

Prostaglandins during pregnancy and the perinatal period

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Introduction

Administration of prostaglandins (PGs) E-2 and F-2 α will provoke contractions of the human uterus at any stage of pregnancy. The use of these compounds for the induction both of labour at term and of abortion is now widespread and well documented (Bygdeman, 1980). Recently, it has been found that PGs can effect cervical ripening and this property is being put to good clinical advantage (Bygdeman, 1980). There is evidence also that prostaglandin synthetase inhibitors (PGSI) can inhibit uterine contractions in pregnant and non-pregnant women (Wiqvist, 1979). Unfortunately, the therapeutic potential of PGSI, as a treatment for pre-term labour, is drastically reduced by the adverse side effect (now well documented) of closure of the ductus arteriosus *in utero*, after transplacental passage of the drug, leading to primary pulmonary hypertension of the newborn. The occurrence of this phenomenon is consistent with results from studies using experimental animals, strongly suggesting that PGE maintains the patency of the ductus arteriosus *in utero* (Coceani, Olley & Bodach, 1976).

There is, therefore, much evidence that PGs probably play a major part in physiological processes associated with pregnancy and parturition. The present paper describes the trends in prostanoid (prostaglandin-like) concentrations in the maternal, fetal and neonatal circulations as well as in amniotic fluid during pregnancy and the events surrounding delivery of the baby. The potential sources of prostanoids at this time are also considered.

Prostanoids in the maternal circulation

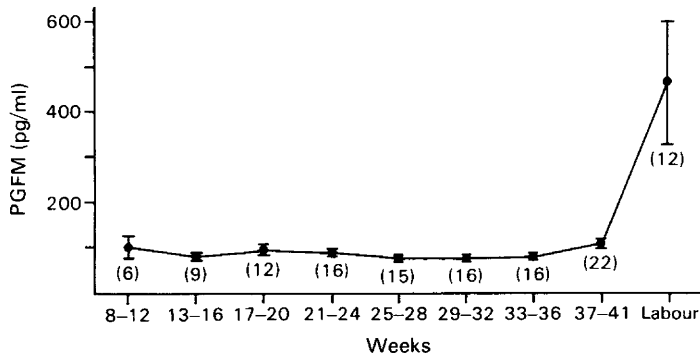
Reliable measurements of PGE-2 and PGF-2 α in peripheral plasma are difficult to obtain because of the low endogenous concentrations present and the ability of platelets to synthesize PGs. 13,14-Dihydro-15-keto-PGF (PGFM) is a major metabolite of PGF which circulates in 10–30-fold higher concentrations than PGF and is not formed by platelets: hence its measurement in peripheral plasma provides a more reliable monitor of PG production (Samuelsson, 1973). The measurement of 13,14-dihydro-15-keto-PGE remains technically difficult due to its instability in aqueous media (Mitchell, Sors & Flint, 1977).

Labour is without effect on circulating levels of PGE and PGF, although PGFM values rise progressively (Mitchell *et al.*, 1978b) (Table 1), suggesting that the lungs (and other organs) can metabolize the increasing quantities of E and F PGs secreted by the uterus during labour as reflected by elevated PGFM levels. Raised levels of PGFM in labour had been noted previously in a smaller study (Gr en, Bygdeman, Toppozada & Wiqvist, 1974) and little change in concentrations could be found before labour. Recent work (unpublished observations) has confirmed the latter finding (Text-fig. 1) in a group of 16 women who gave blood at monthly

Table 1. Concentrations of prostaglandins (mean \pm s.e.m., $n = 5-13$) in plasma samples from patients during late pregnancy (>34 weeks gestation), early labour (cervix ≤ 4 cm dilated) and late labour (cervix 5–8 cm dilated)

Prostaglandin	Plasma conc. (pg/ml)		
	Late pregnancy	Early labour	Late labour
PGE	4.8 \pm 1.0	6.8 \pm 1.5	5.4 \pm 2.2
PGF	6.2 \pm 0.5	7.9 \pm 0.7	12.4 \pm 3.5
13,14-Dihydro-15-keto-PGF	59.0 \pm 7.8	142.0 \pm 32.3	282.7 \pm 55.3

After Mitchell *et al.*, 1980.



