Topical prostaglandin \( E_2 \) gel for cervical ripening and closure of the ductus arteriosus in the newborn

R Y T Sung, J A Yin, E P L Loong, T F Fok, J Lau

Abstract

The closure time of the ductus arteriosus was investigated in 29 full term babies born vaginally after induction with prostaglandin \( E_2 \) and in 22 controls. Serial Doppler echocardiography studies showed a significantly prolonged closure time in babies induced by prostaglandin \( E_2 \). Whether the difference is related to changes in fetal prostaglandin \( E_2 \) concentration remains to be established.

In sheep prostaglandin \( E_2 \) given intravenously to the ewe can gain access to the fetus and cause fetal hypertension and vasoconstriction of the fetal renal, placental membrane, and umbilical circulations.\(^1\) In pregnant woman local instillation of prostaglandin \( E_2 \) is being increasingly used to ripen the cervix before induction of labour. It is desirable therefore to find out whether vaginal administration of prostaglandin \( E_2 \) affects haemodynamic function in the fetus during the perinatal period. This study reports maternal and fetal blood concentrations of prostaglandin \( E_2 \) after local application, and compares the closure times of the ductus arteriosus in babies born after induction of labour with prostaglandin \( E_2 \) with those in a control group born by spontaneous delivery.

Patients and methods

Fifty one babies born at full term by vaginal delivery were studied. Twenty nine babies (mean (SD) gestational age 39:86 (1:66) weeks) were born to mothers who had received a 3 mg prostaglandin \( E_2 \) pessary (Upjohn) to ripen the cervix before induction of labour. Twenty two babies (mean (SD) gestational age 39:82 (1:14) weeks) whose mothers did not receive prostaglandin \( E_2 \) acted as controls.

DETERMINATION OF DUCTAL CLOSURE TIME

Serial Doppler echocardiography studies were done with an Aloka SSD-280S ultrasound scanner within 12 hours of birth, then twice daily at intervals of about 12 hours until ductal shunting could no longer be detected.\(^2\)

MEASUREMENT OF MATERNAL AND CORD PROSTAGLANDIN \( E_2 \) CONCENTRATIONS

Cord blood was drawn from the umbilical vein immediately after clamping and cutting of the cord, and before placental separation. Paired maternal venous blood samples were collected at the same time. The samples were then transferred into prechilled polypropylene tubes containing EDTA and indomethacin, and cen-
Concentrations of prostaglandin E2 in maternal and cord blood in patients treated with prostaglandin E2 and controls

<table>
<thead>
<tr>
<th>Group treated with prostaglandin E2</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of samples</td>
<td>Mean (SD) concentration (pg/ml)</td>
</tr>
<tr>
<td>Maternal blood</td>
<td>23</td>
</tr>
<tr>
<td>Cord blood</td>
<td>20</td>
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</tbody>
</table>

There was no significant difference between the groups.

...trifuged immediately at 2000 g for 15 minutes at 4°C. Plasma was separated and stored in aliquots at −70°C until assay. A commercial kit for the measurement of prostaglandin E2 by radioimmunoassay (Amersham) was used.3

STATISTICAL METHODS
Because the exact time of closure of each ductus arteriosus was not known, a generalised Kaplan–Meier method was applied to compare the times between the study and control groups.4 The prostaglandin E2 concentrations of the mother and cord blood in the study and control groups were compared by Student’s t-test. Multiple logistic regression analysis was used to calculate whether cord blood concentrations of prostaglandin E2 and birth weight were factors affecting ductal closure time.

Results
Mean birth weights of the treatment and control groups were similar, being 3246 g (range 2500–4200) and 3317 g (range 2150–4500), respectively. The mean time interval between application of the gel and delivery was 13 hours (range 3 to 28).

CLOSURE TIME OF THE DUCTUS ARTERIOSUS
In the treated group half of the ductus arteriosuses closed at 28 hours compared with 15 hours in the controls. The difference was significant (p<0.05).

PROSTAGLANDIN E2 CONCENTRATIONS IN BLOOD
The results are shown in the table. There were no significant differences in the prostaglandin E2 concentrations between the control and treatment groups either in maternal or cord blood. No correlation between the maternal and cord blood concentrations was seen in the control group, but a significant correlation was noted in the treatment group (r²=0.39, p=0.03).

Multiple logistic regression analysis showed that birth weight and cord blood prostaglandin E2 concentration are not significant variables when predicting whether the closure time of the ductus arteriosus would be shorter or longer than 24 hours (p values 0·06 and 0·21, respectively).

Discussion
The results of this study show that there was delay in closure time of the ductus arteriosus in newborn babies whose mothers had had prostaglandin E2 pessaries for ripening of the cervix before the onset of labour. No clinical problems resulted, however. Whether delayed ductal closure also occurs in premature babies whose mothers are given prostaglandin E2 deserves further investigation, especially as patent ductus arteriosus causes so many problems in preterm babies.

Maternal and cord blood concentrations of prostaglandin E2 were, unexpectedly, not significantly higher in the treated group, but this might be because of the time that the blood was sampled. It has been reported that after vaginal administration of 3 mg prostaglandin E2 in patients during weeks 9–14 of pregnancy, peak plasma concentrations of between 3500 and 10 000 pg/ml were observed three to six hours after the start of treatment; these returned to normal after 10 hours.5 Whether the same dose of prostaglandin E2 given to pregnant women at full term results in similar plasma concentrations is unknown. The low maternal and cord blood concentrations in our study, however, may be related to the interval between application of the gel and delivery (about 13 hours). Repeated maternal and fetal blood sampling at a predetermined time after the prostaglandin E2 has been given may shed light on the relation between maternal and fetal blood concentrations.

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