

Fetal and neonatal prostacyclin and thromboxane in relation to mode of delivery

O YLIKORKALA, M POHJAVUORI, AND L ROVAMO

Departments of Obstetrics and Gynaecology and Pediatrics, University of Helsinki, Helsinki, Finland

SUMMARY To study whether prostacyclin and thromboxane A₂ might play a role in neonatal adaptation pieces of the umbilical arteries of infants born vaginally (n=18) or by elective caesarean section (n=11) were superfused in vitro and the release of 6-keto-PGF_{1a} (hydration product of prostacyclin) and thromboxane B₂ (metabolite of thromboxane A₂) measured by radioimmunoassay. In addition, the capacity of fetal platelets to produce thromboxane A₂ and the neonatal urinary concentrations of 6-keto-PGF_{1a} were measured. Infants born by caesarean section had lower diastolic blood pressure, higher heart rate, and smaller differences between rectal and skin temperature compared with infants born vaginally during the first two hours of life. The only difference encountered in the prostanoids between the groups was reduced urinary excretion of 6-keto-PGF_{1a} in infants born by caesarean section, whose release of 6-keto-PGF_{1a} by the umbilical artery was positively correlated with heart rate, respiration frequency, and dermal temperature. Thus prostacyclin may be a regulatory determinant, particularly in infants born by caesarean section.

Although cortisol, oxytocin, vasopressin, and other hormones that behave differently in infants born vaginally and by caesarean section^{1 2} may influence neonatal adaptation, they can hardly explain all the haemodynamic differences encountered in these infants.² The fetal vascular tissues, particularly the umbilical vessels, produce both the vasodilatory prostacyclin and its endogenous antagonist, thromboxane A₂, evidently for control of fetal blood flow in utero and at birth.³⁻⁵ Thromboxane A₂ is also produced abundantly by fetal and neonatal platelets.⁶⁻⁷ No comparative data exist on prostacyclin and thromboxane A₂ in infants born vaginally and by caesarean section.

Subjects and methods

Twenty nine healthy women with uncomplicated pregnancies and their infants were studied with the approval of the committee of ethics (Table 1). The infants were healthy except for one who had an atrial and ventricular septal defect. Eighteen infants were delivered vaginally and 11 by elective caesarean section because of breech presentation or fetopelvic disproportion under epidural (nine cases) or general anaesthesia (two). The pH, oxygen and carbon dioxide tensions, and base excess from the

umbilical artery blood were measured routinely in each infant. Gestational ages at delivery, birth weights, and Apgar scores were comparable between the study groups (Table 1).

Measurement of prostacyclin. Fetal prostacyclin was measured from the specimens of the umbilical arteries, which were collected immediately after birth. Their capacity to produce prostacyclin, as assessed by its hydration product, 6-keto-PGF_{1a}, was determined in a tissue superfusion.⁸ Briefly, umbilical artery samples (10-20 mg of dry weight tissue) were perfused with Eagle's medium (pH 7.4, 37°C, carbon dioxide/oxygen: 5%/95%). After the wash out period of two and half hours a one hour fraction was collected and its content of

Table 1 *Clinical characteristics of the infants studied. Values are mean (range)*

	Group (according to mode of delivery)	
	Vaginal delivery	Caesarean section
No of infants	18	11
Gestational age (weeks)	39.9 (37-41)	39.3 (38-40)
Birth weight (g)	3611 (2550-4730)	3717 (3030-4190)
Apgar score at one minute	8.5 (7-10)	9.0 (8-10)

6-keto-PGF_{1a} was measured by radioimmunoassay. The result was expressed as nanograms of 6-keto-PGF_{1a} per minute per one gram of dry weight tissue. In this system various prostaglandin synthesis inhibitors added into the perfusion buffer inhibited dose dependently the release of 6-keto-PGF_{1a}.⁸

