Prostaglandins at parturition and in the neonatal infant

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In man, administration of prostaglandin E\textsubscript{1} or F\textsubscript{2\alpha} will stimulate labour and abortion (Embrey, 1971; Thiery, 1979), whereas administration of prostaglandin synthase inhibitors will delay delivery and suppress pre-term labour (Wieqvist, 1979). Measurements of prostaglandins E\textsubscript{1} and F\textsubscript{2\alpha} in peripheral plasma are hampered by the low concentrations present (Samuelsson, 1973) due to rapid clearance by the lungs and also by the problem of prostaglandin production by platelets (Smith & Wilkins, 1970). A major metabolite of prostaglandin F\textsubscript{2\alpha} is 13,14-dihydro-15-oxoprostaglandin F\textsubscript{2\alpha} (prostaglandin FM), which circulates in 10–30-fold higher concentrations, is not formed by platelets and hence is measured in peripheral plasma as a monitor of prostaglandin production (Samuelsson, 1973). Circulating concentrations of prostaglandin FM apparently increase slightly during late gestation, with a massive elevation occurring during labour (Grienen et al., 1974). Peripheral plasma concentrations of prostaglandins E\textsubscript{1} and F\textsubscript{2\alpha} do not change significantly with labour (Mitchell et al., 1978a), suggesting that the lungs have the capacity to cope with the increased production of prostaglandins at this time. It should be noted that many uterine tissues have a considerable capacity to metabolize prostaglandins, although the activity of the main enzyme concerned, 15-hydroxyprostaglandin dehydrogenase, does not alter with labour in the tissues studied (Keirse, 1978).

The discoveries of thromboxane A\textsubscript{2} (Hamberg et al., 1975) and prostacyclin (prostaglandin I\textsubscript{2}) (Moncada et al., 1976) as physiologically active metabolic products of prostaglandin endoperoxides (see Scheme 1) have necessitated investigation of their possible roles in parturition. Owing to the extreme lability of thromboxane A\textsubscript{2} and prostacyclin, measurements have been confined to their respective inactive degradation products, thromboxane B\textsubscript{2} and 6-oxoprostaglandin F\textsubscript{1\alpha}. Little change occurs in the circulating concentrations of these compounds during pregnancy and labour (Mitchell et al., 1978a; M. D. Mitchell, unpublished work).

Amniotic fluid may provide a better reflection of uterine prostaglandin production, and, since it contains negligible prostaglandin-synthesizing and -metabolizing activities, it has been the fluid of choice for measurements. The concentrations of prostaglandins E, F and FM and of arachidonic acid (the precursor fatty acid) are higher in amniotic fluid during labour than before labour, and increase rapidly as labour progresses (Keirse, 1979) (Fig. 1). Both 6-oxoprostaglandin F\textsubscript{1\alpha} and thromboxane B\textsubscript{2} exhibit similar trends in their amniotic-fluid concentrations, with higher values in labour than beforehand, but no progressive increase during labour (Turnbull et al., 1980). Taken in conjunction with previous results, these findings suggest a general enhancement of prostanoid (prostaglandin-like) production in labour, with a preferential flow through the synthetic pathways for formation of prostaglandins E\textsubscript{1} and F\textsubscript{2\alpha}.

The precise origin of the raised prostaglandin concentrations in amniotic fluid and peripheral plasma during labour remains uncertain. Decidua, foetal membranes and myometrium (Keirse, 1979) have all been postulated as possible sources. Interpretation of measurements of tissue concentrations of prostaglandins, however, must be cautious, since the trauma of amniotomy (rupture of foetal membranes) in women at term

![Graph](image-url)

Fig. 1. Concentrations of prostaglandin F (means ± S.E.M.) in amniotic fluid obtained by amniotomy before the onset of labour (O) and during spontaneous (○) and oxytocin-induced (■) labour

[After Keirse (1979).]
Scheme 1. Pathways of arachidonic acid metabolism
Before moving to a description of prostaglandins in the human fetus and neonatal infant, the following points should be noted. Studies with animals have suggested that prostaglandins (particularly prostaglandin E) play an important part in maintaining the patency of the ductus arteriosus during foetal life (Coceani et al., 1976). This area of research has gained such momentum that the use of prostaglandins and prostaglandin synthase inhibitors to manipulate the ductus in human neonatal infants is now well documented. It has also been postulated that prostaglandins are of importance in the pulmonary and renal function of the foetus and neonatal infant. Furthermore, the potent constrictor properties of most prostaglandins on the umbilical cord have led to the suggestion that cord closure is prostaglandin-dependent.

