# Title: Maternal and prenatal factors influencing the outcome of prostaglandin E2 induced labour

Running title: prostaglandin E2 and labour induction.

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Summary

In this retrospective cohort study involving 393 singleton pregnancies, we evaluated the maternal and prenatal factors influencing the use of and the outcome of prostaglandin E2 (PGE2) induced labours. Only a nulliparous pregnancy was shown to be a significant predictor of the use of more than one dose of PGE2 (odds ratio [OR] 2.73, 95% confidence interval [CI] 1.61 to 4.63). When the type of delivery was assessed, nulliparous status was significantly also associated with a decreased chance of vaginal delivery (OR 0.12, 95% CI 0.045 to 0.32). Other variables that positively influence the chance of vaginal delivery include a mother’s age being under 30 years (OR 2.63, 95% CI 1.51 to 4.58) and a single dose of PGE2 (OR 2.86, 95% CI 1.21 to 6.79). Gestational age, size of the baby and maternal BMI have much less impact on PGE2 use and chance of successful vaginal delivery than parity.

**Keywords**: Body Mass Index, Fetal birth weight, Gestation, Labour induction, Prostaglandin E2, Prostin.

#### Introduction

Induction of labour is a common procedure in obstetrics, observed in up to 30% of pregnancies (Laws and Sullivan, 2004). Vaginal prostaglandin E2 (PGE2) is widely used as a cervical ripening and labour-inducing agent at term. However, despite the importance of inducing labours to end pregnancies, this intervention may result in adverse maternal or foetal effects (Kundodyiwa et al, 2009). Therefore it should only be indicated if the benefits of delivery outweigh the risks of awaiting spontaneous labour (RCOG, 2008). The established indications of induction are usually universal e.g. hypertensive disorders of pregnancy, post-term pregnancy, preterm-prelabour rupture of membranes, intrauterine growth restriction, diabetes, and other maternal or fetal conditions (RCOG 2008; Yeast, 1999; Sanchez-Ramos, 2005; Lydon-Rochelle et al, 2007).

There has been a rise in caesarean section rates in the last decade which has subsequently led to an increase in neonatal morbidity and mortality (Wax, 2006; MacDorman et al, 2008). In order to slow the rise in caesarean section rates, induction of labour has been seen as an alternative to conducting caesarean sections (Coonrod et al, 2008). On the basis of above factors, this study was undertaken to assess what factors influence the success of induction of labour when induced with PGE2.

# Patients and methods

**Study design and patients**

We conducted a retrospective cohort study concerning women who delivered at the maternity unit of a general district hospital in the UK, and who were prescribed one or more doses of PGE2. The indications were post-dates pregnancy (n=169; 43%), pregnancy induced hypertension and pre-eclampsia (n=73, 18), small for gestational age (n=56, 14%), prelabour spontaneous rupture of membranes for > 24 hours (n=30, 8%), or other causes such as diabetes, large for dates, obstetric cholestasis (n=65, 17%). Use of PGE2 was also indicated due to Bishop score being 6 or lower.

A total of 393 singleton pregnancies were included, covering the period January 2006 to December 2008. Multiple pregnancies were excluded from analysis as were those where the BMI of the expectant mother was not recorded. There were no other exclusion criteria applied, like e.g. age constrictions or contraindication for vaginal delivery. Administration of PGE2 is performed as follows: first two 3mg tablets each 6 hours apart, followed by third 3 mg tablet if required 12 hours after 2nd dose. The patients in this cohort were given three doses of PGE2 only when they were nulliparous or had given birth vaginally previously. For those who had a previous caesarean section the maximum number of PGE2 given was 2, not 3.

**Variables and statistical analysis**

For a simplified overview that can be translated to a clinical environment all variables were categorised rather than presented as continuous data, including age and BMI. Body Mass Index is categorised according to World Health Organisation levels: up to 25, underweight and normal range; 25 to 29, overweight; 30 and over, obese class I-III (WHO, 1995). For the type of delivery, no distinction was made for unaided vaginal delivery and vaginal delivery using an instrument. Regression was applied to determine which variables are associated with the use of PGE2 in pregnancy and labour induction, and the type of delivery respectively. Statistical analysis was performed using SPSS version 17 (SPSS Inc., Chicago, USA). A P-value of 0.05 or less was considered to be statistically significant.