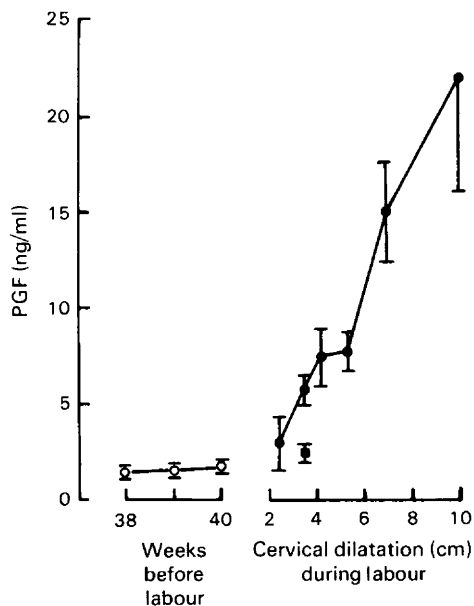
Text-fig. 1. Peripheral plasma concentrations (mean \pm s.e.m., no. of samples in parentheses) of 13,14-dihydro-15-keto-PGF (PGFM) in 16 women throughout pregnancy and in labour.

intervals throughout most of their pregnancies and were delivered of live, healthy infants at term. Measurements of PGFM, 6-keto-prostaglandin F-1 α (6-keto-PGF-1 α , the hydrolysis product of prostacyclin) and thromboxane (TX) B-2 (the degradation product of TXA-2) revealed no trend in their circulating concentrations during gestation, or indeed of TXB-2 and 6-keto-PGF-1 α , with labour. In labour, therefore, it appears that there is a redistribution in the flow through different prostanoid pathways favouring PGF (and PGE).

Prostanoids in amniotic fluid

Measurements of prostanoids in amniotic fluid may provide a better reflection of uterine prostanoid production than measurements in maternal plasma and are relatively reliable since amniotic fluid does not contain significant prostanoid synthesizing or metabolizing activities (Turnbull *et al.*, 1977). There are no changes in the levels of the various prostanoids that have been studied in amniotic fluid during late gestation. The concentrations of PGE, PGF, PGFM and arachidonic acid are all higher in amniotic fluid during labour than before labour and increase progressively with labour, correlating with cervical dilatation (Keirse, 1979) (see Text-fig. 2). These findings demonstrate that labour is associated with an overall increase in the rate of prostanoid production and again suggest the introduction of a bias towards the secretion of PGE and PGF.

Measurements in amniotic fluid also provided the first indication that amniotomy rapidly increases PG secretion within the uterus, since concentrations of PGF and PGFM are higher in amniotic fluid collected at amniotomy than in liquor obtained by amniocentesis (Turnbull *et al.*, 1977) (Text-fig. 3). This rapid enhancement of PG secretion by amniotomy is reflected in

