Labor Induction in Primiparous Women and Women with an Unripe Cervix

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Abstract

Objective: To compare the efficacy and safety of oral prostaglandin in solution, vaginal prostaglandin gel and transcervical catheter for labor induction in primiparous women and women with an unripe cervix.

Design: A retrospective study.

Methods: Data from original obstetric records at a university hospital in Sweden in 2012-2013.

Results: In primiparous women, vaginal birth <24 h was achieved in 54% with oral prostaglandin, 71% with vaginal prostaglandin, and 71% with catheter, whereas caesarean section was needed in 25%, 41% and 26% respectively. In women with an unripe cervix, vaginal birth <24 h was achieved in 86% with oral prostaglandin, 79% with vaginal prostaglandin, and 77% with catheter, while caesarean section was carried out in 21%, 33% and 21% respectively. The induction to vaginal delivery interval was the shortest with catheter and the longest with oral prostaglandin. The rates of obstetric bleeding, chorioamnionitis, uterine hyperstimulation and neonatal asphyxia were comparable.

Conclusion: Oral prostaglandin in solution was less effective than vaginal prostaglandin gel and transcervical catheter in achieving vaginal birth <24 h. However, oral prostaglandin and catheter were safer, since they resulted in fewer caesarean sections without increasing maternal morbidity or neonatal asphyxia.

Keywords: Catheter; Caesarean section; Prostaglandin; Dinoprostone; Misoprostol; Vaginal birth

Introduction

Labor is induced in 20-30% of all pregnancies. It has increased in Sweden from 7% in the early 1990s to 16% in 2012-2013 [1-3]. Induced labor involves increased risks for prolonged delivery and cesarean section (CS). These risks are high in primiparous women and women with an unripe cervix. Among these women, pre-induction cervical ripening is important for a successful vaginal birth (VB). To our knowledge, there are very few reports on labor induction with oral prostaglandin (OPG) in solution, vaginal prostaglandin (VPG) gel and transcervical catheter in primiparous women and women with an unripe cervix. The meta-analyses reviewers do not report such analyses [4-6].

Approximately two out of three CS are carried out in women with a previous CS. The rising CS rates are followed by increasing reports on maternal mortality and morbidity such as life-threatening obstetric bleeding, placenta complications and peripartal hysterectomy, as well as neonatal and infant complications, e.g. breathing disturbances, altered gut microbiota and DNA-methylation in white blood cells [7-9]. An uncomplicated first delivery is the primary positive prognostic factor for a later uncomplicated delivery. Thus, if a woman achieves an uncomplicated first delivery, she can probably avoid undergoing a CS later in life [7].

Labor induction with transcervical catheter was described in the 1860s [10]. The catheter separates the fetal membranes from the uterine wall, which leads to prostaglandin and oxytocin release from the fetal membranes and uterine decidua [11]. The catheter may also stimulate neuroendocrine pathways interrelated with oxytocin synthesis and release, i.e., the Ferguson reflex [12].

VPG treatment was used for labor induction since the 1980s. OPG treatment was avoided until the 1990s, because of presumed less efficacy due to first pass liver metabolism and gastrointestinal side effects [1,5,6]. PGs are the key mediators for cervical ripening and act via membrane bound G-coupled receptors. They promote cervical ripening via leukocyte chemotaxis and extravasation and a changed progesterone receptor A to B expression resulting in progesterone withdrawal. These events result in an increased collagenase enzyme activity, a changed proteoglycan composition and dispersed collagen fibrils, allowing for cervical effacement and dilatation [3,11,13].

The aim of this study was to compare the efficacy and safety of OPG in solution, VPG gel and transcervical catheter for labor induction in primiparous women and women with an unripe cervix. Our hypothesis was that OPG in solution would be safer than and at least as effective as VPG gel and catheter.

Methods

The study was approved by the Ethics Board for Medical Sciences in Stockholm, Sweden, on April 9th 2015, Dnr 2014/255-31. The World
Health Organization (WHO) International Classification of Diseases (ICD)-10 and the obstetric records for all women who had labor induced with OPG, VPG or catheter at the Department of Women’s and Children’s Health, Karolinska University Hospital, Solna, Sweden in 2012-2013 were investigated. Inclusion criterion was gestational age ≥ 34+0 weeks. Between January 1st 2012 and December 31st 2013, there were 7868 deliveries in the unit. Labor was induced in 1658 women (21%). Prostaglandins were used for labor induction in 542 women (33%) and catheter in 478 women (29%). Part of this material is described in related studies [14,15]. The remaining 638 women, all with a ripe cervix Bishop score >5, had labor induced with amniotomy or oxytocin infusion. Women suffering from intraterine fetal death (n=25) were excluded from the calculations (Figure 1).

