ORIGINAL ARTICLE

Maternal intravaginal prostaglandin E_2 gel before elective caesarean section at term to induce catecholamine surge in cord blood: randomised, placebo controlled study

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Objective: To test the hypothesis that the application of intravaginal prostaglandin E_2 gel before elective caesarean section (ECS) will induce a catecholamine surge in umbilical arterial blood.
Design: Randomised, double blind, placebo controlled trial.
Setting: A regional perinatal referral centre.
Patients: Mothers booked for ECS at or above 38 weeks gestation.
Interventions: Thirty six consenting mothers were randomly allocated to receive either 2 mg intravaginal prostaglandin E_2 gel (study group; n = 18) or an equal volume of K-Y jelly as a placebo (control group; n = 18) 60 minutes before the ECS. Computer generated random numbers contained in coded, sealed envelopes were used for allocation. The obstetric and neonatal teams were blinded to the randomisation status of enrolled mothers.
Main outcome measures: Catecholamine concentrations in the umbilical arterial blood samples collected at delivery.
Results: The median (interquartile range) neonatal gestation and birth weight were 271 (269–274) days and 3605 (3072–3970) g for the study group and 271 (270–273) days and 3340 (3000–3622) g for the control group. Median (interquartile range) noradrenaline (norepinephrine) concentrations in the umbilical arterial blood were significantly higher in the study group than the control group (15.9 (9.8–28.92) *v* 4.6 (1.65–14.4) ng/l, p=0.03). Adrenaline (epinephrine) concentrations did not differ significantly between the two groups (1.6 (< 0.5–3.1) *v* 1.4 (< 0.5–2.75) ng/l, p = 0.6). No treatment related complications occurred.
Conclusion: A labour related catecholamine surge could be simulated by intravaginal prostaglandin E_2 gel.

Significant respiratory morbidity is reported after elective caesarean section (ECS) delivery before the onset of labour, even if at term, reflecting the importance of labour in neonatal extrauterine adaptation.[1 2] Various mechanisms have been proposed to explain the neonatal respiratory distress after ECS delivery, including retained lung fluid and lack of the catecholamine surge that occurs during labour.[3 4] The catecholamine surge during labour has been shown to decrease fetal lung fluid secretion and increase its resorption even before birth and promote surfactant synthesis and secretion to enhance lung aeration.[5 6] Although the complex physiological mechanisms are not fully understood, respiratory problems are clearly fewer after onset of labour and with increased gestational age.[7 8] For neonates delivered by ECS, the odds ratio is 6.8 for developing respiratory problems compared with those delivered vaginally, and 2.9 compared with those delivered by caesarean section during labour.[7] The incidence of respiratory morbidity has been reported to be significantly higher in neonates delivered by caesarean section before the onset of labour (35.5/1000) than in those delivered by caesarean section during labour (12.2/1000) (odds ratio 2.9; 95% confidence interval (CI) 1.9 to 4.4; p < 0.001).[8] Yang *et al*[9] have also documented that respiratory distress occurred less often in term neonates delivered after the onset of labour than in those delivered before the onset of labour (11.1% *v* 31.8%, p < 0.002). In addition, the incidence of persistent pulmonary hypertension of the newborn (PPHN) was recently reported to be 0.37% among neonates delivered by ECS, almost fivefold higher than in those delivered vaginally.[10] Such higher incidence of PPHN may be related to the lack of labour related increase in circulating vasodilating substances such as prostacyclin and nitric oxide. Faxelius *et al*[4] have reported that two hours after birth there was a significant correlation (r = 0.84) between the catecholamine concentrations of the neonates born vaginally and lung compliance. They hypothesised that the lower dynamic lung compliance in infants delivered by ECS may be explained by delayed absorption of liquid in the lung because of the lack of a catecholamine surge. Hagnevik *et al*[3] have reported a significant correlation between catecholamine concentrations at birth and the increase in functional residual capacity from 30 to 120 minutes in the caesarean section group. The importance of the labour associated catecholamine surge (mainly noradrenaline) in the cardiorespiratory adaptation of neonates is also well documented.[3–6 11]