Investigations of circulating prostaglandins in the human fetus are necessarily limited to measurements in umbilical-cord plasma. It has been established that umbilical plasma concentrations of prostaglandins E, F and FM are greater than those in maternal plasma, and that higher concentrations are found in umbilical plasma obtained after spontaneous vaginal delivery when compared with samples taken at elective Caesarean section (Turnbull et al., 1980). Moreover, a significant arterio-venous difference has been demonstrated for prostaglandin E, with higher umbilical venous concentrations after either spontaneous vaginal delivery or elective Caesarean section. This suggests that the placenta is a major source of the prostaglandin E in the foetal circulation. Neither 6-oxoprostaglandin F₁₆ nor thromboxane B₂ exhibits a significant arterio-venous difference across the umbilical circulation (Mitchell et al., 1978a, 1980). Umbilical plasma concentrations of thromboxane B₂ exceed circulating concentrations in the mother, but the mode of delivery does not influence measured values. It should be noted that vessels in the umbilical cord produce a full range of prostanoids, with 6-oxoprostaglandin F₁₆ as the major quantitative product (Mitchell et al., 1980).

Infants born at term have significantly lower circulating concentrations of prostaglandin E by the sixth post-natal day compared with values at birth (Mitchell et al., 1978b). Mean concentrations of prostaglandins F and FM are also lower, although the difference is not significant. These findings are consistent with the suggestion that the placenta is a major source of prostaglandin E in the foetal circulation at birth and that severance at birth leads particularly to lowered concentrations of prostaglandin E. Infants born pre-term (before 37 completed weeks of pregnancy), but uncomplicated by major disease, exhibit similar plasma concentrations of prostaglandins E, F and FM on the sixth day of life. Hence delivery before term does not appear to be associated grossly with an altered capacity for prostaglandin synthesis or metabolism during early neonatal life. At 2 months after delivery pre-term the plasma concentration of prostaglandin E is similar to that of the adult; those of prostaglandins F and FM are significantly lower than at birth, but remain approximately 3-fold those of adult values (Fig. 3).

Infants born with a patent ductus arteriosus have abnormally high circulating concentrations of prostaglandins E, F and FM (Lucas & Mitchell, 1978a). Furthermore, falling plasma concentrations of prostaglandin F with rising prostaglandin E concentrations have been reported shortly before clinical symptoms of patent ductus arteriosus appear (Friedman & Demers, 1978; Lucas & Mitchell, 1978b). Although medical treatment with indomethacin (a prostaglandin synthase inhibitor) consistently lowers prostaglandin concentrations in the plasma, it does not always close the ductus. Moreover,
The functional requirements of the uterine cervix change considerably in pregnancy. As the uterus grows to accommodate the developing conceptus, the cervix forms an essential mechanical barrier. This role in pregnancy is a remarkable contrast with that at delivery, when the cervix must become soft and constitute the main body of the uterus (Danforth, 1947; Rorie & Newton, 1967). Fig. 1 is an electron micrograph of sheep cervical tissue in late pregnancy that shows the organization of collagen fibrils into tight bundles at this stage of gestation. The functional transformation that the cervix undergoes late in pregnancy may lead to an 'unripe' cervix at term, which is a bad prognostic sign of a difficult labour. An understanding of the mechanisms involved in both the maintenance of structural integrity of the tissue in pregnancy and the biochemical changes underlying cervical softening at parturition would improve our ability to treat these clinical problems.

Connective-tissue changes in pregnancy and labour

The human cervix, and that of other species, is dense connective tissue and contains little smooth muscle when compared with the main body of the uterus (Danforth, 1947; Rorie & Newton, 1967). Fig. 1 is an electron micrograph of sheep cervical tissue in late pregnancy that shows the organization of collagen fibrils into tight bundles at this stage of gestation. The functional transformation that the cervix undergoes late in pregnancy may lead to an 'unripe' cervix at term, which is a bad prognostic sign of a difficult labour. An understanding of the mechanisms involved in both the maintenance of structural integrity of the tissue in pregnancy and the biochemical changes underlying cervical softening at parturition would improve our ability to treat these clinical problems.

The hormonal control of connective-tissue changes in the uterine cervix in pregnancy and at parturition

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The functional requirements of the uterine cervix change considerably in pregnancy. As the uterus grows to accommodate the developing conceptus, the cervix forms an essential mechanical barrier. This role in pregnancy is a remarkable contrast with that at delivery, when the cervix must become soft and distensible to permit cervical dilatation and passage of the fetus. Abnormalities of cervical function result in considerable obstetric problems and contribute significantly to perinatal mortality and morbidity. Softening of the tissue early in gestation may lead to 'cervical incompetence' and dilatation in the absence of uterine contractions, and failure of the normal changes later in pregnancy may lead to an 'unripe' cervix at term, which is a bad prognostic sign of a difficult labour. An understanding of the mechanisms involved in both the maintenance of structural integrity of the tissue in pregnancy and the biochemical changes underlying cervical softening at parturition would improve our ability to treat these clinical problems.

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