# Results

In our cohort, the administration of PGE2 for cervical ripening and labour induction resulted in a nearly eighty percent successful vaginal delivery (78.4%). Table 1 shows an overview of the baseline characteristics regarding the cohort studied. Analysis of what factors may predict or influence the total number of PGE2 doses used before vaginal delivery was achieved or caesarean section was decided upon reveals that only factor included in our study is significantly linked to an increased number of PGE2 doses: parity. Nulliparous women are significantly more likely to be administered more than one dose (see Table 2). Otherwise, there is very little indication that variables, including patient’s age, gestational age, maternal BMI and centile of the baby, are likely to predict an increased dosage of PGE2.

Table 3 summarizes the results of a multiple ordinal regression analysis of factors predicting the eventual outcome of the labour process: vaginal delivery or caesarean section. In addition to the factors analysed in the multiple regression analysis for the numbers of PGE2 doses used, this outcome dependent was itself used as a factor for the dependent of this analysis: type of delivery. Younger patients (OR 2.63, 95% CI 1.51 to 4.58) and a single dose of PGE2 (OR 2.86, 95% CI 1.21 to 6.79) are statistically significant predictors of induction of vaginal delivery. Conversely, nulliparous women are less likely to achieve a vaginal delivery. The rate of vaginal delivery drops from as high as 93.6% for women with two or more children to 67.3% for nulliparous women (OR 0.12, 95% CI 0.045 to 0.32). Although women with a BMI of less than 25 are approximately 9% more likely to deliver vaginally than those with a BMI above 25, this difference is not statistically significant. Similarly, the baby’s gestational age or weight expressed as a percentile does not lead to significant changes in delivery outcome.

#### Discussion

The outcomes of this study add to the existing evidence on the contribution or inhibitive effects that maternal and prenatal variables can have on the ultimate mode of delivery in labour (Wing et al, 2002; Crane et al, 2004; Pevzner et al, 2009a). However, most of the published analyses to date have looked at labour induction with misoprostol, rather than dinoprostone. Our results align with the available literature on prostaglandins in that parity is the single most important predictor of a successful vaginal delivery in women who require PGE2 medication (Pevzner et al, 2009a). Parity is also the biggest predictor for requiring more than one dose of PGE2. Nulliparous women are more likely than those who already have children to require multiple doses of PGE2. The low pseudo R2 value (0.078) for the multiple regression analysis of the number of PGE2 doses does demonstrate and confirm that cervical ripening and labour induction is a complex biological process which is likely to involve many triggers, inhibitors and activators (Calder, 1994).

The results of the multiple ordinal regression analysis into those factors that influence the type of delivery show that administering multiple doses of PGE2 does not mean that the rate of vaginal deliveries can be sustained, as shown by a reduction of 30% in vaginal deliveries between those receiving one dose and three doses of PGE2 (84.5% to 54.1%).

Recently, Pevzner and colleagues (2009b) showed a significant correlation between obesity and caesarean delivery rates in a cohort of patients in the United States. Although the WHO classification for BMI was applied, the categories were < 30, 30-39, and >40, which differs from our categories < 25, 25 – 29 and >30. This perhaps reflects the difference in average weight of people in general in the US and UK & Europe, respectively. This makes a direct comparison rather hard; our data shows that there is a considerable jump in caesarean rate between those with a BMI in the underweight to normal range (<25; 17.2% caesarean sections) and those who are overweight (25- 29; 25.5%). Increased caesarean rates will ultimately mean higher risk of complications. Therefore, although no statistically significant correlation between BMI groups and mode of delivery were obtained here, obese patients (BMI over 30) may certainly benefit from more intensive obstetric management as suggested by Jarvie & Ramsay (2010).

The increase in caesarean sections carried out in the UK may certainly have been caused partly by increased average age at which women have children (Thomas and Parajothy, 2001). Our data supports this notion, with those over 30 years of age being at significant higher risk of requiring a caesarean section compared to women under the age of 30. Although not significant, there appears to be a trend in that the longer the pregnancy has lasted, the more likely it is that a vaginal delivery is achieved. Similarly, a higher percentile for the projected weight of the baby at birth is associated with a moderately reduced vaginal birth rate.

The vast majority of the women included in this study Caucasian, therefore race was not included as a predictive factor. The reason for induction (indication) was not included in our analyses since it involves nominal data, although prolonged pregnancy was included by virtue of gestational age. The factors included in the multiple ordinal regression analysis were nevertheless reasonably capable of predicting the type of delivery outcome (Pseudo R2 = 0.217), considering labour is such a complex and multifaceted process.