VPG was the only available PG method in 2012. A total of 252 women had labor induced with this method, 207 in 2012 and 45 in 2013, due to the individual physician’s choice. Endogenous PGE gel dinoprostone (Minprostin®, Pfizer, SE-19138 Sollentuna, Sweden) 2 mg was inserted in the posterior vaginal fornix every 6-8 h up to a maximum of 3 doses. According to the manufacturer, the endogenous PGE2 dinoprostone preparation is followed by a peak plasma concentration after 30-45 min after vaginal administration. The fetal heart activity was monitored with cardiotocography (CTG) 20 min before each dose and at labor onset. OPG in solution was introduced for labor induction in 2013, and 265 women had labor induced with this method. The smallest available synthetic, esterified PGE analogue misoprostol tablet (Cytotec®, Pfizer, SE-19138 Sollentuna, Sweden) 200 μg was dissolved in 20 mL of water resulting in a concentration of 10 μg/mL. An adequate concentration was obtained [16]. 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 fresh solution 25 μg was continued every 2 h until labor onset up to a maximum of 8 doses. The synthetic, esterified PGE1 analogue misoprostol is followed by a peak plasma concentration after 30 min after oral administration, decreasing significantly within 120 min [17]. 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. 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 (Systocinon®, CD Pharma, SE-751 83 Uppsala, Sweden) infusion 5 U/500 mL NaCl 0.9% was administered for augmentation of labor, if no progress within 1 h following ruptured fetal membranes.

Mechanical induction was carried out with a 22 Charrière Foley catheter (Meteko Instruments AB, Stockholm, Sweden), which was inserted into the extra amniotic space at speculum investigation or digital examination according to the preference of the physician. A total of 478 women had labor induced with catheter, 314 in 2012 and 164 in 2014. After insertion, the catheter balloon was filled with water or NaCl 0.9% 50 mL and fastened to the thigh without traction. The position of the catheter was controlled by traction every 30 min. Amniotomy was performed immediately after expulsion of the catheter. According to the clinical guidelines, the catheter was removed if no expelled after 8 h and amniotomy was performed. Oxytocin infusion 5 U/500 mL saline was started within 1 h after amniotomy if no uterine contractions were observed, and immediately after catheter expulsion in women with pre-labor rupture of the membranes. The fetal heart activity was monitored with CTG 20 min before and after application and at labor onset.

Post-term pregnancy was gestation ≥ 42+0 weeks. Pre-labor rupture of the fetal membranes was diagnosed visually and labor was induced after 36-48 h. The hypertensive disease group was women with essential hypertension, gestational hypertension and preeclampsia. The group imminent fetal distress included reduced fetal movements with oligohydramniosis, intraterine 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, e.g. labour induction after external version of breech presentation, fetal 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) had labor induced at 41 weeks. A prolonged latency phase was cervical dilatation ≤ 3 cm after uterine contractions for 18 hours or more.

Dichoriotic 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 BS model, where a BS ≤ 5 was the criterion for an unripe cervix [18]. Hyper stimulation 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 new-borns [19].

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 analysed with one-way analysis of variance (ANOVA). Assumptions for parametric statistics were tested by Levene's test. Categorical data were analysed with non-parametric Mann-Whitney test. Statistical significance was set at p<0.05. We assumed that 40% with OPG and 60% with VPG and catheter would achieve VB<24 h.

Aiming at a significance level of 5% and 90% power, 125 observations would be needed in each group. We assumed that the CS rate would be 20% with OPG and 30% with VPG and catheter. Aiming at a significance level of 5% and 90% power, 194 observations would be needed in each group [1-4,6,19]. All data were entered into the computer.
program Statistica, version AX, Stat Soft, Inc., Tulsa, Oklahoma, US (2014).

Results

The indications for induced labor are shown in Table 1.

Table 1: Indications for labor induction. Differences all variables (NS).

The indications and the criteria for prolonged labor were unchanged. 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.

Table 2: Demographic data. Differences all variables (NS).

