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New Prospects in the Control of Arachidonic Acid Metabolism in the Fetus and the Neonate

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Introduction

The human fetus exists in an environment in which there is an apparent over-abundance of prostaglandins (PGs). Neonates are also believed to contain high concentrations of PGs. Since both fetus and neonate have a significant potential for prostaglandin catabolism, it may be inferred that some benefits accrue from a prostaglandin rich environment and that prostaglandins (PGs) are serving important roles in both intrauterine and early extra uterine life. Prostaglandins are formed from non-esterified arachidonic acid by the action of cyclooxygenase (COX). Arachidonic acid may be metabolized also by way of lipoxygenase enzyme pathways. Products of this pathway are known to modulate prostaglandin biosynthesis. Little information is available concerning these pathways in fetal and neonatal tissues. In this review the results of studies designed to evaluate arachidonic acid metabolism in the fetus and neonate are described. In addition, arachidonic acid metabolism in uterine and intrauterine tissues is also considered, since the products of such metabolism are important for normal fetal growth and development.

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Concentrations of prostanoids in fetal and neonate plasma

Fetal circulation

Information on the concentrations of hormones in the plasma of human fetuses has been limited to measurements in umbilical plasma obtained at delivery. Recently, however, prostaglandin concentrations have been determined in blood samples obtained by fetoscopy, at 16-20 weeks of gestation. The prostaglandins measured in the study were PGE_2 and 6-keto-PGF_1 alpha, the non-enzymatically formed product of prostacyclin degradation. Concentrations of these prostaglandins in fetal plasma are found to be greater than in maternal peripheral plasma (Johson ***et al.***, 1936).

In a recent study a dual perfused human placental cotyledon preparation was used to examine the production, transfer from maternal to fetal circulation and metabolism of potent vasoactive and myometrial stimulants. PGE2 output was higher than PGF2 and concentrations of PGE2 and PGF2 metabolites were greater in both fetal and maternal outputs when compared with primary prostaglandins (Greystoke ***et al.***, 2000). Strikingly, the concentrations of 6-keto-PGF_1 alpha in fetal plasma are manifold greater than concentrations in the maternal circulation. These findings are suggestive that prostacyclin may serve an important role in the fetus during early pregnancy. Whether prostacyclin circulating in the fetus is influencing fetal organogenesis or is exerting a tonic effect on the placental vascular bed is uncertain. Prostacyclin inhibits platelet aggregation and also is a highly active vasodilatory agent (Moncada ***et al.***, 1976). Prostacyclin circulating in the fetus may be a part of a biological protection mechanism for the fetus. Prostanoids, the products of COX pathway appear to be important regulators of blood flow in neonates. It has been demonstrated that COX activity in cultured endothelial cells in micro vessels from autopsy specimens of neonatal human cerebral cortex and cerebellum(22-26 week gestational age) resulting in production of vasodilator prostanoids, prostacyclin(6-keto-PGF_1 alpha) and PGE2 from Arachidonic acid (Parfenova ***et al.***, 2002).

Umbilical circulation

Concentrations of PGE_2, PGF_2 alpha and 13, 14-dihydro-15-keto-PGF_2 alpha (PGFM; the major circulating metabolite of PGF_2 alpha) in umbilical plasma are greater than in maternal plasma (Craft ***et al.***, 1973). On the other hand, maternal and fetal plasma concentrations of 6-keto-PGF_1 alpha and thromboxane B_2 (TXB_2, the degradation product formed from TXA_2) are similar (Mitchell ***et al.***, 1980). Concentrations of PGE, PGF and PGFM are all significantly raised in umbilical plasma obtained after the onset of labour (Mitchell ***et al.***, 1978); indicating that labour is a stimulus to prostaglandin production by the fetal placental unit. Umbilical plasma concentration of 6-keto-PGF_1 alpha and TXB_2, however, are unaffected by labor. A significant arterio-venous difference exists across the umbilical circulation for PGE_2 with higher concentrations in venous plasma. This arterio-venous difference exists both before and after the onset of labour. In normal ovine pregnancy arterial levels of PGI2 are increased, which may in part reflect increased uteroplacental production. Moreover the gravid ovine uterus also appears to produce PGE2 and metabolize PGF2 alpha. (Maqness ***et al.***, 1990) Similar arterio-venous plasma differences cannot be demonstrated for PGF, PGFM, 6-keto-$PGF_1\alpha$ or TXB_2. The finding that PGE concentrations are

higher in umbilical venous blood than in umbilical arterial blood has been considered as suggestive that PGE in the fetal circulation is, at least partly, placental in origin.

