Reproduction (2002) **124**, 1–17

Review

Prostaglandins and mechanisms of preterm birth

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Increased uterine contractility at term and preterm results first from activation and then stimulation of the myometrium. Activation can be provoked by mechanical stretch of the uterus, and by an endocrine pathway resulting from increased activity of the fetal hypothalamic–pituitary–adrenal axis. In sheep fetuses, increased cortisol output during pregnancy regulates expression of prostaglandin synthase type 2 (PGHS-2) in the placenta in an oestrogen-independent manner, resulting in increased concentrations of prostaglandin E_2 (PGE_2) in the fetal circulation. Later increases in maternal uterine expression of PGHS-2 require increases in oestrogen and lead to increased concentrations of $PGF_{2\alpha}$ in the maternal circulation. Thus, regulation of PGHS-2 at term is differentially controlled in fetal (trophoblast) and maternal (uterine epithelium) tissue. This difference may reflect expression of glucocorticoid receptor but not oestrogen receptor (ER) in placental trophoblast cells. In women, cortisol also contributes to increased prostaglandin production in fetal tissues through upregulation of PGHS-2 (amnion and chorion) and downregulation of 15-OH prostaglandin dehydrogenase (PGDH; chorion trophoblasts). The effect of cortisol on expression of PGDH in the chorion reverses a tonic stimulatory effect of progesterone, potentially through a paracrine or autocrine action. In membranes, cortisol may be derived from cortisone through activity of 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1, in addition to secretion from the maternal or fetal adrenal glands. In placenta, 11β-HSD-2 oxidase activity predominates and expression of this enzyme is reduced with hypoxaemia and in placentae from pre-eclamptic pregnancies. In these circumstances, increased concentrations of maternal cortisol may cross into the fetal compartment, contributing to growth restriction and programming later life disease.

Preterm birth (birth before week 37 of gestation) occurs in approximately 5–10% of all pregnancies. This value may be higher in certain population groups and has not decreased over the past 20–30 years. Although some preterm births may be elective, approximately 30% occur in association with an underlying infectious process, and about 50% are idiopathic preterm births of unknown cause. Preterm birth is associated with 70% of neonatal deaths, and up to 75% of neonatal morbidity. Infants born preterm have an increased incidence of blindness, deafness, cerebral palsy, neurological disorders and pulmonary disorders (Morrison, 1990; Copper *et al.*, 1993; Lopez-Bernal *et al.*, 1993; Lumley, 1993; Stubblefield, 1993; Villar *et al.*, 1994). All of these risks are associated with increased health care costs (estimated at around $8 billion annually in the USA) and great emotional burdens for the family. Spontaneous preterm labour affects both developed and underdeveloped countries and its prevention is a major aim of modern obstetrics (Creasy, 1991). Established risk factors for preterm labour include previous low birth weight or preterm delivery, multiple second trimester abortions, multiple gestations, placental anomalies, cervical and uterine anomalies, gestational bleeding, *in vitro* fertilization pregnancy, hydramnios, infection, cigarette smoking, single marital status, low socio-economic class and black race (Creasy and Gummer, 1980; Mercer *et al.*, 1996). At present, there are no effective diagnostic indicators of preterm birth, and there are no effective treatments for this condition. Thus, the