The groups with an unripe cervix BS ≤ 5 included similar proportions of primiparous women: in the OPG group 146 (61%) women were primiparous, 85 (36%) parous and 7 (3%) had a previous CS.

In the VPG group, 151 (62%) women were primiparous, 68 (28%) parous and 25 (10%) had a previous CS. In the catheter group 201 (50%) women were primiparous, 146 (46%) parous and 55 (14%) had a previous CS. Maternal and neonatal outcomes are shown in Table 3.

Table 3: Maternal and neonatal outcomes.

Most CS, more than 60% with all treatments, were carried out because of a prolonged first stage of 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 all treatments was a prolonged second stage of labor. No uterine ruptures were observed. There was no episode of uterine hyper stimulation with OPG or catheter, whereas one CS in the VPG group was carried out because of uterine hyper stimulation resulting in fetal

| Variable                        | OPG n=265 (%) | VPG n=252 (%) | Catheter n=478 (%) |
|---------------------------------|---------------|---------------|--------------------|
| Post-term pregnancy             | 64 (24)       | 57 (23)       | 97 (20)            |
| Pre-labor rupture of fetal      | 41 (15)       | 35 (14)       | 110 (23)           |
| Hypertensive disease            | 36 (14)       | 31 (12)       | 54 (11)            |
| Imminent fetal distress         | 36 (14)       | 31 (12)       | 61 (13)            |
| Psychosocial indication         | 24 (9)        | 20 (8)        | 52 (11)            |
| Maternal illness                | 22 (8)        | 26 (10)       | 33 (17)            |
| Other fetal indications         | 17 (6)        | 16 (6)        | 14 (3)             |
| Diabetes                        | 10 (4)        | 12 (5)        | 18 (4)             |
| Primiparous women ≥ 40 years    | 7 (3)         | 14 (6)        | 16 (3)             |
|                                  | after IVF     |               |                    |
| Latency phase prolonged         | 6 (2)         | 5 (2)         | 17 (4)             |
| Duplex pregnancy                | 2 (1)         | 5 (2)         | 6 (1)              |

| Variable                        | OPG n=265 (%) | VPG n=252 (%) | Catheter n=478 (%) | p value | p value |
|---------------------------------|---------------|---------------|--------------------|---------|---------|
| Vaginal birth                   | 214 (80.8)    | 171 (67.9)    | 382 (79.9)         | NS      | NS      |
| Vaginal birth <24 h             | 141 (56.9)    | 136 (79.5)    | 373 (78.0)         | p<0.001 | p<0.001 |
| Instrumental delivery           | 48 (18.1)     | 30 (11.9)     | 69 (14.4)          | NS      | NS      |
| Cesarean section                | 51 (19.2)     | 81 (32.1)     | 96 (20.1)          | NS      | NS      |
| Obstetric bleeding              | 19 (7.1)      | 20 (7.9)      | 28 (5.9)           | NS      | NS      |
| Chorioamnionitis                | 8 (3.0)       | 4 (1.6)       | 9 (1.9)            | NS      | NS      |
| Primiparous women               | 114 (42.8)    | 117 (46.1)    | 231 (48.9)         | NS      | NS      |
| Vaginal birth                   | 123 (75.0)    | 92 (58.6)     | 181 (73.9)         | NS      | NS      |
| Vaginal birth <24 h             | 66 (53.7)     | 65 (70.7)     | 175 (71.4)         | p<0.001 | p<0.001 |
| Instrumental delivery           | 43 (26.2)     | 24 (15.2)     | 45 (18.4)          | NS      | NS      |
| Cesarean section                | 41 (25.0)     | 65 (41.4)     | 64 (26.1)          | p<0.03  | NS      |
| Bishop score ≤ 5                | 238 (92.7)    | 244 (92.1)    | 402 (86.2)         | NS      | NS      |
| Vaginal birth                   | 189 (79.4)    | 164 (67.2)    | 319 (79.3)         | NS      | NS      |
| Vaginal birth <24 h             | 125 (86.1)    | 129 (78.7)    | 311 (77.3)         | p<0.01  | p<0.001 |
| Instrumental delivery           | 44 (18.5)     | 30 (12.3)     | 56 (13.9)          | NS      | NS      |
| Cesarean section                | 49 (20.6)     | 80 (32.8)     | 83 (20.6)          | NS      | NS      |
| Neonatal outcomes               | n=265         | n=252         | n=478              |         |         |
| Birth weight (g)                | 3472 ± 579    | 3521 ± 602    | 3514 ± 560         | NS      | NS      |
| Apgar score <7 at 5 min (%)     | 4 (1.5)       | 1 (0.3)       | 9 (1.9)            | NS      | NS      |

