misoprostol was obtained according to laboratory investigations by the Swedish Medical Products Agency [10]. A solution of 2.5 mL containing 25 μg misoprostol was aspirated in a 3-mL syringe, whereupon the woman sprayed the solution in her mouth. Then, water was aspirated and swallowed. Treatment with a new solution 25 μg was continued every 2 h until labor onset up to a maximum of eight doses. The fetal heart activity was monitored with CTG 20 min before each dose and at labor onset. If uterine contractions were monitored, the following dose was postponed for 2 h, given that active labor had not started. Vaginal misoprostol was not chosen as a method for labor induction because of reports on uterine hyperstimulation with this method.

Amniotomy was performed when a ripe cervix with a Bishop score (BS) > 5 points was achieved. Alternatively, a transcervical catheter was inserted and amniotomy performed after expulsion of the catheter. Oxytocin (Syntocinon®, CD Pharma, Sweden) infusion 5 U/500 mL saline was administered for augmentation of labor, if no progress within 1 h following ruptured fetal membranes.

Post-term pregnancy was gestational age $\geq 42+0$ weeks according to ultrasound dating in the second trimester [11]. Prelabor rupture of the fetal membranes was diagnosed visually and labor was induced after 36–48 h. The hypertensive disease group included women with essential hypertension, gestational hypertension and pre-eclampsia. The group imminent fetal distress included oligohydramniosis and reduced fetal movements, intrauterine growth restriction, decidual bleeding or Rhesus immunization. Psychosocial indications were fear of childbirth and pregnancy ailments. Maternal illness included thrombophilia, malignancy, heart disease and other systemic diseases. Other fetal indications were for example labor induction after external version of breech presentation, anomalies and cardiac arrhythmia. Women with gestational diabetes or diabetes mellitus had labor induced at 38–40 weeks. Primiparous women ≥40 years after *in vitro* fertilization (IVF) were planned for induction at 41 weeks. A prolonged latency phase was cervical dilatation ≤3 cm, despite uterine contractions for 18 h or more. Dichorionic twin pregnancies with symmetric fetal growth were induced at 38 weeks and monochorionic with the same criteria at 37 weeks. Cervical ripeness was categorized according to a simplified Bishop score model, monitoring dilatation, effacement, consistency and position, and a BS ≤ 5 was the criterion for an unripe cervix [12]. Hyperstimulation was defined as >5 contractions every 10 min during 20 min as monitored by CTG. An Apgar score <7 at 5 min was the criterion for neonatal asphyxia since Apgar scores, but not umbilical blood gas values, were registered for all newborns [13].

The primary outcomes were VB <24 h and the CS rate. Secondary outcomes were the induction to vaginal delivery interval, the proportions of obstetric bleeding, chorioamnionitis, uterine hyperstimulation, uterine rupture and neonatal asphyxia.

Continuous data were analyzed with one-way analysis of variance. Assumptions for parametric statistics were tested by Levene's test. Categorical data were analyzed with non-parametric Mann–Whitney test. Statistical significance was set at $p < 0.05$. According to previous data, we assumed that at least 40% in the oral PG group and 60% in the vaginal PG group would achieve VB <24 h (4). Aiming at a significance level of 5% and 90% power, 125 study participants should be observed in each group. We assumed that the CS rate would be 20% in the oral PG group and 30% in the vaginal PG group [4,5]. Aiming at a significance level of 5% and 90% power, 194 participants should be observed in each group. All data were entered into the computer program Statistica, version AX, StatSoft, Inc., Tulsa, OK (2014).

Results

Indications for labor induction are shown in Table 1. The indications and the criteria for prolonged labor were comparable in the years studied. Prolonged labor was lack of progress for 3–4 h during the first stage of labor and for 2–3 h during the second stage. Demographic data are shown in Table 2. The group BS ≤ 5 included primiparous and multiparous women. In the oral PG group with BS ≤ 5, 146 women (61.3%) were primiparous, 85 (35.7%) parous and 7 (2.9%) had a previous CS. In the vaginal PG group with BS ≤ 5, 151 women (61.9%) were primiparous, 68 (27.9%) parous and 25 (10.2%) had a previous CS. Maternal and neonatal outcomes are shown in Table 3. Most CSs, more than 70% with both methods, were carried out because of prolonged labor. The second indication was imminent fetal distress defined as a pathologic CTG or fetal scalp lactate >4.8 mmol/L. The main indication for an instrumental delivery with both methods was a prolonged second stage of labor.