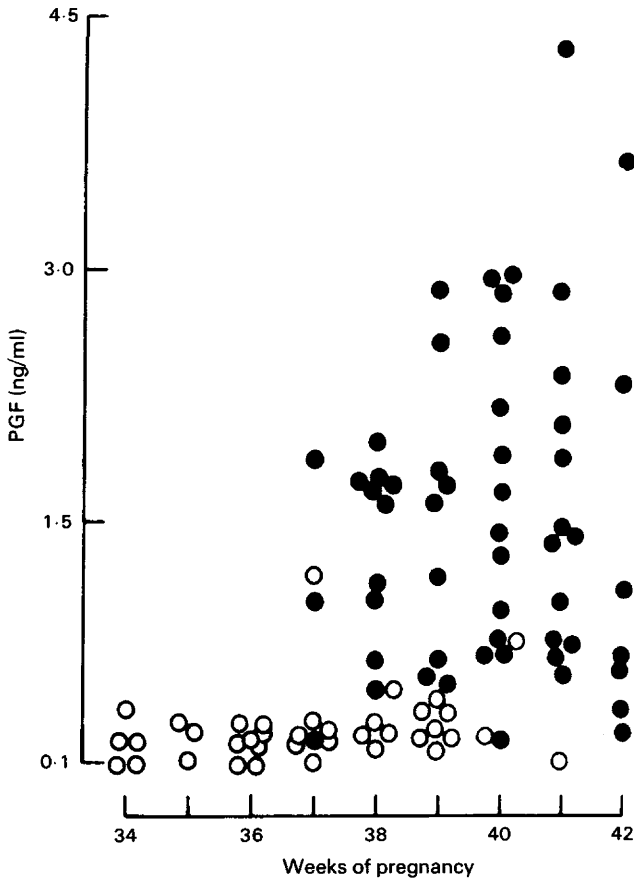


Text-fig. 2. Concentrations of PGF (mean \pm s.e.m.) in amniotic fluid obtained by amniotomy before the onset of labour (○) and during spontaneous (●) and oxytocin-induced (■) labour. (After Keirse, 1979.)

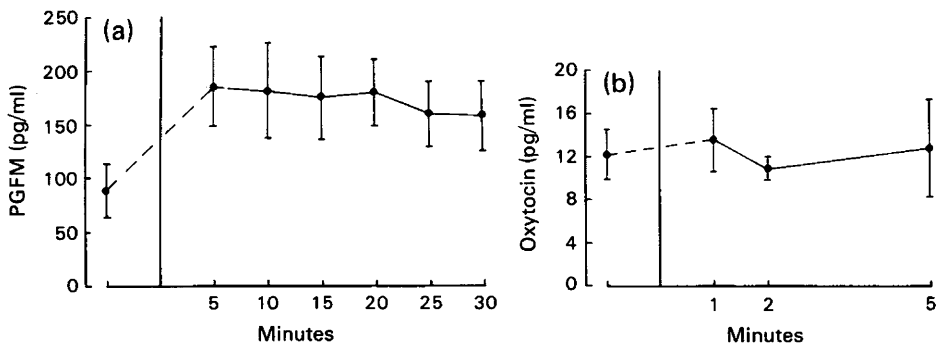
circulating levels of PGFM which are significantly raised within 5 min of amniotomy or vaginal examination at term (Turnbull *et al.*, 1980) and remain elevated for at least 30 min (Sellers, Hodgson, Mitchell, Anderson & Turnbull, 1980) (Text-fig. 4a). The rapidity of the increase in PG levels and especially their appearance in amniotic fluid led to the suggestion that there is a local control of PG synthesis within the uterus. Consistent with this hypothesis are the facts that amniotomy in women at term does not result in oxytocin secretion (Sellers *et al.*, 1980) (Text-fig. 4b) and that epidural anaesthesia is without effect on the PG response to amniotomy (Mitchell, Bibby, Forsling, Anderson & Turnbull, 1978a). Hence the mechanism that has been demonstrated in late pregnant sheep (Flint, Forsling, Mitchell & Turnbull, 1975), whereby oxytocin released in response to vaginal and cervical stimulation causes PG secretion by the uterus, is not operative in women at term.

Potential sources of prostanoids

The origin of the raised levels of PGs in both amniotic fluid and peripheral plasma during labour remains controversial. Decidua, fetal membranes and myometrium have all been suggested as possible sources (see Keirse, 1979). However, measurements of tissue concentrations of PGs should be judged cautiously, since trauma is a potent stimulus to PG secretion (Piper & Vane, 1971). For this reason we have developed a method of tissue superfusion which allows PG production *in vitro* to be determined under steady state conditions. Using this methodology it has been demonstrated that the amnion is a major source (per unit weight) of PGE but that the rate of production of PGE by amnion does not appear to be enhanced during labour (Turnbull *et al.*, 1980) (Table 2). Chorion, decidua and placenta all produce PGs although only the rate of production of 6-keto-PGF-1 α by amnion is significantly greater after labour (Table 2). It is possible, therefore, that prostacyclin plays a part in the onset or progression of labour; whether its role is merely permissive is uncertain. Nevertheless, prostacyclin can potentiate the action of



Text-fig. 3. Concentrations of PGF in amniotic fluid obtained by (○) amniocentesis and by (●) amniotomy before the onset of labour. (From Turnbull *et al.*, 1980.)