| Variable                        | OPG n=265 (%) | VPG n=252 (%) | Catheter n=478 (%) |
|---------------------------------|---------------|---------------|--------------------|
| Age (median and range)          | 32 (18-46)    | 32 (18-47)    | 32 (17-50)         |
| Primiparous (%)                 | 164 (63.6)    | 157 (62.8)    | 245 (51.2)         |
| Previous cesarean section (%)   | 8 (3.1)       | 25 (10.0)     | 64 (13.4)          |
| Gestational age (median and     | 39 (34-42)    | 39 (34-42)    | 40 (34-42)         |
| range)                          |               |               |                    |
| Gestational age<37+0 weeks (%)  | 13 (4.9)      | 9 (3.6)       | 9 (1.9)            |

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randomized study comparing OPG in solution with VPG gel, which compared to OPG, and 5-7 h shorter versus VPG.

The treatments, 20% vs. 23% [4]. However, OPG and catheter were safer, since they resulted in fewer CS compared with VPG in all women, primiparous women and women with an unripe cervix. The overall CS rate in 2012-2013 was 22% and the CS rate after induced labor was 30%. Thus, OPG and catheter resulted in lower CS rates and VPG in higher, than was generally observed at induced labor. The rates of VB <24 h were higher than was assumed with all methods.

The higher instrumental delivery rate with OPG could be explained by the longer induction to vaginal 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 overall incidence, being 6.7% in 2012-2013. The rates of chorioamnionitis in the study groups did not differ from the overall incidence, being 1.3%. The proportions of new-borns 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 average, 5 doses of OPG and 1 dose of VPG respectively, were used. The cost for 5 fresh OPG doses was €9.2 which was less than 5% of the cost for 1 dose of VPG gel. The cost for 1 Foley catheter was €2.2.

The present findings differed from the PROBAAT-II study on labor induction with VPG gel vs. catheter, which report similar CS rates with the treatments, 20% vs. 23% [4]. The present findings also differed from the PROBAAT-II study on labor induction with OPG capsules vs. catheter, which report similar CS rates with the treatments 17% vs. 20% [6]. However, our findings were in concordance with amulticenter randomized study comparing OPG in solution with VPG gel, which report a lower CS rate with OPG, 21% vs. 26% [20]. Our findings were also in agreement with a recent systematic review and network meta-analysis on labor induction with PGs. The authors conclude that OPG in solution is the safest PG method, and note that OPG tablets are, despite the worst overall ranking in their analysis [5].

Limitations in this study were the retrospective character and the lack of information about umbilical cord blood gas values [21]. Strengths were the high number of observations and that all data were collected from original medical records.

In conclusion, labor induction with OPG in solution was less effective than VPG gel and catheter in achieving VB<24 h. However, OPG and catheter were safer, since they resulted in fewer CS in all women, primiparous women and women with an unripe cervix. The induction to vaginal delivery interval was the shortest with catheter and the longest with OPG. Despite this, the incidence of obstetric bleeding, chorioamnionitis and neonatal asphyxia were comparable with the treatments.

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

| Variable | OPG | VPG | Catheter | OPG vs. VPG | OPG vs. Catheter |
|----------|-----|-----|----------|-------------|-----------------|
| All women | 21.6 ± 0.6 | 18.2 ± 0.7 | 12.9 ± 0.3 | p<0.001 | p=0.001 |
| Primiparous | 24.9 ± 0.8 | 21.4 ± 0.9 | 14.4 ± 0.4 | p<0.01 | p<0.001 |
| Bishop score ≤5 | 22.7 ± 0.6 | 20.4 ± 0.6 | 13.1 ± 0.3 | p<0.01 | p=0.001 |

### Discussion

The primary findings were that VPG gel and catheter were more effective than OPG in solution in achieving VB<24 h. However, OPG and catheter were safer, since they resulted in fewer CS compared with VPG in all women, primiparous women and women with an unripe cervix. The overall CS rate in 2012-2013 was 22% and the CS rate after induced labor was 30%. Thus, OPG and catheter resulted in lower CS rates and VPG in higher, than was generally observed at induced labor. The rates of VB <24 h were higher than was assumed with all methods.

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