This study adds to the body of evidence related to maternal and prenatal factors that influence the success of vaginal delivery in those women who require prostaglandins for cervical ripening and labour induction. Generally speaking, there appears to be little to no difference in terms of what type of prostaglandin is used, mistropol or dinoprostone, and the associations that maternal and prenatal factors have with pregnancy outcomes as measured by type of delivery.

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**Table I**. Demographics of pregnant women & prenatal variables and summary of events during labour

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Categories** | **N**  | **Percentage of total**  |
| total nr of pregnancies |  | 393 | 100% |
| PGE2 doses | 1 | 155 | 39.4% |
|  | 2 | 201 | 51.1% |
|  | 3 | 37 | 9.4% |
| type of delivery | vaginal | 308 | 78.4% |
|  | caesarean section | 85 | 21.6% |
| patient age | up to 29 yrs | 192 | 48.9% |
|  | 30 yrs or over | 201 | 51.1% |
| parity | nulliparous | 208 | 52.9% |
|  | one child | 106 | 27.0% |
|  | two of more children | 79 | 20.1% |
| gestation | up to 40 wks | 148 | 37.7% |
|  | 40 to 41 weeks | 98 | 24.9% |
|  | 42 weeks | 147 | 37.4% |
| BMI | up to 24 | 180 | 45.8% |
|  | 25 to 29 | 110 | 28.0% |
|  | 30 and over | 103 | 26.2% |
| centile | up to 50th | 232 | 59.0% |
|  | above 50th | 161 | 41.0% |

**Table II**. Multivariable ordinal regression analysis of factors predicting the number of PGE2 doses used.

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** |  | **OR**  | **95% CI** |
| patient age | up to 29 yrs | 1.12 | 0.75 to 1.67  |
|  | 30 yrs or over | 1.0 |  |
| parity | nulliparous | 2.73\* | 1.61 to 4.63 |
|  | one child | 1.19 | 0.67 to 2.12 |
|  | two of more children | 1.0 |  |
| gestation | up to 40 wks | 0.91 | 0.58 to 1.44 |
|  | 40 to 41 weeks | 1.0 | 0.60 to 1.65 |
|  | 42 weeks | 1.0 |  |
| BMI | up to 24 | 0.70 | 0.43 to 1.13 |
|  | 25 to 29 | 0.73 | 0.43 to 1.23 |
|  | 30 and over | 1.0 |  |
| centile | up to 50th | 0.79 | 0.53 to 1.18 |
|  | above 50th | 1.0 |  |

Pseudo R2 = 0.078 (Nagelkerke); P value < 0.05

**Table III**. Multivariable ordinal regression analysis of factors predicting the success of achieving vaginal delivery.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** |  | **Vaginal delivery achieved (N)** | **(%)** | **OR** | **95% CI** |
| patient age | up to 29 yrs | 160/192 | 83.3% | 2.63\* | 1.51 to 4.58 |
|  | 30 yrs or over | 148/201 | 73.6% | 1 | . |
| parity | nulliparous | 140/208 | 67.3% | 0.12\* | 0.045 to 0.32 |
|  | one child | 94/106 | 88.7% | 0.47 | 0.155 to 1.42 |
|  | two of more children | 74/79 | 93.6% | 1 | . |
| gestation | up to 40 wks | 116/148 | 78.4% | 0.69 | 0.37 to 1.29 |
|  | 40 to 41 weeks | 75/98 | 76.5% | 0.85 | 0.44 to 1.67 |
|  | 42 weeks | 117/147 | 79.6% | 1 | . |
| BMI | up to 24 | 149/180 | 82.8% | 1.36 | 0.71 to 2.60 |
|  | 25 to 29 | 82/110 | 74.5% | 0.96 | 0.48 to 1.92 |
|  | 30 and over | 77/103 | 74.8% | 1 | . |
| centile | up to 50th | 188/232 | 81.0% | 1.59 | 0.93 to 2.71 |
|  | above 50th | 120/161 | 75.0% | 1 | . |
| PGE2  | one dose | 131/155 | 84.5% | 2.86\* | 1.21 to 6.79 |
|  | two doses | 157/201 | 78.1% | 2.16 | 0.97 to 4.78 |
|  | three doses | 20/37 | 54.1% | 1 | . |

Pseudo R2 = 0.217 (Nagelkerke); P value < 0.05