Text-fig. 4. Peripheral plasma concentrations (mean \pm s.e.m., $n = 6$) of (a) PGFM and (b) oxytocin before and after amniotomy (vertical line). (From Sellers *et al.*, 1980.)

oxytocin on the rat uterus *in vivo* (Williams, El-Tahir & Marcinkiewicz, 1979) and perhaps a similar action in women may provide a role for prostacyclin in the mechanism of labour. Certainly the high rates of production of prostanoids by amnion are consistent with the

suggestion that the trigger for the onset of human labour may reside in the fetal membranes and be prostaglandin in nature (Liggins, Forster, Grieves & Schwartz, 1977).

Table 2. Production of prostanoids (ng/g dry wt per min) by pregnant human intrauterine tissues superfused *in vitro*

Tissues		Decidua	Placenta	Chorion	Amnion
Elective Caesarean section	PGE	2.50 ± 0.57	2.84 ± 0.47	3.13 ± 0.59	9.62 ± 1.62
	PGF	0.80 ± 0.25	0.82 ± 0.24	0.76 ± 0.20	0.74 ± 0.19
	TXB-2	2.76 ± 1.09	4.84 ± 1.05	0.88 ± 0.26	2.42 ± 0.79
	6KF-1 α	1.41 ± 0.38	1.11 ± 0.21	1.76 ± 0.40	2.37 ± 0.65
Spontaneous vaginal delivery	PGE	1.72 ± 0.24	2.02 ± 0.38	2.89 ± 0.46	13.17 ± 2.21
	PGF	0.49 ± 0.09	0.66 ± 0.13	0.51 ± 0.12	0.83 ± 0.19
	TXB-2	2.13 ± 0.38	4.94 ± 0.39	0.61 ± 0.19	1.59 ± 0.37
	6KF-1 α	1.46 ± 0.43	1.33 ± 0.39	2.43 ± 0.64	6.31 ± 2.40

Values are means \pm s.e.m. of 10 individual determinations.

There has been great interest in the possible role of PGs in cervical softening, effacement and dilatation. In a study of the potential of the human cervix to produce prostanoids (Ellwood, Mitchell, Anderson & Turnbull, 1980), tissues obtained during the first trimester of pregnancy produced PGE, PGF, PGFM and 6-keto-PGF-1 α but minimal TXB-2. Preliminary evidence from experiments on tissues taken at Caesarean hysterectomy during the third trimester of pregnancy suggested that the cervix may exhibit an enhanced rate of prostanoid production with labour (Text-fig. 5). Hence it is possible that the cervix may produce prostanoids *in vivo* which could act locally during pregnancy and parturition and perhaps contribute to the change in cervical state during labour (Ellwood *et al.* 1979).

A further potential source of PGs is the umbilical cord and in particular the umbilical vessels (Tuvemo, Strandberg, Hamberg & Samuelsson, 1976; Mitchell, Sellers, Jamieson & Turnbull, 1980). The major PGs produced by the umbilical vessels are PGE and 6-keto-PGF-1 α (Table 3). Since PGE contracts and prostacyclin dilates umbilical vessels it is possible that their respective rates of intra-mural production regulate the tone of the vessels and that alterations in the ratio of their production rates may contribute to closure at birth.