Results of animal experiments suggest that the use of pharmacological agents to induce labour may be a method for reducing the occurrence and severity of perinatal respiratory distress.[12] Intravaginal prostaglandin E_2 gel is widely used for cervical ripening and induction of labour.[13–15] Moreover the resulting labour is similar to spontaneous labour.[13] About 50% of women induced with prostaglandin E_2 have been

Abbreviations: ECS, elective caesarean section; HPLC, high pressure liquid chromatography; PPHN, persistent pulmonary hypertension of the newborn

reported to go into labour and deliver within 24 hours, often within a few hours.[13] Episodes of fetal heart rate abnormalities (< 1% of cases) caused by uterine hyperstimulation are usually noted within the first hour of the gel application.[13] We therefore hypothesised that application of maternal intravaginal prostaglandin E_2 gel one hour before ECS at ⩾ 38 weeks gestation will simulate a labour associated catecholamine surge in the umbilical arterial blood. The timing of the application of the gel was expected to maximise the chances of early detection and treatment of uterine hyperstimulation/hypertonus if it occurred.

The aim of the study was to compare plasma catecholamine concentrations in neonatal umbilical arterial blood after maternal application of either intravaginal prostaglandin E_2 gel or a placebo (K-Y jelly) 60 minutes before an ECS for delivery at ⩾ 38 weeks gestation.

DESIGN AND METHODS

A prospective, randomised, placebo controlled study in a regional neonatal tertiary care centre was used.

Entry criteria and method of randomisation

All expectant mothers eligible for an ECS at ⩾ 38 weeks gestation were enrolled into the study after written informed consent had been obtained, as approved by the institutional ethics committee. Sealed, coded, opaque, and sequentially numbered envelopes containing computer generated random numbers were used to ensure concealment of the allocation until the point when the enrolled mothers were assigned to either the study group or the placebo group by the independent research assistant. Enrolled mothers then received either 2 mg prostaglandin E_2 gel (Prostin E_2 vaginal gel; Upjohn, Kalamazoo, Michigan, USA; study group) or an equal volume of K-Y lubricating jelly (Johnson and Johnson; placebo group) intravaginally (into the posterior fornix to avoid cervical application) for initiation of labour 60 minutes before the ECS depending on their allocation status. A dose of 2 mg was chosen in view of its safety and efficacy compared with a high (3–5 mg) dose.[11] Gel application for 60 minutes before the ECS was considered to be adequate to initiate the process of labour, as its onset of action is reported to be about 10 minutes.[13 15]

Exclusion criteria

(1) Pregnancies with known fetal malformation/s or chromosomal aberration

(2) Presence of absolute contraindications for use of prostaglandin E_2 vaginal gel—for example, history of adverse reactions to prostaglandin preparations

(3) ECS deliveries before 38 weeks gestation

(4) Failure to obtain informed consent

Problems with blinding

Technical difficulties were involved in developing prepackaged and loaded syringes similar in appearance to commercially available Prostin gel syringes but containing the placebo (K-Y jelly). An independent research assistant was hence appointed to administer the study drug or placebo to the enrolled mothers 60 minutes before their transfer to the operating theatre. Blinding of the primary care teams of the mother and the neonate as well as the primary investigators of the research projects was thus ensured. The author involved in the catecholamine assay (DN) as well as the statistician analysing the data (PB) were also blinded to the allocation status of the enrolled mothers.

Observations and data collection

Continuous cardiotocographic monitoring was undertaken after maternal application of intravaginal prostaglandin E_2 gel or K-Y jelly by the research assistants to detect any evidence of uterine hyperstimulation and fetal distress. An injectable preparation of terbutaline was kept ready for treatment of any uterine hyperstimulation. The surgical and anaesthetic teams were in a state of complete readiness for the ECS from the time of maternal application of the gel/jelly after enrolment. Details on maternal fluid–electrolyte status during ECS were recorded, as maternal fluid overload is reported to be associated with respiratory distress in the newborn.[16]