The elegant studies of (Starling and Elliot, 1974) have clearly indicated that PGE maintains the patency for the ductus arteriosus in utero in experimental animals and this is likely the case in the human fetus. Later studies by the same authors suggest that the sensitivity of ductus arteriousus to PGE2 is decreased by oxygen exposure. Cytochrome P450 affect the patency by causing constriction of the ductus arteriosus, as inhibitors of cytochrome P450 cause ductus to relax (Olley and Coceani, 1987). Hence, the high PGE concentration in the umbilical circulation at birth reflects an intra-uterine environment in which patency of the ductus arteriosus would be maintained with PGE being dominant over PGF. Hammerman's study suggests that increased synthesis and/release of prostacyclin possibly mediated by hypoxia of the cyanotic ductal dependent lesion contributes to persistent patency of ductus arteriosus. (Hammerman ***et al.***, 1987) Needleman ***et al.***, (Needleman, 1981) have raised the possibility that products of arachidonate lipoxygenase may play a part in the mechanism of ductal closure. However, (Coceani ***et al.***, 1982) do not agree and have provided the evidence that lipoxygenase derived products of arachidonic acid do not play a role in closure of the ductus arteriosus.

Neonatal circulation

The first report describing plasma prostaglandin levels in the neonatal period came from (Siegler ***et al.***, 1977) who measured PGE in cord blood after term delivery and in peripheral plasma at 2-3 days of age and throughout childhood. The plasma level of PGE was found to be significantly lower at 2-3 days of age compared with values in cord blood but then was increased continuously thereafter until adult life. The authors speculated that low levels of PGE may reflect functional peculiarities of the immature kidney. These results must be interpreted with caution since the adult plasma levels of PGE described were approximately ten-fold greater than accepted values. In a study of the possible relationship between prostaglandin and respiratory distress syndrome (Friedman and Demers, 1978) measured plasma levels of PGE and PGF in a control group of infants over the first ten days of life following preterm delivery. No difference was found in circulating levels of either PGE or PGF between the first and tenth day after delivery. These authors did not comment on the sustained high levels of PGE and PGF during the period of ductal closure, when enhanced prostaglandin catabolism would be expected.

Using radioimmunoassay (Mitchell ***et al.***, 1978) techniques, it has been found that circulating concentrations of PGE in neonates born at term are significantly reduced by the sixth day of extra uterine life compared with levels at birth (Mitchell ***et al.***, 1978). Mean concentration of PGF and PGFM also are lowered in the first week of life. Quite a different pattern appears for circulating concentrations of 6-keto-PGF_1 alpha and TXB_2 in the perinatal period (Mitchell ***et al.***, 1981). By six days neonates born at term have higher circulating levels of both 6-keto-PGF_1 alpha and TXB_2 than at birth. Infants born before term, but uncomplicated by major diseases also have plasma concentrations of PGE, PGF and PGFM on the sixth day of life similar to those infants born at term. Delivery before term is not, therefore, associated with obvious difference in capacity for prostaglandin biosynthesis or metabolism in the neonatal period. It has been found that

prostaglandin concentrations in the plasma of pre-term infants are raised above those of adults for at least 60 days. Importantly, concentrations of PGE in neonatal plasma decline more rapidly than concentrations of other prostaglandins and this reduction may play an active or facilitatory role in closure of the ductus arteriosus. It should be noted that prostacyclin and TXA_2 have little action on the ductus arteriosus. COX1 and COX2 develop unevenly in the ductus while both enzymes contribute to PGE2 formation at term, COX1 is the major isoform in the premature. COX2, however, may acquire greater importance before-term following physiological & pathophysiological stimuli (Coceani ***et al.***, 2001). Vasodilator prostaglandins PGE2 and PGI2 increase steadily during pregnancy while TX A2, a potent vasoconstrictor remains low during pregnancy and increases shortly before delivery helping in the closure of umbilical vessels and ductus arteriosus. In pregnancy related hypertension increase in synthesis of TxA2 occurs early during pregnancy (Reyes, 1993).