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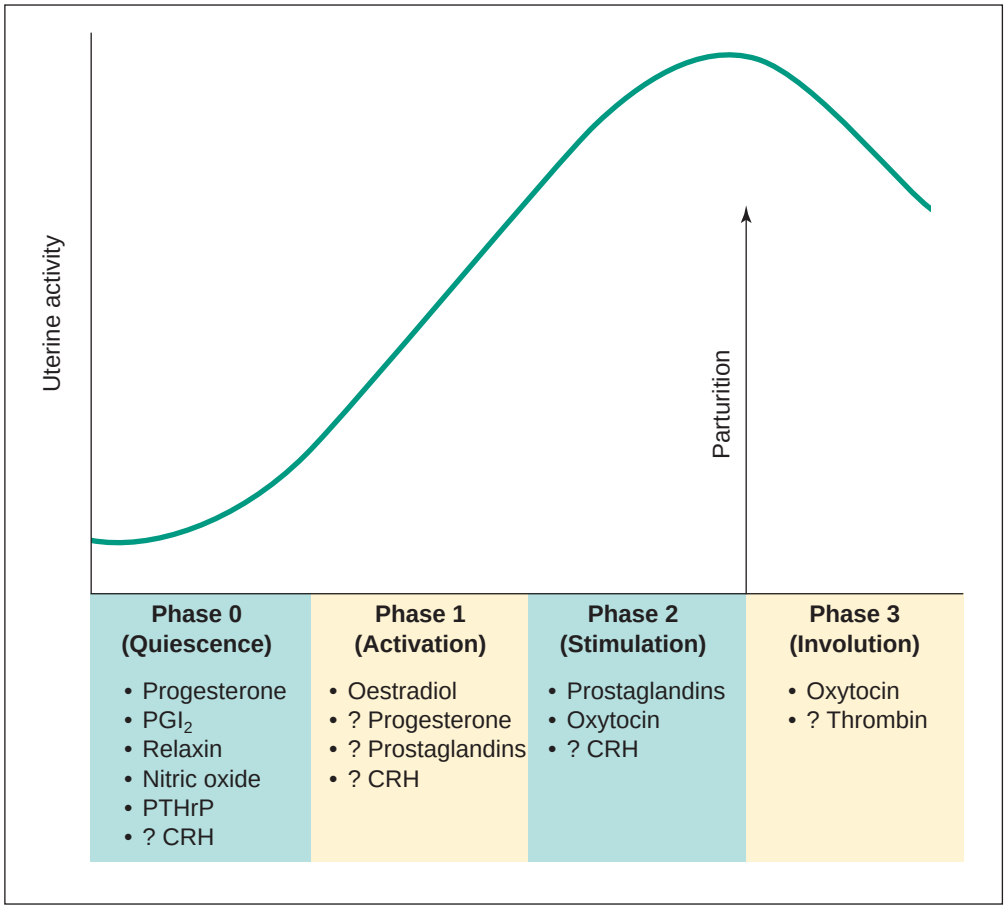

Fig. 1. Phases of uterine activity. A listing of the various agents involved during quiescence (phase 0), activation (phase 1), stimulation (phase 2) and involution (phase 3) of the uterus during pregnancy are represented. PGI_2: prostacyclin; PTHrP: parathyroid hormone related peptide; and CRH: corticotrophin-releasing hormone. (Adapted from Challis and Gibb, 1996.)

focus of current research is to understand the underlying biochemistry of the birth process, and to use that understanding to develop better diagnostic indicators, and improve methods of therapeutic management. This strategy would minimize inappropriate use of maternal glucocorticoids in women with threatened preterm labour.

Phases of parturition

Uterine contractility during pregnancy and parturition can be divided into at least four distinct phases (Lye *et al.*, 1998; Challis *et al.*, 2000) (Fig. 1). In phase 0 (pregnancy), the uterus is maintained in a relatively quiescent state through the separate or combined autocrine–paracrine actions of inhibitors such as progesterone, prostacyclin (PGI_2), relaxin, parathyroid hormone-related peptide (PTHrP), calcitonin gene-related peptide, adrenomedullin, vasoactive intestinal peptide, nitric oxide, and corticotrophin-releasing hormone (CRH), which may both inhibit and stimulate uterine contractility (Challis *et al.*, 2000). The diminished production of one or more of these agents during late gestation may lead to preterm or term uterine activity, whereas administration of these compounds or their analogues may help maintain uterine quiescence. These agents act in different ways but, in general, result in increased intracellular concentrations of cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP). These nucleotides inhibit intracellular calcium release and reduce the activity of myosin light chain kinase (MLCK), which is required for shortening of the myofilaments. Several current strategies for managing preterm labour are directed at increasing intracellular cAMP and reducing the availability of calcium. Phase 1 of parturition is associated with activation of uterine function, wherein mechanical stretch or uterotrophic priming leads to upregulation of a cassette of genes required for contractions. These contraction-associated proteins (CAPs) include connexin43 (Cx43, a key component of gap junctions), agonist receptors (prostaglandins (PGs) and oxytocin), and proteins encoding ion channels. In phase 2 of parturition, the uterus can then be stimulated by utero-

tonins including PGs, oxytocin, and CRH. Phase 3 of parturition includes uterine involution after delivery of the fetus and placenta, and has been attributed primarily to the effects of oxytocin. The initiation of parturition may be defined as the transition from phase 0 (quiescence) to phase 1 (activation) during which there is a release from the mechanisms maintaining uterine quiescence throughout pregnancy and a recruitment of factors promoting uterine activity, including biomechanical factors such as uterine stretch and tension caused by the fully grown fetus.