Standardisation of umbilical cord clamping

During the study period, umbilical cords were clamped 30 seconds after the delivery while the neonate was held at the level of the perineum to avoid excessive placental transfusion, which may alter the cardiorespiratory status of the neonate.[17]

Catecholamine measurements

Umbilical arterial blood (2 ml) was collected for measurement of pH, adrenaline, and noradrenaline concentrations using high pressure liquid chromatography (HPLC). Catecholamines were extracted from plasma by adsorption on activated alumina. After elution, noradrenaline and adrenaline were measured by HPLC using a C18 reversed phase column, an amperometric electrochemical detector, and quantitation by integration of peak heights. Three levels of calibrator and two levels of quality control were run with patient specimens.[18 19]

Neonatal observations

After the delivery room care details had been noted, neonatal heart rate, respiratory rate, and signs of respiratory distress—for example, grunting, chest wall retractions, nasal flaring—were recorded hourly in the postnatal ward for eight hours and once only at 24 hours of age after delivery. Management of a neonate with respiratory distress (defined as respiratory rate at rest > 60/min and/or signs of respiratory distress) was left to the neonatal team. Severity of illness, provisional and final diagnosis, and outcome (death/discharge home/transfer to other hospital) were recorded if any neonate was admitted to the neonatal intensive care unit for respiratory distress.

Statistical methods

The data set was comparatively small, impeding an informative picture of the distribution of numerical variables. Thus all numerical variables were reported as median (interquartile range). Categorical variables were given in percentages. Bivariate comparisons assessing differences between the intervention and the control group were conducted, using the non-parametric Mann-Whitney-Wilcoxon test and Fisher's exact test. A significance level of 0.05 was assumed throughout the analysis. The data were analysed using SPSS for Windows, release 6.1 3.

RESULTS

After they had given written informed consent, 36 consecutive mothers were randomly allocated to receive either 2 mg intravaginal prostaglandin gel (study group; n = 18) or an equal volume of K-Y jelly as placebo (control group; n = 18) 60 minutes before an ECS at ⩾ 38 weeks gestation. No mothers refused to participate in the study. Each of the 36 enrolled mothers gave birth to a singleton infant (table 1).

Gestation, birth weight, cord arterial pH, and bicarbonate concentrations did not differ significantly between the two groups (tables 1 and 2). Plasma noradrenaline concentrations

Table 1 Characteristics of the 36 mothers enrolled in the study

	Study group (n = 18)	Control group (n = 18)
Age (years)	25 (22–30)	29 (22.5–31.5)
Blood loss (×100 ml)	6.5 (4–11)	7 (6–10.5)
Bishop score	3 (3–4)	3 (3–6.5)
Number of children	1 (0–2)	1 (1–2)
PCS	9 (50%)	10 (59%)
Gestation (days)	271 (269–274)	271 (270.5–273.5)
Epidural anaesthesia	18	16
General anaesthesia	0	1
Opiate induction	0	0
Antenatal glucocorticoids	0	0
Cervical dilation (cm)	1.5 (1–3)	2 (1–2)
Time to delivery after gel (minutes)	107 (70–122.75)	103 (79–120)

Values are median (interquartile range), n (%), or n. The study group received 2 mg intravaginal prostaglandin gel and the control group received an equal volume of K-Y jelly as placebo.
PCS, Previous caesarean section.

were significantly higher than adrenaline concentrations in all cord blood samples. Adrenaline concentrations did not differ significantly between the two groups, but the noradrenaline concentrations in the umbilical arterial blood were significantly higher in the study group than in the control group (table 2, fig 1). Treatment related complications, such as uterine hyperstimulation/hypertonus and fetal distress, did not occur. Except for one neonate in the control group who developed probable transient tachypnoea of neonates not requiring oxygen or admission to the intensive care nursery, no respiratory difficulties were noted.