Neonatal diseases

Infants with a patent ductus arteriosus have been shown to have excessively high circulating concentrations of PGE, PGF and PGFM (Lucas and Mitchell 1978). This finding has been disputed by (Friedman and Demers, 1978) who reported that concentrations of PGF fall and levels of PGE rise shortly before the appearance of clinical symptoms of patent ductus arteriosus in neonates. In another study (Lucas and Mitchell, 1978) concentrations of both PGE and PGF were found to be elevated shortly clinical symptoms of patent ductus arteriosus were noted. However, it was found that the PGE to PGF ratio increased markedly. At the same time PGE_2 has been used to maintain the ductus arteriosus patent in neonates with certain forms of congenital cyanotic heart disease in whom oxygenation is dependent upon a patent ductus arteriosus (Silove ***et al.***, 1981).

Constriction of the ductus arteriosus of human fetuses by the maternal administration of an inhibitor of prostaglandin synthesis has been demonstrated (Levin ***et al.***, 1978). In a proportion of neonates born to mothers who have ingested such drugs, persistent pulmonary hypertension of the newborn (Manchester ***et al.***, 1976) and drastically reduced plasma PGE concentrations have been reported (Wilkinson ***et al.***, 1979). If PGE_2 in the fetal circulation is of critical importance for maintaining the patency of the ductus arteriosus, then maintenance of high circulating levels of PGE_2 constitutes a biological protection mechanism. In infants with ductus arteriosus-dependent congenital heart disease, ductal patency is maintained by intravenous administration of PGE1.Only recently has it been elaborated that ductal patency during the infusion of PGE1 in infants with ductus arteriosus-dependent congenital heart disease might be mediated by the EP4(one of the PGE2 receptors) and IP receptor(PGI2 receptor).The data further suggests that a heterogeneous population of prostanoid receptors may contribute to the regulation of ductus arteriosus tone in humans. This study by Leonhardt et al employed used Rt-PCr and immunohistochemistry to study expression of prostanoid receptors in newborn infants with ductus arteriosus. (Leonhardt ***et al.***, 2003) Though medial management of patent ductus arteriosus with indomethacin (a prostaglandin synthetase inhibitor) consistently lowers prostaglandin concentrations in plasma it does not always results in ductal closure (Lucas and

Mitchell, 1978). surgical ligation of the ductus arteriosus does not immediately alter circulating prostaglandin concentrations (Lucas and Mitchell, 1978).

(Friedman and Demers 1978) have suggested that neonates who develop respiratory distress syndrome have raised plasma levels of PGE and PGF. Studies in infants (Mitchell and Lucas, 1978) with hyaline membrane disease have demonstrated that concentrations of PGE are normal in such infants. However, whether treatment with prostaglandin synthetase inhibitors may be of some benefit to infants with hyaline membrane disease remains an open question.

Metabolism of arachidonic acid

Cyclooxygenase pathway

The potential for prostanoid (essentially prostaglandin and thromboxane) biosynthesis by human fetal tissues has been evaluated in detail. This study reports that human fetal tissues were obtained from pregnancies in the first and second trimesters of gestation. Tissues were minced and super fused. The method of tissue super fusion allows prostanoids (formed acutely due to the traumatisation of tissues) to be removed before commencing timed collections under steady state conditions. The results of this study show that the rate of formation of 6-keto-PGF_1 alpha by all tissues studied was generally greater than the rate of formation of PGF_2 or PGE_2. The rate of formation of 6-keto-PGF_1 alpha was highest in aorta. This is not surprising as 6-keto-PGF_1 alpha is a metabolite of prostacyclin. Prostacyclin formation was greatest in vascular tissues since the intimal lining is considered to be a major site of prostacyclin biosynthesis (Moncada ***et al.***, 1977). Furthermore, vascular tissue from fetuses of other animal species has been shown to produce PG predominantly which serves to prevent platelet adhesion and clumping. Intriguingly, the second highest rate of formation of 6-keto-PGF_1 alpha was by fetal stomach. Decidua produced 12 to 28 times more prostaglandins than placenta and fetal membranes with 6-keto PGF1 (alpha) as the main metabolite (Wetzka ***et al.***, 1993). In adults it is thought that prostacyclin may act in the stomach to have a cytoprotective effect. The fetal lung and adrenal also produce prostacyclin although at lower rates. The adult lung has been thought to be a major source of prostacyclin (Gryglewski ***et al.***, 1978). Formation of prostacyclin by the human fetal adrenal is of interest since prostacyclin is a potent stimulant of adenylate cyclase activity (Gorman ***et al.***, 1977) and hence may be of importance in regulating steroid hormone formation. The capacity for the production of PGE2 and PGf2 alpha is higher in the secretory phase of endometrium than in the proliferative phase and the maximum formation of PGE2 and PGF2 alpha was found in the mid secretory phase and the late secretory phase, respectively (Ishihara ***et al.***, 1986). In general, in the other tissues investigated the rate of production of PGF_2 alpha was greater than of PGE_2. This finding is consistent with the results of Pace-Asciak (Pace-Asciak 1978) using fetal tissues from sheep early in gestation.