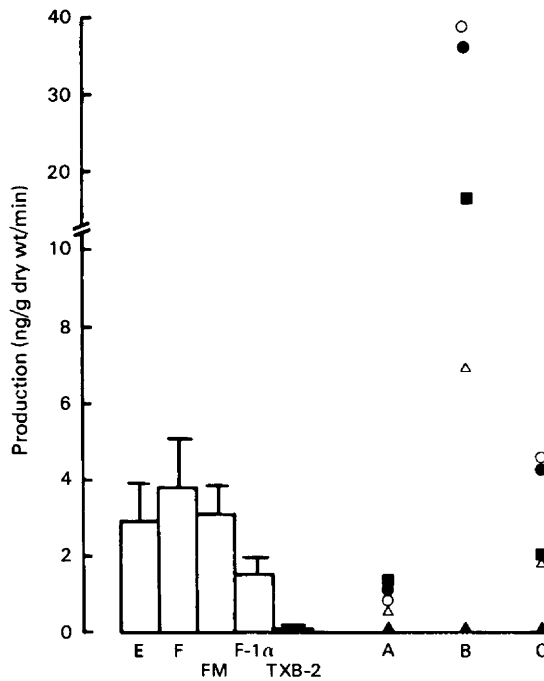
Table 3. Prostanoid production by umbilical tissue and vessels (data from Mitchell *et al.*, 1980a)

Tissue	Prostanoid production (ng/g dry wt/min)				
	PGE-2	PGF-2 α	PGFM	TXB-2	6-Keto-PGF-1 α
Amniotic epithelium	4.67 ± 1.59	0.89 ± 0.29	0.39 ± 0.25	0.17 ± 0.11	1.65 ± 0.45
Artery	4.62 ± 1.08	1.87 ± 0.70	0.21 ± 0.06	0.11 ± 0.05	11.9 ± 2.56
Vein	3.61 ± 1.18	1.45 ± 0.29	0.34 ± 0.13	0.27 ± 0.23	10.07 ± 0.96

Values are mean \pm s.e.m. for 7 samples.

Prostanoids in the fetal and neonatal circulations

Investigations of circulating PGs in the human fetus have been limited, until recently, to measurements in umbilical plasma. The development of fetoscopy may soon lead to a greater knowledge of PGs in the fetal circulation early in pregnancy (see MacKenzie, MacLean & Mitchell, 1980). Concentrations of PGE, PGF and PGFM in umbilical plasma are greater than those in maternal plasma (Turnbull *et al.*, 1980). Higher concentrations of these three PGs are



Text-fig. 5. The rates of production of prostanoids by cervical tissues obtained from 3 patients in the third trimester of pregnancy are shown in comparison with the mean values for patients in the first trimester. Patient A, elective Caesarean section at 37 weeks gestation. Patient B, emergency Caesarean section at 34 weeks gestation, cervix 6–7 cm dilated. Patient C, emergency Caesarean section at 40 weeks gestation, cervix fully dilated. For each patient the production rates are shown for PGE (●), PGF (○), PGFM (Δ), 6-keto-PGF-1α (■) and TXB-2 (▲). (From Ellwood *et al.*, 1980.)

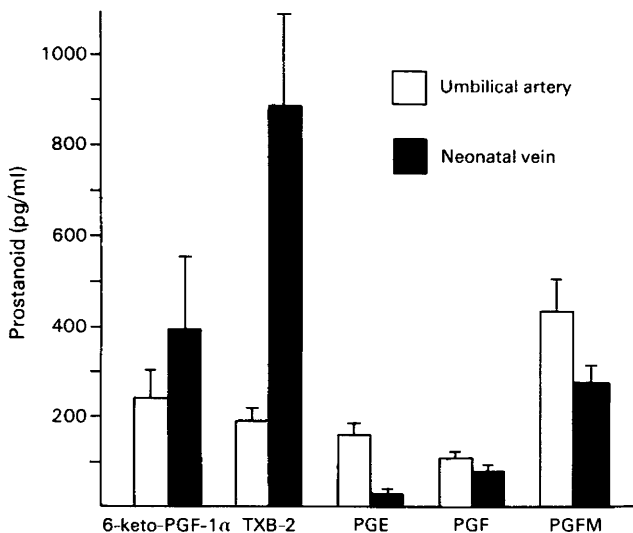
found in umbilical plasma obtained after spontaneous vaginal delivery when compared with samples taken at elective Caesarean section (Bibby *et al.*, 1979) (Table 4). A significant arterio-venous difference has been demonstrated for PGE, with raised umbilical venous concentrations, after both spontaneous vaginal delivery and elective Caesarean section. This would suggest that the placenta is an important source of PGE in the fetal circulation during late pregnancy.