DISCUSSION

This study shows the efficacy of a single application of maternal intravaginal prostaglandin E_2 gel before ECS delivery at $\geqslant$ 38 weeks gestation in initiating a surge in plasma catecholamine concentrations in umbilical arterial blood. The median catecholamine concentrations (noradrenaline 15.9 ng/l, adrenaline 1.6 ng/l) are comparable to those after vaginal delivery as reported by Nordstrom *et al*[20] (noradrenaline 14.6 ng/l, adrenaline 1.8 ng/l), and Faxelius *et al*[21] (noradrenaline 14.07 ng/l, adrenaline 2.56 ng/l). Our results also confirm that the fetal response to the stress of labour is predominantly a rise in noradrenaline.[22] Despite the successful simulation of a labour related catecholamine surge in our study, we caution that the clinical efficacy of such raised catecholamine concentrations and the safety of the proposed intervention needs to be studied in large trials. The methodology also needs to be considered in explaining the observed lack of significant rise in adrenaline concentrations in the study group compared with the placebo group. HPLC assay is known to be imprecise at low concentrations of catecholamine.[18 19] Given that the concentrations of adrenaline are much lower than those of noradrenaline, it is possible that a rise in adrenaline concentration, if it occurred in the study group, was not large enough to be detected consistently by the HPLC assay.

Except for one caesarean section carried out under general anaesthesia in the placebo group, all others were performed under epidural anaesthesia in our study. The effect of maternal analgesia and anaesthesia on the catecholamine surge needs to be discussed. Jason Eliot *et al*[23] reported no significant difference in the mean umbilical arterial and venous plasma noradrenaline and adrenaline concentrations in neonates delivered by caesarean section after general or spinal anaesthesia. Irestedt *et al*[11] reported higher catecholamine concentrations in neonates delivered by caesarean section after an epidural (mean (SD) noradrenaline and adrenaline concentrations, 9.5 (6.4) and 4.0 (4.5) nmol/l respectively) than after general anaesthesia (3.2 (2.7) and 1.0 (1.4) nmol/l respectively).

Table 2 Neonatal characteristics and outcomes

	Study group (n = 18)	Control group (n = 17)	p Value
Birth weight (g)	3605 (3072.5–3970)	3340 (3000–3622.5)	0.0988
Apgar score 1 minute	9 (8–9)	9 (9–9)	0.6116
Apgar score 5 minutes	9.5 (9–10)	10 (10–10)	0.0152
Arterial pH	7.31 (7.28–7.37)	7.31 (7.29–7.33)	0.7043
Venous pH	7.36 (7.34–7.39)	7.37 (7.32–7.40)	0.8949
Admission to special care	0 (0%)	2 (11.8%)	0.2286
Adrenaline (ng/l)	1.6 (<0.5–3.1)	1.4 (<0.5–2.75)	0.6
Noradrenaline (ng/l)	15.9 (9.8–28.92)	4.6 (1.65–14.4)	0.03

Values expressed as median (interquartile range) or n (%). Mothers in the study group received 2 mg intravaginal prostaglandin gel and those in the control group received an equal volume of K-Y jelly as placebo. Adrenaline and noradrenaline concentrations were measured in umbilical arterial blood.

Although we found no evidence of potentially very serious side effects such as uterine hyperstimulation or fetal distress in our small study, the issue of safety needs to be discussed further. Uterine hyperstimulation—defined as six or more contractions in 10 minutes for a total of 20 minutes—has