Lipoxygenase pathways

The first detailed evaluation of arachidonic acid metabolism by way of lipoxygenase pathways in human fetal tissues was first described in 1983 (Saeed and Mitchell, 1983). Human fetal tissues were obtained after voluntary termination of pregnancy between 12 and 18 weeks of gestational

age. Tissues were minced, homogenized prior to incubation with radiolabel led arachidonic acid. Products were extracted and subjected to thin layer chromatography and various lipoxygenase products, were determined. All tissues investigated formed lipoxygenase derivatives of arachidonic acid. It was found that liver was a major source of lipoxygenase metabolites. The high rates of conversion of arachidonic acid to lipoxygenase metabolites are similar to the rates of conversion of arachidonic acid to lipoxygenase metabolites in adult rat liver (Capdevila ***et al.***, 1981).

Although absolute identification of the products formed is not available lipoxygenase products formed by human fetal tissues had chromatographic mobilities identical with (5S) 5-hydroxy-6, 8, 11, 14-eicosatetraenoic acid (5-HETE) and 12-HETE respectively. The production of prostaglandins and HETEs by pregnancy specific human tissues was investigated in a short - term culture system. The main arachidonic acid metabolite in all tissues from lipoxygenase pathway was 12HETE (Wetzka ***et al.***, 1993). It is interesting to note that the formation of 5-HETE which reflects the biosynthesis of the precursor 5-HPETE which is an essential intermediate in the formation of leukotrienes (Samuelsson ***et al.***, 1980). Both 12-HPETE and 15-HPETE have been shown to inhibit prostacyclin formation (Moncada ***et al.***, 1976) and hence the production of 12-HETE by tissues may well form part of a self regulatory mechanism of arachidonic acid metabolism. Prolonged exposure to HETEs may compromise the anti thrombotic and vasodilator properties of endothelium by reducing its capacity to produce eicosanoids including PGI2 (prostacyclin).12HETE released by activated platelets and macrophages reduced prostacyclin formation in the bovine aortic endothelial cultures by as much as 70% (Hadjiagapiou and Spector 1986). However, the rate of formation of prostacyclin also has been shown to be enhanced by certain leukotrienes. The relative rates of formation of different lipoxygenase derivatives may therefore be of importance in the regulation of prostacyclin formation by fetal tissues.

Metabolism of arachidonic acid in uterine and intrauterine tissues

Cyclooxygenase pathway

Using the technique of tissue superfusion a concerted series of experiments have been performed to evaluate the production of prostanoids by uterine and intra-uterine tissues. Amnion is a significant source of PGE_2 and indeed PGE_2 is the major prostanoid synthesized by most tissues. Substantial formation of TXB_2 occurs in deciduas vera and placenta. The mean rate of formation of PGE_2 by amnion tissue after labor in one study (Mitchell ***et al.***, 1978; Meadows ***et al.***, 2003 and Macchia ***et al.***, 1997) was higher than before labor, although the difference was not statistically significant. Subsequently, it was demonstrated that there is a significant increase in prostaglandin synthase in amnion during labour (Okazaki ***et al.***, 1981). It is widely considered that the biosynthesis of PGE_2 by fetal membranes and in particular amnion is vital in the events culminating in the onset and maintenance of labor. Classical excitatory effect of PGE and PGF is followed by hyper polarization .This restricts the response to a single contraction and decreases the frequency of subsequent contractions. The amplitude of the hyper polarization decreases during labor allowing contraction frequency to increase .Its persistence at this time ensures complete relaxation between each single robust contraction preventing spasm of the