Table 4. Concentrations (mean \pm s.e.m.) of prostaglandins in umbilical plasma after delivery at term

PG	Source	PG conc. (pg/ml)	
		Spontaneous labour and vaginal delivery (n = 12)	Elective Caesarean section (n = 10)
PGE	Vein	242 \pm 25	138 \pm 31
	Artery	109 \pm 27	74 \pm 20
PGF	Vein	88 \pm 11	52 \pm 6
	Artery	80 \pm 10	47 \pm 5
PGFM	Vein	631 \pm 107	193 \pm 18
	Artery	640 \pm 180	172 \pm 16

The concentrations of 6-keto-PGF-1 α and TXB-2 in umbilical plasma have also been determined. Neither 6-keto-PGF-1 α nor TXB-2 have a significant arterio-venous difference across the umbilical circulation (Mitchell, 1980). Umbilical plasma concentrations of these prostanoids exceed or are similar to circulating concentrations in the mother but the mode of delivery does not influence measured levels.

The circulating concentrations of PGE in neonates born at term are significantly reduced by the 6th day of life compared with levels at birth (Mitchell, Lucas, Etches, Brunt & Turnbull, 1978c) (Text-fig. 6). Mean concentrations of PGF and PGFM are also lower although their differences are not statistically significant. These findings are consistent with the suggestion that the placenta provides a large proportion of the PGE in the fetal circulation at birth and that removal of this source leads to a rapid decline in PGE levels circulating in the neonate. Siegler, Walker, Crouch, Christenson & Jubiz (1977) also found a fall in plasma PGE levels by 2–3 days of age; they suggested that levels then increased into adult life; but the extremely high levels of PGE measured in adult peripheral plasma in the study raise some doubts about this finding. Quite a different pattern obtains for 6-keto-PGF-1 α and TXB-2 in the perinatal period. By 6 days after vaginal delivery at term neonates have higher circulating levels of both 6-keto-PGF-1 α and TXB-2 than at birth (Text-fig. 6).

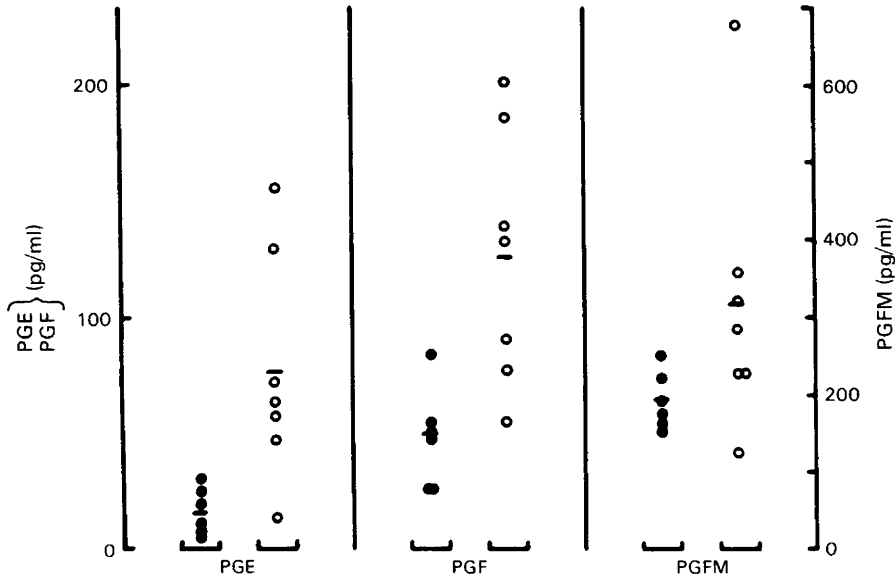


Text-fig. 6. Concentrations of prostanoids (mean \pm s.e.m., $n = 6-20$) in umbilical arterial plasma at birth and in peripheral venous plasma 6 days after birth.