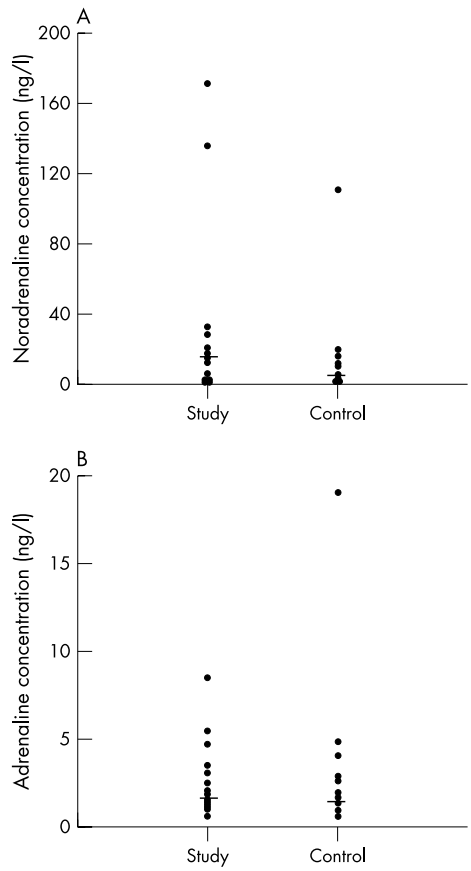

Figure 1 Catecholamine concentrations in the umbilical arterial blood. Mothers in the study group received 2 mg intravaginal prostaglandin gel and those in the control group received an equal volume of K-Y jelly as placebo. (A) Noradrenaline; (B) adrenaline. Median values are represented by a horizontal bar.

been reported in 5–16.5% of cases where labour was induced with intravaginal prostin E_2 gel (2–5 mg dose).[14 24] The gel is thus clearly contraindicated in the presence of labour because of the risk of uterine hyperstimulation and fetal compromise. A recent case report has documented uterine rupture two hours after a single vaginal application of 2 mg prostaglandin gel in a primiparous woman for induction of labour at 41 weeks and 4 days.[25] Aerosolised salbutamol was initially used to treat the uterine hyperstimulation, as injectable terbutaline was not immediately available. After recovery, the mother and baby were discharged from the hospital on day five. The authors stated ''It may be arguable that terbutaline could have prevented the uterine rupture''.[25] Uterine hyperstimulation usually occurs within one hour of prostin E_2 gel application.[26 27] Continuous cardiotocographic monitoring, ready availability of subcutaneous terbutaline, and absolute readiness for a caesarean section are thus strictly necessary to prevent the potentially disastrous consequences of uterine hyperstimulation in such situations.[25 27] It is suggested that prostaglandin E_2 has the same ''softening'' effect on the fibrous tissue of the uterine scar as it has on the cervix.[28] Thus the risk of scar rupture may be high with induction of labour in women with a previous caesarean section scar.[29] In a systematic review of this controversial issue, Vause and Macintosh[30] have estimated that the risk of uterine rupture after induction of labour in women with a previous caesarean section scar was no greater than 0.6%, similar to that quoted for spontaneous labour. They concluded that uterine scar rupture was such an uncommon event that an impractically large randomised controlled trial would be needed to address the issue properly. Caution is clearly warranted despite the uncommon occurrence of such potentially disastrous adverse effects.

Evidence indicates that prenatal induction predominantly of a noradrenaline surge may be beneficial in cardiopulmonary adaptation of the neonate after ECS delivery. Animal experiments have shown that noradrenaline can reduce lung liquid production when at plasma concentrations present at birth.[31] Unlike adrenaline, it was able to produce reabsorption of lung fluid even at high concentrations without any reduction in responses. Differences in species specific responses, however, need to be considered before extrapolation of these findings to the human fetus.[32 33] Prenatal adrenaline infusion has been shown to increase postnatal Pao_2 by enhancing clearance of fetal lung fluid in the newborn lamb experiments. However, this beneficial effect was outweighed by the severe acidosis that developed after prolonged adrenaline treatment.[34]

Another important issue with regard to the beneficial fetal effects of labour is the difficulty in defining the optimum duration of labour (or concentration of catecholamines) that is protective enough for the cardiopulmonary adaptation of a given fetus without having other adverse effects. Despite its beneficial effects, a ''significant'' duration of labour (as in a proper ''trial of labour''—TOL) before ECS delivery may not be the most appropriate method to minimise associated neonatal respiratory morbidity. Hook *et al*[35] have reported association of TOL with increased rates of respiratory morbidity, suspected and proven sepsis, and prolonged hospital stay in neonates delivered after caesarean section after a failed TOL.