uterus that would restrict blood flow to the fetus during delivery (Parkington ***et al.***, 1999). cAMP may be involved in the labor induced by PGE2 and cGMP in that induced by oxytocin (Nagata ***et al.***, 1988). The low rates of formation of PGE_2 by the tissues are consistent with an environment in which the production of substances with vasoconstrictor activity should be minimized. However, PGE from villous trophoblast can influence the function of many leucocytes by raising intracellular cAMP concentrations and hence might be important In maintenance of pregnancy (Kelly ***et al.***, 1995). Prostacyclin formation by various intrauterine tissues may provide a tonic stimulus to uteroplacental blood flow and hence be protective of fetal development. Date are also available suggesting that cervix is a major source of prostaglandin, particularly of the E series and it has been hypothesized that softening and dilation of the cervix at term are dependent upon locally formed prostaglandins (Ellwood ***et al.***, 1979). Such an action is a protective mechanism for the fetus since without cervical softening and dilatation, the onset of labor would result in contractions and the fetus would be pressed against an inflexible structure. The combination of cervical ripening with intracervical PG gel application and induction of labor by extra-amniotic PG gel under epidural anesthesia is an efficient and safe method for treatment of intrauterine fetal death (Rath and Kuhn 1985). Prostaglandin formation has also been demonstrated in myometrium.

Lipoxygenase pathways

Human uterine and intrauterine tissues have the potential to from lipoxygenase metabolites of arachidonic acid (Saeed and Mitchell, 1982). The major lipoxygenase product formed by human amnion, deciduas vera and placenta has been found to be 12-HETE. The chorion produces only a trace amount of 12-HETE. It has been postulated that, since various HETEs are potent chemotactic agents for human neutrophils, eosinophil and macrophages, production of these metabolites by human intra-uterine tissues may serve to regulate leukocyte and/or macrophage infiltration during pregnancy and parturition (Mitchell ***et al.***, 1983). Such infiltration occurs in cervical tissue during cervical ripening (Liggins 1981) and it has been demonstrated that cervix produces lipoxygenase derivatives of arachidonic acid (Saeed and Mitchell 1982) that also reside in the myometrium (Mitchell ***et al.***, 1983 and Erkinheimo ***et al.***, 2000). The biosynthesis of lipoxygenase derivatives of arachidonic acid by placental tissue may be critical in the maintenance of fetal hemostasis since changes in formation of prostacyclin and/or other prostanoids in this tissue could lead directly to changes in utero-placental blood flow. Hence, the production of lipoxygenase metabolites in these tissues may be considered of utmost importance for fetal well being.

Regulation of the metabolism of arachidonic acid by inhibitory factors

Inhibition of prostanoid biosynthesis

In 1977, Saeed and co-workers (Saeed ***et al.***, 1977) demonstrated the existence of circulating inhibitors of prostaglandin synthase. These were named endogenous inhibitors of prostaglandin synthase (EIPS). EIPS activity in the plasma of pregnant women was demonstrated (Mitchell ***et al.***, 1981) to be significantly lower during the third trimester of pregnancy

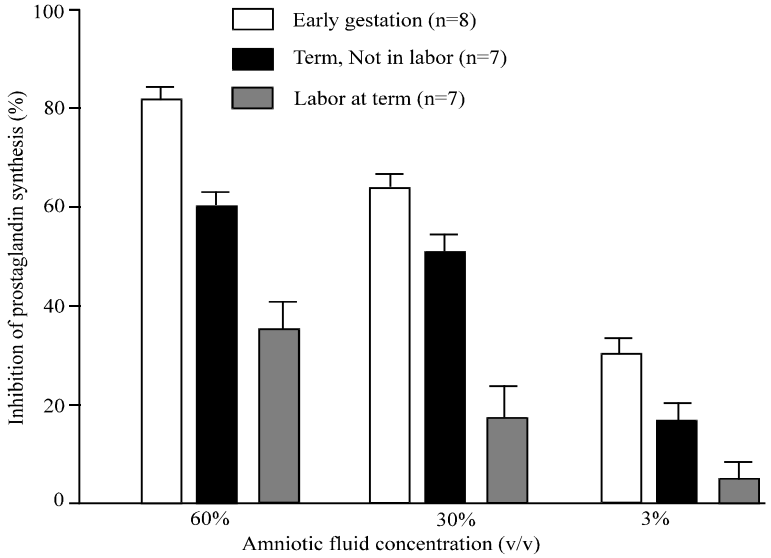

Fig. 1: The inhibition of prostaglandin synthesis by human amniotic fluid in relation to gestation and labor. Results are presented as mean (±SE) inhibitory activities for amniotic fluid (at three concentrations) obtained in early gestation (15-17 weeks) term gestation and term gestation in spontaneous labor. At all three concentrations of amniotic fluid thr inhibitory activity of samples at term was less than the activity in early gestation ($p = 0.05$) and samples obtained in labor demonstrated lower inhibitory activity than either early ($p < 0.001$) or term ($p < 0.01$) samples