Production of neonatal prostacyclin was studied from the urinary concentration of 6-keto-PGF_{1a}. A 2 ml sample from the first neonatal urine was acidified to pH 3.0 with 1.0 isotonic hydrochloric acid, passed through an octadecylsilyl silica cartridge (Sep-Pak C18 Cartridges Waters Ass, Inc, Milford, Massachusetts, United States), and pre-washed successively with 5 ml of ethanol, water, and 0.1 isotonic acetic acid.⁹ The cartridge was then washed with 15% ethanol (5.0 ml) and petroleum ether (5.0 ml). The 6-keto-PGF_{1a} that had been absorbed was eluted in 2 ml of ethylacetate and evaporated to dryness under a nitrogen stream. The sample was further purified with high performance liquid chromatography (Spectra Physic M=740, Santa Clara, California, United States), utilising a Sherisorb 5 µ ODS II column (Phase Separations Ltd, Industrial Estate, Queensberry, Clwd, United Kingdom) and a mobile phase of water:acetic acid 69.95:30.0:0.05 with a flow rate 2 ml/min. The 6-keto-PGF_{1a} eluted at three minutes and separated totally from other prostanoids. The fraction containing 6-keto-PGF_{1a} was collected, evaporated to dryness, and dissolved in phosphate buffered saline with 0.1% gelatin. Two different size aliquots, both in duplicate, were taken for radioimmunoassay, as described elsewhere.¹⁰ The mean (SD) recovery of 6-keto-PGF_{1a} added into urine (200–400 pg/ml) was 79.6 (8.9)% (n=10) and the interassay variation was 10.8% (n=10) after the whole procedure.

Measurement of fetal thromboxane. The fetal vascular production of thromboxane A₂ was measured as thromboxane B₂ (a metabolite of thromboxane A₂) released from the superfused umbilical artery.⁸ This was possible because the thromboxane B₂ antibody did not crossreact significantly (only 0.04% at the 50% displacement level) with 6-keto-PGF_{1a}.¹¹

To study the capacity of the fetal platelets to form thromboxane A₂ mixed umbilical blood samples were collected into dry plastic tubes and allowed to clot spontaneously at 37°C for 60 minutes. Serum was then separated and its concentration of thromboxane B₂ was measured by radioimmunoassay¹¹ and expressed as nanograms of thromboxane B₂/10⁶ platelets.

Monitoring of the neonatal condition. The systolic and diastolic blood pressure (Dinamap 847), heart

and respiration rate (Hewlett-Packard, 8025 B), and rectal and heel temperature (Thermistor, Olli Product, Turku, Finland) were registered at the ages of 30, 60, 90, and 120 minutes.

Statistical analysis. The data were normally distributed and subjected to *t* tests and linear regression analysis.

Results

The infants born by caesarean section, when compared with those born vaginally, had reduced diastolic blood pressure, increased heart rate, and decreased differences between rectal and dermal

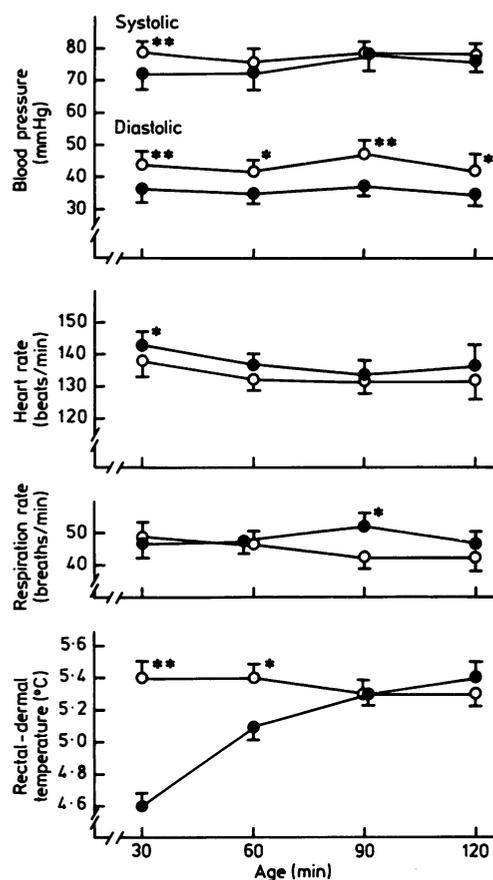


Fig. 1 Blood pressure, heart rate, respiration rate, and difference between rectal and dermal temperature in infants born vaginally (○) (n=18) and by elective caesarean section (●) (n=11). Values are mean (SE).