It is clear that activation of myometrial function (phase 1) is driven by the fetal genotype, and effected through two separate but interdependent pathways (Lye *et al.*, 1998). One pathway involves activation of the fetal hypothalamic–pituitary–adrenal (HPA) axis. The second pathway involves mechanical distension of the uterus, leading to stretch-related upregulation of CAP gene expression.

Activation of fetal hypothalamic–pituitary–adrenal axis

Maturation of fetal HPA function during late pregnancy occurs in most mammals, including primates (Liggins and Thorburn, 1994; Lye *et al.*, 1998; Challis *et al.*, 2000). Extensive studies in sheep fetuses have shown increased expression of CRH mRNA in parvocellular neurones of the paraventricular nucleus of the hypothalamus and of pro-opiomelanocortin (POMC) mRNA in the pars distalis of the fetal pituitary in late pregnancy. These changes correlate with increased concentrations of adrenocorticotrophic hormone ($ACTH_{1-39}$) in the fetal circulation. ACTH acts on the fetal adrenal gland to increase expression of key enzymes required for cortisol production (especially $P450_{C17}$), and to upregulate ACTH receptors in the fetal adrenal cortex. This mechanism allows enhanced binding and coupling to adenylate cyclase, resulting in increased sensitivity of the fetal adrenal gland to further stimulation by ACTH.

Activation of the fetal HPA axis occurs in the presence of an adverse intrauterine environment, for example with compromised uteroplacental blood flow or conditions of fetal hypoxaemia. Sheep fetuses made transiently hypoxaemic had increased concentrations of hypothalamic CRH mRNA and pituitary POMC mRNA (Lye *et al.*, 1998). In late gestation, hypoxaemia also led to increased concentrations of fetal adrenal ACTH receptor mRNA, consistent with increased overall responsiveness of the fetal HPA axis. When fetuses at two-thirds of term gestation were subjected to hypoxaemia by repeated umbilical cord occlusion over several days, the adrenal cortisol response relative to the concentration of ACTH stimulation increased. Other experimental models of sustained, but episodic, fetal hypoxaemia produce similar fetal hormonal and cardiovascular responses, and may result in shortened gestation.

Increases in fetal HPA function in animal species such as sheep lead to changes in the placental output of progesterone before birth. During pregnancy, progesterone is required for uterine growth, but it simultaneously suppresses expression of CAP genes (Lye *et al.*, 1998). At term, in most animal species, the influence of progesterone on the myometrium declines, uterine stretch no longer stimulates uterine growth and the increase in wall tension caused by continued fetal growth becomes translated into increased expression of CAP genes and myometrial activation. Mechanical stretch probably contributes to the greater incidence of preterm birth in pregnancies with multiple fetuses, and may account for the higher incidence of preterm birth in pregnancies in which the fetal size is large for gestational age. However, in human parturition there does not appear to be a decline in circulating progesterone concentrations prepartum. We suggest below that this represents a mechanism to maintain relaxation of the lower uterine segment at the time of birth, and that local antagonism of progesterone action in the fundal region of the uterus facilitates development of uterine contractions predominantly in the fundal region (Lye *et al.*, 1998; Challis *et al.*, 2000).

Prostaglandins and parturition

There is compelling evidence that PGs, particularly those produced within the intrauterine tissues, play a central role in the initiation and progression of labour in most mammalian species studied (Novy and Liggins, 1980; Okazaki *et al.*, 1981; Bleasdale and Johnston, 1984; Mitchell, 1984; Challis and Lye, 1994; Challis *et al.*, 2000). Specifically, PGs have been shown to induce myometrial contractility (Carraher *et al.*, 1983; Wiqvist *et al.*, 1983; Ritchie *et al.*, 1984; Bennett *et al.*, 1987a) and to play a role in regulating changes in extracellular matrix metabolism associated with cervical ripening (Ellwood *et al.*, 1980; Ulmsten *et al.*, 1982; Calder and Greer, 1991; Keirse, 1993) at the onset of labour. In addition, other roles have been postulated, including fetal adaptation to the labour process (PGs inhibit fetal movement and breathing to conserve energy) (Kitterman, 1987; Thorburn, 1992), upregulation of the fetal HPA axis (Challis *et al.*, 2000), membrane rupture (So, 1993; Vadillo-Ortega *et al.*, 1994), and maintenance of uterine and placental blood flow (Rankin, 1976; Sastry *et al.*, 1997, 1999; Carter, 1998; Challis, 2001).