Table 1: Rates of Production of Prostanoids by Human Intrauterine tissues Superfused *in vitro*

		Production of prostanoid (ng/mg per g dry wt)			
	Prostanoid	Amnion	Chorion	Decidua	Placenta
Tissues obtained after spontaneous vaginal delivery	Prostaglandin E	13.17 ± 2.21	2.89 ± 0.46	1.72 ± 0.24	2.02 ± 0.38
	Prostaglandin F	0.83 ± 0.19	0.51 ±0.12	0.49 ± 0.09	0.66 ± 0.13
	Thromboxane B_2	1.59 ±0.37	0.61 ± 0.19	2.12 ± 0.38	4.94 ± 0.39
	6-keto prostaglandin F_{1X}	6.31 ± 2.40	2.43 ± 0.64	1.46 ± 0.43	1.33 ± 0.39
Tissues obtained at elective Caesarean section					
	Prostaglandin E	9.62 ± 1.62	3.13 ± 0.59	2.50 ± 0.57	2.84 ± 0.47
	Prostaglandin F	0.74 ± 0.19	0.76 ± 0.20	0.80 ± 0.25	0.82 ± 0.24
	Thromboxane B_2	2.42 ± 0.79	0.88 ± 0.26	2.76 ± 1.09	4.84 ± 1.05
	6-ket 6-keto-prostaglandin F_{1X}	2.37 ± 0.65	1.76 ± 0.40	1.41 ± 0.38	1.11 ± 0.21

Values are means ± S.E.M. for ten individual determinations

(Brennecke ***et al.***, 1982). Recently, significant fall in the activity of EIPS in amniotic fluid during labor has been demonstrated (Fig. 1) (Saeed ***et al.***, 1982). This is a key observation since amniotic fluid bathes the amnion, is the key structure in the mechanisms of the onset of human labor through its production of PGE_2 (Table 1). Hence it is possible that the biosynthesis of prostaglandins is tonically inhibited throughout pregnancy and that such inhibition is withdrawn

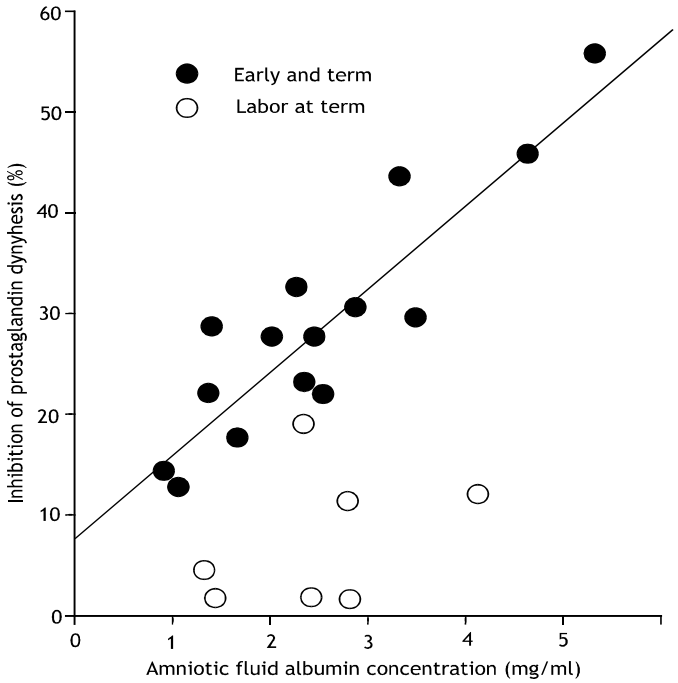

Fig. 2: The relationship of prostaglandin synthesis inhibition by human amniotic fluid to albumin concentration in the samples, at an assay concentration of 3% (v/v) amniotic fluid. Samples obtained in early gestation and at term, not in labor, showed a significant ($p < 0.001$) linear correlation ($r = 0.90$) between inhibitory activity and albumin concentration. Samples obtained in labor did not exhibit a significant correlation ($r = 0.390$, $p > 0.30$) between inhibitory activity and albumin concentration