Table 1. Indications for labor induction.

Variable	Oral PG $n = 265$ (%)	Vaginal PG $n = 252$ (%)
Post-term pregnancy	64 (24)	57 (23)
Prelabor rupture of fetal membranes	41 (15)	35 (14)
Hypertensive disease	36 (14)	31 (12)
Imminent fetal distress	36 (14)	31 (12)
Psychosocial indication	24 (9)	20 (8)
Maternal illness	22 (8)	26 (10)
Other fetal indications	17 (6)	16 (6)
Diabetes	10 (4)	12 (5)
Primiparous women ≥40 years after IVF	7 (3)	14 (6)
Latency phase prolonged	6 (2)	5 (2)
Duplex pregnancy	2 (1)	5 (2)

Differences all variables (NS).

Four out of eight women in the oral PG group who were treated for chorioamnionitis had labor induced because of prelabor rupture of the fetal membranes. One out of four women in the vaginal PG group who were treated for chorioamnionitis had labor induced because of prelabor rupture of the fetal membranes. There was no episode of uterine hyperstimulation with oral PG, whereas one CS in the vaginal PG group was carried out due to uterine hyperstimulation with fetal bradycardia. The induction to vaginal delivery intervals are shown in Table 4.

Discussion

The main findings were that oral PG in solution was less effective than vaginal PG gel in achieving VB <24 h. However, oral PG was safer, since it resulted in fewer CS compared with vaginal PG. The rates of VB <24 h were higher than was assumed with both methods in all women, women with an unripe cervix and primiparous women, and the differences between the methods smaller than was expected. The CS rates were in accordance with our assumptions in all women and women with an unripe cervix, but higher than expected with both methods in primiparous women, particularly with vaginal PG. The overall CS rate in 2012–2013 was 22% and the general CS rate after labor induction was 30%. Thus, oral PG resulted in a lower CS rate in all groups, and vaginal PG in a higher, than was generally observed at labor induction.

The clinical outcomes with the treatments depend on the dose regimen, the route of administration and the vehicle. Oral misoprostol in solution is followed by a peak plasma concentration after 30 min, declining significantly within 120 min [14]. Thus, the oral PG treatment was a continuous low dose regimen. Vaginal dinoprostone gel leads to a peak plasma concentration after 30–45 min according to the manufacturer, and the vaginal PG treatment was therefore an intermittent high dose regimen. Despite the difficulty to measure plasma levels of endogenous PG because of the rapid metabolism of the hormone, endocrine and paracrine actions proceed in the cervix and uterus after vaginal application [1–3]. The higher instrumental delivery rate with oral PG could be explained by the longer induction to delivery interval, since most instrumental deliveries were carried out because of a prolonged second stage of labor. The proportions of obstetric bleeding >1000 mL at vaginal delivery in the study groups were comparable to the total incidence in the obstetric unit, being 6.7% in 2012–2013. The rates of chorioamnionitis in the study groups did not differ from the overall incidence, being 1.3% in the years studied. The proportions of newborns with an Apgar score <7 at 5 min were similar to the total incidence at a gestational age ≥34 + 0 weeks, which was 1.0% in the years studied. In average, five doses of oral PG and one dose of vaginal PG, respectively, were used. The cost for five fresh oral PG doses was €9.2, which was less than 5% of the cost for one dose of vaginal PG gel.