In summary, neonatal respiratory distress, transient tachypnoea of neonates, and PPHN continue to complicate ECS deliveries at term. The socioeconomic and medicolegal implications of severe neonatal respiratory morbidity associated with ECS cannot be overemphasised considering the rising incidence of ECS at term. Our results indicate that the labour related noradrenaline surge can be simulated by a single application of maternal intravaginal prostin gel before ECS. This may provide a simple strategy to reduce the occurrence and severity of neonatal respiratory distress after ECS at $\geqslant$ 38 weeks gestation. We estimate that a hypothetical study would need 776 deliveries per group to detect a 50% reduction in the reported 5.8% incidence of respiratory distress after an ECS at 38 weeks gestation, with 80% power and overall significance level set at 0.05.[36] The corresponding numbers needed to treat before one event is avoided (one baby without respiratory distress) will be 35. As the rate of complications (uterine hyperstimulation) in such a trial is estimated to be 36–128, it is necessary to weigh the benefits against the risks of the proposed intervention before planning such large trials.

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REFERENCES

1 **Wax JR**, Herson V, Carignan E, *et al*. Contribution of elective delivery to severe respiratory distress at term. *Am J Perinatol* 2002;**19**:81–6.
2 **Halliday HL**. Elective delivery at ''term'': implications for the newborn. *Acta Pediatr* 1999;**88**:1180–3.
3 **Hagnevik K**, Faxelius G, Irestedtl L, *et al*. Catecholamine surge and metabolic adaptation in the newborn after vaginal delivery and caesarean section. *Acta Paediatr Scand* 1984;**73**:602–9.
4 **Faxelius G**, Lagercrantz H, Yao A. Sympathoadrenal activity and peripheral blood flow after birth. Comparison in infants delivered vaginally and by elective cesarean section. *J Pediatr* 1984;**105**:144–8.
5 **Olver RE**. Of labour and lungs. *Arch Dis Child* 1981;**56**:559.
6 **Bland RD**. Formation of fetal lung fluid and its removal near birth. In: Polin RA, Fox WW, eds. *Fetal and neonatal physiology*. 2nd ed. Philadelphia: WB Saunders, 1998:1047–54.
7 **Cohen M**, Carson BS. Respiratory morbidity benefit of awaiting onset of labour after elective cesarean section. *Obstet Gynecol* 1985;**65**:818–24.
8 **Morrison JJ**, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. *Br J Obstet Gynaecol* 1995;**102**:101–6.
9 **Yang JY**, Fang LJ, Tsou Yau KI. Labor pain before elective cesarean section reduces neonatal respiratory distress. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi* 1997;**38**:38–43.
10 **Levine EM**, Ghai V, Barton JJ, *et al*. Mode of delivery and risk of respiratory diseases in newborns. *Obstet Gynecol* 2001;**97**:439–42.
11 **Irestedt L**, Lagercrantz H, Hjemadahl P, *et al*. Fetal and maternal plasma catecholamine levels at elective cesarean section under general or epidural anesthesia versus vaginal delivery. *Am J Obstet Gynecol* 1982;**142**:1004–10.
12 **Norlin A**, Folkesson HG. Alveolar fluid clearance in late-gestational guinea pigs after labor induction: mechanisms and regulation. *Am J Physiol Lung Cell Mol Physiol* 2001;**280**:l606–16.
13 **Rayburn WF**. Prostaglandin E2 gel for cervical ripening and induction of labor: a critical analysis. *Am J Obstet Gynecol* 1989;**160**:529–34.
14 **Kelly AJ**, Kavanagh J, Thomas J. Vaginal prostaglandin (PGE2 and PGEF2a) for induction of labour at term. *Cochrane Database Syst Rev* 2001;**2**:CD003101.
15 **Induction and augmentation of labor**. In: Cunningham FG, Gant NF, Leveno KJ, *et al*, eds. *Williams obstetrics*. 21st ed. New York: McGraw-Hill, 2001:469–81.
16 **Singhi S**, Chookang E. Maternal fluid overload during labour: transplacental hyponatraemia and risk of transient tachypnea in term infants. *Arch Dis Child* 1984;**59**:1155–8.
17 **Erkkola R**, Kero P, Kanto J, *et al*. Delayed cord clamping in cesarean section with general anesthesia. *Am J Perinatol* 1984;**1**:165–9.
18 **Hallman H**, Farnebo LO, Hamberger B, *et al*. Sensitive method for determination of plasma catecholamines using liquid chromatography with electrochemical detection. *Life Sci* 1978;**23**:1049–52.
19 **Duncan MW**, Smyth G, Lazarus L. Measurement of norepinephrine and 3,4-dihydroxyphenylglycol in urine and plasma for the diagnosis of phaeochromocytoma. *N Engl J Med* 1988;**319**:136–42.
20 **Nordstrom L**, Marcus C, Persson B, *et al*. Lactate in cord blood and its relationship to pH and catecholamines in spontaneous vaginal deliveries. *Early Hum Dev* 1996;**46**:97–104.
21 **Faxelius G**, Hagnevik K, Lagercrantz H, *et al*. Catecholamine surge and lung function after delivery. *Arch Dis Child* 1983;**58**:262–6.
22 **Costa A**, De Flippis V, Voglino M, *et al*. Adrenocorticotropic hormone and catecholamines in maternal, umbilical and neonatal plasma in relation to vaginal delivery. *J Endocrinol Invest* 1988;**11**:703–9.
23 **Jason Eliot R**, Lam R, Leake RD, *et al*. Plasma catecholamine concentrations in infants at birth and during the first 48 hours of life. *J Pediatr* 1980;**96**:311–15.