at the onset of labor. This inhibition is of benefit to fetus since it prevents labor before term and may reduce excessive prostaglandin formation near the utero-placental vascular bed which could lead to vascular constriction. The fetus has less EIPS activity in its plasma that the adult; this is true both in sheep and in man. Umbilical plasma has less EIPS activity than adult plasma although no arterio- venous differences have been found. EIPS concentration in the neonate increase gradually during the first month of life to reach adult levels by 1 - 2 months of life. A reciprocal relation ship was found between plasma EIPS levels and previously reported plasma prostaglandin concentrations. This result supports the role for EIPS in the control of prostaglandin biosynthesis in humans (Saeed ***et al.***, 1977 and Brennecke ***et al.***, 1984). Interestingly this is just the opposite of circulating prostaglandin levels. More recently it has been shown that amniotic fluid inhibits PG production at the level of PG synthase enzymes (Fig. 2). Endogenous prostaglandin inhibitors in amniotic fluid may play a role in maintaining uterine quiescence throughout gestation and its withdrawal at term may be involved in the initiation of labor (Saeed ***et al.***, 1977 and Rice ***et al.***, 1987).

Inhibition of human platelet aggregation

Recently we demonstrated that human plasma contains endogenous inhibitor(s) of platelet aggregation (EIPA) (Saeed and Suria, 1985). The in vivo role of EIPA in pregnancy and parturition remains to be defined though we have postulated EIPA may regulate platelet aggregation triggered by arachidonic acid metabolites and other physiologically important aggregating agents. More recently, we have demonstrated EIPA activity to be significantly lower in the plasma of pregnant women as compared to adult non-pregnant females (Saeed and Suria, 1985).

Inhibition of lipoxygenase activities

An endogenous inhibitor of lipoxygenase activity has been described (Saeed ***et al.***, 1980). No substantial information is available on such activity during pregnancy and parturition, although we have obtained results that such an inhibitor is present in human amniotic fluid. If this inhibitor does circulate in pregnant women it may serve to regulate lipoxygenase activities and hence may be important in preventing the potential deleterious effects of 12-HPETE and 15-HPETE on prostacyclin within the uterus.

Inhibition of phospholipase activities

The elegant studies of (Flower and Blackwell, 1979 and Johansen ***et al.***, 2000) have suggested that glucocorticoids act to inhibit prostaglandin formation by inhibition of phospholipase activities. The mediator of this effect has been named macrocortin or lipomodulin. In a recent study, human fetal adrenal tissue has been shown to respond to glucocorticoids by inhibition of prostaglandin formation in a manner consistent with the formation of lipomodulin (Mitchell ***et al.***, 1982). This finding may be significant for the understanding of the regulation of adrenal growth and the secretion of steroids by the tissue. Moreover, it may be of importance in the understanding of the regulation of regression of the fetal zone of the adrenal during early neonatal life. The suppression of prostaglandins that have vasodilatory properties could provide a mechanism whereby the blood supply to the inner fetal zone of the adrenal is reduced or completely abolished and hence the fetus would regress rapidly. Glucocorticoids downregulate COX1 gene expression and prostacyclin synthesis in fetal pulmonary artery endothelium (Jun ***et al.***, 1999). It has been demonstrated that glucocorticoids affect prostaglandin formation by human amnion cells in monolayer culture. Interestingly, human myometrial cells in monolayer culture do respond to glucocorticosteroid by reduced formation of prostaglandin. The latter observation is particularly interesting since the major prostaglandin formed by the myometrium is prostacyclin (Abel and Kelly, 1979); an inhibitor of uterine activity in sheep (Lye and Challis, 1982). Hence an increased rate of glucocorticosteroid biosynthesis during labor may act to reduce the rate of biosynthesis of a uterine relaxant and thus allow the effects of uterotonic prostaglandins to be dominant. Studies conducted by Mc. Laren ***et al*** indicate that glucocorticoid induced PG production is due to increased formation of PGHS 2 isozyme in ovine cotyledon (McLaren ***et al.***, 2000). The presence of glucocorticosteroids sensitive within fetal and uterine environments provides another regulatory mechanism for prostanoid formation during the pregnancy and parturition.