Our results were partly in accordance with a multicenter randomized study on labor induction in 3592 deliveries, where oral PG in solution mostly 20 μg every 2 h is compared with vaginal PG gel. The rates of VB <24 h are similar, whereas the CS rate 21% with oral PG is lower than the 26% with vaginal PG (RR 0.88 and CI 0.78–0.99). The reviewers do not report any subgroup analyses for primiparous women or women with an unripe cervix. Only one study includes women with ruptured fetal membranes, where the rates of VB <24 h are similar, whereas the CS rate 16% with oral PG is slightly lower compared to 20% with vaginal PG (RR 0.80 and CI 0.58–1.11) [15]. Our findings were in agreement with a recent systematic review and network meta-analysis on labor induction with PGs. The authors conclude that oral misoprostol in solution has the best safety profile and note that this method is not recommended by the WHO, whereas oral 25 μg tablets every 2 h are, despite the worst overall ranking in their network meta-analysis [4].

Limitations in this study were the retrospective character and the lack of information about umbilical cord blood gas values [16]. Strengths were the high number of observations and that all data were collected from original medical records.

Table 2. Demographic data.

Variable	Oral PG $n = 265$	Vaginal PG $n = 252$
Age (median and range)	32 (18–46)	32 (18–47)
Primiparous (%)	164 (61.9)	157 (62.3)
Previous cesarean section (%)	8 (3.0)	25 (9.9)
Gestational age (median and range)	39 (34–42)	39 (34–42)
Gestational age <37 + 0 weeks (%)	13 (4.9)	9 (3.6)

Differences all variables (NS).

Table 3. Maternal and neonatal outcomes.

Variable	Oral PG	Vaginal PG	*p* values
All women	$n = 265$ (%)	$n = 252$ (%)	
Vaginal birth	214 (80.8)	171 (67.9)	NS
Vaginal birth <24 h	141 (65.9)	136 (79.5)	$p < 0.001$
Instrumental delivery	48 (18.1)	30 (11.9)	$p = 0.02$
Cesarean section	51 (19.2)	81 (32.1)	$p = 0.02$
Obstetric bleeding >1000 mL	**19 (7.1)**	**20 (7.9)**	NS
Chorioamnionitis	8 (3.0)	4 (1.6)	NS
Uterine hyperstimulation	0	1	NS
Uterine rupture	0	0	NS
Primiparous women	$n = 164$ (%)	$n = 157$ (%)	
Vaginal birth	123 (75.0)	92 (58.6)	NS
Vaginal birth <24 h	66 (53.7)	65 (70.7)	$p = 0.01$
Instrumental delivery	43 (26.2)	24 (15.2)	$p = 0.03$
Cesarean section	41 (25.0)	65 (41.4)	$p = 0.03$
Bishop score ≤5	$n = 238$ (%)	$n = 244$ (%)	
Vaginal birth	189 (79.4)	164 (67.2)	NS
Vaginal birth <24 h	125 (66.1)	129 (78.7)	$p = 0.01$
Instrumental delivery	44 (18.5)	30 (12.3)	$p = 0.04$
Cesarean section	49 (20.6)	80 (32.8)	$p = 0.04$
Neonatal outcomes	$n = 265$	$n = 252$	
Birth weight (g) (mean ± SD)	3472 ± 579	3521 ± 602	NS
Apgar score <7 at 5 min (%)	4 (1.5)	1 (0.3)	NS

Table 4. Induction to vaginal delivery interval in hours (mean ± standard error).

Variable	Oral PG	Vaginal PG	*p* values
All women	21.6 ± 0.6	18.2 ± 0.7	$p < 0.001$
Primiparous women	24.9 ± 0.8	21.4 ± 0.9	$p < 0.01$
Bishop score ≤5	22.7 ± 0.6	20.4 ± 0.6	$p < 0.01$

In conclusion, labor induction with oral PG in solution was less effective than vaginal PG gel in achieving VB <24 h. However, oral PG was safer, since it resulted in fewer CS in all women, in primiparous women and in women with an unripe cervix. Despite a 3–4 h longer induction to vaginal delivery interval with oral PG, the proportions of obstetric bleeding, chorioamnionitis and neonatal asphyxia were not increased with this treatment.

Declaration of interest

The authors report no declaration of interest.

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