24 **Crane JM**, Young DC, Butt KD, *et al*. Excessive uterine activity accompanying induced labour. *Obstet Gynecol* 2001;**97**:926–31.
25 **Selo-Ojeme DO**, Ayida GA. Uterine rupture after a single vaginal 2 mg prostaglandin gel application in a primiparous woman. *Eur J Obstet Gynecol Reprod Biol* 2002;**101**:87–8.
26 **Miller AM**, Rayburn WF, Smith CV. Patterns of uterine activity after intravaginal prostaglandin E2 during preinduction cervical ripening. *Am J Obstet Gynecol* 1991;**165**:1006–9.
27 **Egarter CH**, Husslein PW, Rayburn WF. Uterine hyperstimulation after low-dose prostaglandin E2 therapy: tocolytic treatment in 181 cases. *Am J Obstet Gynecol* 1990;**163**:794–6.
28 **Keirse MJNC**, van Oppen ACC. Comparison of prostaglandins and oxytocin for inducing labour. In: Chalmers I, Enkin M, Keirse MJNC, eds. *Effective care in pregnancy and child birth*. Oxford: Oxford University Press, 1989:1080–111.
29 **Mackenzie IZ**. Previous caesarean section and labour induction with PGE2. In: Egarter C, Husslein P, eds. Prostaglandins for cervical ripening and/or induction of labour. *Vienna Facultas Universtatsverlag* 1988:53–7.
30 **Vause S**, Macintosh M. Use of prostaglandins to induce labour in women with a caesarean section scar. *BMJ* 1999;**318**:1056–8.
31 **Doe S**, Woods B, Perks AM. Effects of norepinephrine on lung liquid production by in vitro lungs from guinea pigs. *Can J Physiol Pharmacol* 1998;**76**:967–74.
32 **Woods BA**, Doe S, Perks AM. Effects of epinephrine on lung liquid production by in vitro lungs from fetal guinea pigs. *Can J Physiol Pharmacol* 1997;**75**:772–80.
33 **Hata T**, Manabe A, Makihara K, *et al*. Plasma catecholamines and Doppler-derived cardiac time intervals in vaginally and cesarean delivered neonates. *Gynecol Obstet Invest* 1997;**44**:173–6.
34 **Berger PJ**, Kyriakides MA, Smolich JJ, *et al*. Influence of prenatal adrenaline infusion on arterial blood gases after caesarean delivery in the lamb. *J Physiol* 2000;**527**:377–85.
35 **Hook B**, Kiwi R, Amini SB, *et al*. Neonatal morbidity after elective repeat cesarean section and trial of labour. *Pediatrics* 1997;**100**:348–53.
36 **Shrivastava A**, Al-Shinewi D, Hutchings A. Significance of mode of delivery in relation to neonatal respiratory morbidity [abstract]. *Arch Dis Child* 1999;**A30**(suppl 1):G62.