Regulation of arachidonic acid metabolism by stimulatory factors

Circulating substances

A variety of substances found in the maternal circulation have been reported to stimulate prostanoid formation. The substances include oxytocin, bradykinin and estrogens (William and El-Tahir, 1980). In systems using isolated human endometrial fragments, progesterone has been shown to inhibit PG production markedly. Data collected by Kelly and workers shows that the inhibition of PG production shown by progesterone, acting on secretory phase endometrium cultured as tissue fragments, is reversible by the receptor blocking antiprogestins (Kelly and Smith 1987). Whether the substances have tonic effects on prostaglandin biosynthesis by uterine tissues is unknown. Chorionic renin may have a novel role in the regulation of amnion cell PGE2 production that is independent of angiotensin formation (Lundin-Schiller and Mitchell, 1991). Recent findings indicate that Histamine may act as a local regulator of PGA2 and PGF2, production in human term decidua and may involve interaction with IL-1 (Schrey ***et al.***, 1995). It seems somewhat unlikely that such substances would play a major role in maintaining fetal homeostasis since the stimulation of any prostanoid by these substances would occur not only within the uterus but also in other maternal tissues. Moreover recent data suggest that hCG may also have a biological role in the regulation of PG synthesis in early human placenta (North ***et al.***, 1991).

Jones and Challis support the possibility of paracrine stimulation by CRH and ACTH of PG production in intrauterine tissues and suggest that in part the effects of CRH on placental PG output might be mediated through ACTH (Jones and Challis, 1990).

Substances in uterine and intrauterine tissues

Uterine and intrauterine tissues contain cytosolic factors that cause a stimulation of prostaglandin biosynthesis (Saeed and Mitchell, 1982). The stimulation of biosynthesis is different not only for different prostaglandins but also between different uterine tissues. Indeed the nature of the stimulation is also different. At present no data are available concerning the presence of such stimulation of prostaglandin biosynthesis within intrauterine tissues which may provide yet another regulatory mechanism for arachidonic acid metabolism. Parturition in the sheep is preceded by an increase in the synthesis of prostaglandins by intra uterine tissues. PGG/H synthase (PGHS) is the central enzyme in prostanoid production (McLaren ***et al.***, 1996). Since prostacyclin biosynthesis is increased during pregnancy it is likely that a specific stimulant of prostacyclin formation is present within intrauterine tissues. Pregnancy affects preferential changes in the sub cellular distribution of PGI synthase in myometrial cells. Relative to its PGI synthase content pregnant myometrium contained twice as much PGH synthase as non-pregnant myometrium (Moonen ***et al.***, 1984). It would then seem possible that a reduced activity of such a stimulant could lead to a chronic reduction in uteroplacental blood flow and thus lead to growth retardation and pregnancy-induced hypertension. Given the multitude of effects of prostacyclin within the body the finding of a stimulant of prostacyclin biosynthesis within intrauterine tissues has wider significance since the characterization of such a substance may eventually permit clinical treatment with the substance. Developing the clinical use of

eicosainoid-related drugs and assessing the potential use of these drugs requires a 3 -phase approach : reducing the complications in the treatment of neonates with ductus - dependent congenital heart diseases and primary pulmonary hypertension requiring PGE1, PGE2 and PG12 therapy ;conducting clinical trials of the synthesis inhibitors and receptor antagonists of TXA2 and LT that have already been used in the treatment of adult patients with bronchial asthma; and evaluating the efficacy of new modulators of eicosanoid biosynthesis, such as eicosapentaenoic acid and antiallergy drugs, in the treatment of eicosanoid-related diseases in children (Shimizu, 1998).

The biosynthesis and release of arachidonic acid metabolites (prostaglandins and lipoxygenase products) within the human uterus and by the fetus are extremely complex. It likely involves a series of inhibitory and stimulatory factors that include a combination of different products of arachidonic acid metabolism. However, given the clinical importance of prostaglandin formation by the fetus and the uterus it is of importance that studies are conducted to characterize the ultimate regulator of prostaglandin formation.

Our ability to modulate the formation of prostaglandins and lipoxygenase products during pregnancy will have major clinical implications since prostaglandins do have several protective actions on the uterus and in particular on the fetus and the neonate. On the other hand, it should be recognized that interference with the normal pattern of arachidonic acid metabolism could have disastrous consequences. Hence, there is a great need for extensive basic scientific studies to be conducted before cautious clinical trials of any of the substances described in this review can be considered.

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