*=p<0.05, **=p<0.01 in comparison between the groups.

Table 2 Fetal and/or neonatal production of prostacyclin and thromboxane in infants born vaginally and by caesarean section (mean (SE) range)

Group	n=	Release from the umbilical artery (ng/g of dry weight tissue/min)		Fetal platelets' release of thromboxane B ₂ (ng/10 ⁶ platelets')	Neonatal urinary concentration of 6-keto-PGF _{1α} (pg/ml)
		6-keto-PGF _{1α}	Thromboxane B ₂		
Vaginal delivery	18	95.9 (15.1) 26.7–255.9	1.05 (0.2) 0.73–2.80	0.97 (0.21) 0.19–2.33	564.0 (120.6) 81.6–1533.7
Caesarean section	11	88.4 (10.5) 47.7–143.9	1.39 (0.27) 0.60–3.0	1.04 (0.47) 0.06–2.85	301.2 (58.3)* 75.0–611.1

*p<0.01.

temperatures at some or all recording times, although these differences were less apparent at 120 minutes of life (Fig. 1).

The production of 6-keto-PGF_{1α} by the umbilical artery ranged from 26.7 to 255.9 ng/g/min; the

highest value was found in the infant with the atrial and ventricular septal defect (Table 2). It was unrelated to the mode of delivery or the pH, oxygen and carbon dioxide tensions, and base excess in the umbilical artery in either group of infants.

In infants born by caesarean section the production of 6-keto-PGF_{1α} by the umbilical artery was related to the pulse rate, respiration frequency, and skin temperature at ages from 30 to 120 minutes (Fig. 2). No such relations were encountered in infants born vaginally.

The neonatal urinary concentration of 6-keto-PGF_{1α} was higher in infants born vaginally than in those born by caesarean section (Table 2), but no relation was seen between urinary excretion of 6-keto-PGF_{1α} and production of 6-keto-PGF_{1α} by the umbilical artery. There was no correlation between urinary 6-keto-PGF_{1α} concentrations and the neonatal variables recorded. The release of thromboxane B₂ from the superfused umbilical artery or aggregating platelets (Table 2) was also unrelated to the neonatal variables recorded.

Discussion

In this study infants born by caesarean section had lower diastolic blood pressure, higher heart rate, and increased differences between rectal and dermal temperatures than infants born vaginally. Thus in principle our data confirm the previous findings² that the mode of delivery is an important determinant in early neonatal adaptation. It was noteworthy that the differences between infants born by caesarean section and infants born vaginally were less apparent at 2 hours of age. Thus in theory they were possibly caused by changes in prostacyclin or thromboxane A₂, or both, which are shortacting potent compounds produced instantly at the site of their action.

We studied the production of prostacyclin from the release of 6-keto-PGF_{1α} by the umbilical artery. This presumably reflects the early neonatal vascular prostacyclin capacity as well, although no definitive