Infants born pre-term (before 37 completed weeks of pregnancy) but uncomplicated by major disease, have plasma concentrations of PGE, PGF and PGFM on the 6th day of life similar to those of infants born at term. Delivery before term is not, therefore, associated with obvious differences in capacity for PG synthesis and metabolism in the neonatal period. Prostaglandin concentrations have also been monitored in the plasma of pre-term infants during the first 60 days of life (Mitchell *et al.*, 1978c). PGE levels decline to those of the adult during this period. Levels of PGF and PGFM also fall markedly but are still approximately 3-fold greater than adult levels even 2 months after birth. The more rapid decline in PGE levels may play an active or facilitatory role in the closure of the ductus arteriosus (Coceani *et al.*, 1976).

Patent ductus arteriosus (PDA) is a serious neonatal disorder. Infants born with a PDA have been shown (Lucas & Mitchell, 1978a) to have excessively high circulating concentrations of

PGE, PGF and PGFM (Text-fig. 7), the elevation in PGE levels being particularly impressive. Furthermore, falling plasma concentrations of PGF with rising levels of PGE have been reported shortly before clinical symptoms of PDA appear (Friedman & Demers, 1978; Lucas & Mitchell, 1978b). Medical management using prostaglandin synthetase inhibitors (e.g. indomethacin), whilst consistently lowering PG concentrations in the plasma, does not always result in ductal closure. Moreover, surgical ligation of the ductus arteriosus does not immediately reduce circulating PG levels. There is not, therefore, a simple inverse relationship between circulating levels of PGE and closure of the ductus arteriosus. The roles of factors such as sensitivity of the ductal tissue to various PGs and oxygen tension must be further investigated before a clearer picture can emerge.



Text-fig. 7. Peripheral plasma concentrations of prostaglandins in uncomplicated pre-term infants (●) and infants with patent ductus arteriosus (○), all investigated at 14–28 days after delivery. (After Lucas & Mitchell, 1978a.)

Friedman & Demers (1978) have suggested that neonates who develop the respiratory distress syndrome (RDS) have raised levels of PGE and PGF. The elevation of PGF far exceeded that of PGE and a significant reversal of the usual PGE to PGF ratio ensued. Our own study (Mitchell, Lucas, Whitfield, Brunt & Turnbull, 1978d) of infants with hyaline membrane disease (HMD) indicated that levels of PGE are normal although we also found significantly increased levels of PGF. Furthermore, plasma concentrations of PGFM are raised several-fold over control values and this increase is disproportionate to the increase in PGF levels (Text-fig. 8). Both studies, however, indicated that RDS (or HMD) is associated with an increase in levels of PGF which is a vasoconstrictor. Hence one may tentatively suggest that the use of a prostaglandin synthetase inhibitor may be of some benefit in this condition, although the side effects of most of the present range of these drugs would probably argue against such a treatment at present.

Final comments

There is little doubt that PGs play a significant part in the mechanisms controlling the onset and progression of labour and also probably the process of cervical ripening. Trends in the

viewpoint. In addition, it seems increasingly likely that PGs have a role in the control of fetal and placental haemodynamics and the normal and sometimes pathological alterations in the fetal circulation at birth. The efficacy of PGs and inhibitors of their synthesis (PGSI) in respectively maintaining and closing a patent ductus arteriosus in neonates provides evidence for such a hypothesis. Nevertheless the clinical usefulness of PGs and PGSI can lead to unsuspected problems, e.g. PGSI given to treat pre-term labour can cross the placenta and close the ductus arteriosus *in utero*. This leads to increased pulmonary arterial pressure, enhanced development of pulmonary vascular smooth muscle and eventually to persistent pulmonary hypertension of the newborn. Wilkinson, Aynsley-Green & Mitchell (1979) have shown that this series of events can be linked to unusually low circulating levels of PGE in these neonates (Text-fig. 9). Hence a cautious attitude should be foremost when considering the vast array of possible clinical benefits that PGs and PGSI potentially provide.

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