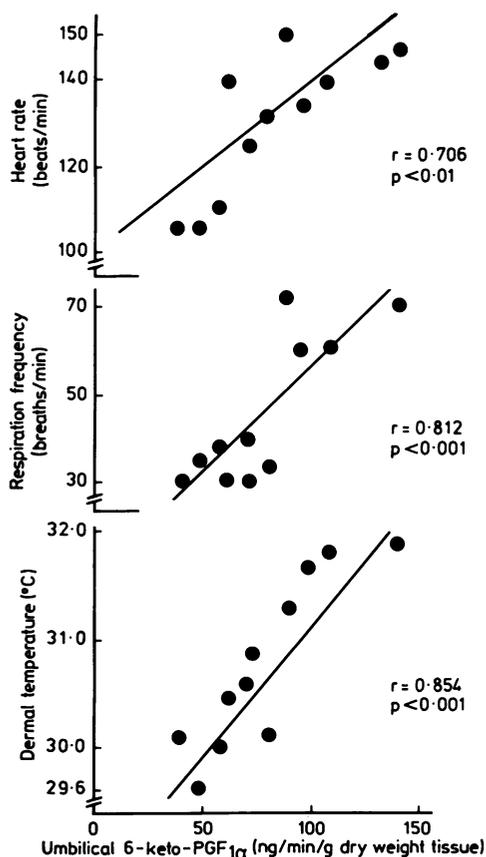


Fig. 2 Relations between production of 6-keto-PGF_{1α} by the umbilical artery and heart rate, respiration frequency, and dermal temperature at one hour of age in 11 infants born by caesarean section.

proof exists in this matter. In addition, neonatal prostacyclin was studied from the urinary concentrations of 6-keto-PGF_{1a}. Although the precise origins of the urinary 6-keto-PGF_{1a} (systemic vascular bed, kidneys) are unknown, the urinary 6-keto-PGF_{1a} is taken as a reliable index of in vivo synthesis of prostacyclin.¹²⁻¹⁶ Its excretion is increased in preterm infants¹² and in infants with respiratory distress syndrome¹³ who also have raised 6-keto-PGF_{1a} concentrations in plasma.¹⁷ The synthesis of thromboxane A₂ was studied both in the umbilical artery wall and platelets. It is known that this synthesis by the fetal/neonatal platelets can be reduced in infants with bleeding disorders⁶ or birth asphyxia.¹⁸ These complications were not seen in our study. Moreover, no conclusive data exist to propose that epidural analgesia, which was mainly employed for caesarean section, could have any effect on prostacyclin or thromboxane A₂, or both, in our study.

In this work we studied the production of prostacyclin and thromboxane A₂ in infants, all except one of whom were healthy, born vaginally or by caesarean section who differed in regard to the diastolic blood pressure, heart rate, and differences between rectal and dermal temperatures. In theory these differences could be results of increased production of prostacyclin or decreased production of thromboxane A₂, or both, in infants born by caesarean section. These infants, however, had decreased production of prostacyclin as seen from reduced urinary 6-keto-PGF_{1a} in this and a previous study.¹⁹ Thus it is possible that various hormones^{1,2} rather than prostacyclin and thromboxane A₂ account for the differences in the blood pressure and heart rate between infants born vaginally and by caesarean section.

One of the most interesting findings of the present work was the significant relations between the production of 6-keto-PGF_{1a} by the umbilical artery and neonatal heart rate, respiration rate, and skin temperature. It was curious that these relations were seen only in infants born by caesarean section. One explanation may stem from the fact that labour is accompanied, primarily or secondarily, by increased synthesis of various prostanoids in the fetoplacental tissue,¹ including prostacyclin,³ as reflected in this study by an increased neonatal urinary 6-keto-PGF_{1a}. Thus the release of 6-keto-PGF_{1a} by the umbilical artery may illustrate the inherent vascular prostacyclin capacity more reliably in infants born by caesarean section than in infants born vaginally. This capacity seems to be of importance in the neonatal regulation of the heart rate, respiration frequency, and temperature, as evident from the present data. It was also of interest that the infant with the atrial and ventricular septal defect had the

highest production of 6-keto-PGF_{1a} by the umbilical artery but normal production of thromboxane A₂. This might imply that an excessive amount of prostacyclin has been needed to guarantee the adequacy of the peripheral blood flow in this fetus.

In conclusion, the fetal and/or neonatal prostacyclin and thromboxane A₂ can hardly explain the haemodynamic and other differences between infants born vaginally and by caesarean section. Nevertheless, the vascular prostacyclin capacity may be an important determinant in the regulation of the neonatal heart rate, respiration frequency, and body temperature, at least in infants born by caesarean section.

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Correspondence to Dr O Ylikorkala, Department of Obstetrics and Gynaecology, University of Helsinki, Haartmaninkatu 2, SF-00290 Helsinki, Finland.

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