Studies in late pregnant sheep have helped clarify the endocrine pathways leading to altered PG output prepartum. In sheep, PGE_2 concentrations increase progressively in the fetal circulation over the last 15–20 days of gestation, corresponding temporally to the prepartum increase in fetal plasma cortisol, and consistent with the suggestion of stimulatory effects of PGE_2 on the fetal HPA axis, and of cortisol on placental prostaglandin synthase type 2 (PGHS-2) gene expression (Lye *et al.*, 1998). $PGF_{2\alpha}$ increases in the maternal circulation, but only as a late event in pregnancy, co-incident with the marked prepartum increase in maternal free oestradiol concentration. Thus, the possibility was raised that, in late gestation sheep, PGE_2 and $PGF_{2\alpha}$ were derived from different tissues within the pregnant uterus, and that their output was regulated by different control mechanisms (Gyomorey *et al.*, 2000).

Previous studies had indicated that the prepartum increase of cortisol increased placental $P450_{C17}$ expression, which resulted in increased placental oestrogen synthesis from C21 steroids. In turn, oestrogen provoked increases in PG output (Challis *et al.*, 2000). However, placental PGHS-2 mRNA and protein were detectable, and increased before changes in placental $P450_{C17}$, and intrafetal oestradiol infusion had no stimulatory effect on placental PGHS-2. Conversely, intrafetal cortisol infusion for about 80 h resulted in increased placental PGHS-2 and fetal plasma PGE_2 concentrations, even in the presence of an aromatase inhibitor. Therefore, this effect did not depend on the prepartum increase in placental oestrogen output (Whittle *et al.*, 2000a). However, maternal uterine PGHS-2 expression and $PGF_{2\alpha}$ output were attenuated by concurrent aromatase inhibition during cortisol infusion. These studies indicated that upregulation of PGHS-2 in placental trophoblasts could be stimulated directly by cortisol. We have now substantiated this conclusion using cultures of ovine placental trophoblasts treated with glucocorticoids *in vitro*. Regulation of PGHS-2 in the maternal uterus required an increase in oestrogen output, even during cortisol infusion. This finding is consistent with observations in non-pregnant sheep that oestradiol treatment increases uterine PG output. In intact sheep at full term, the trophoblast cells express glucocorticoid receptor (GR) but not oestrogen receptor (ER). Similarly, immunoreactive GR and GRα are present in the trophoblast cells, and the abundance of GRα is increased by cortisol infusion, in the presence or absence of aromatase inhibition. Therefore, it appears that the prepartum increase in fetal plasma cortisol increases GRα activity in the placenta, and directly augments placental PG synthase. $P450_{C17}$ concentrations were increased in animals treated with cortisol, and with cortisol plus aromatase inhibition. Therefore, $P450_{C17}$ increases independently of the prepartum increase in oestrogen. These results are consistent with the following sequence: cortisol upregulates placental PGHS-2 and the product PGE_2 stimulates placental $P450_{C17}$, as suggested for other tissues, including the adrenal glands. Definitive studies to demonstrate this relationship between PGE_2 and $P450_{C17}$ in the sheep placenta are still required.

Prostaglandin synthesis and metabolism in human pregnancy

In women, PG production and metabolism are discreetly compartmentalized within the tissues of the pregnant uterus (Challis *et al.*, 2000). Human amnion, which consists of a single layer of epithelial cells and a subepithelial mesenchymal layer, is a major site of PG (predominantly PGE_2) synthesis (Duchesne *et al.*, 1978; Challis and Olson, 1988; Lundin-Schiller and Mitchell, 1990; Olson *et al.*, 1991, 1995; Gibb and Sun, 1996). Both PGHS-1 and PGHS-2 mRNA and immunoreactive (IR) proteins have been identified in amnion (Rose *et al.*, 1990; Teixeira *et al.*, 1994; Hirst *et al.*, 1995a). There is very low or no PG catabolizing enzyme, 15 hydroxyprostaglandin dehydrogenase (PGDH), present in human amnion (Keirse and Turnbull, 1975; Okazaki *et al.*, 1981; Cheung *et al.*, 1990). Interposed between amnion and decidua is the chorion, where a very high concentration of PGDH has been localized to the trophoblast cells (Keirse and Turnbull, 1975; Keirse *et al.*, 1976, 1978, 1985; Okazaki *et al.*, 1981; Cheung *et al.*, 1990; van Meir *et al.*, 1997a). PGHS is also abundant within chorion (Gibb and Sun, 1996). Thus, studies *in vitro* have demonstrated that chorion forms predominantly 13,14-dihydro-15-keto products from endogenous precursors or from added PGE_2 (Skinner and Challis, 1985; Cheung and Challis, 1989). Human decidua, a well-vascularized maternal tissue lying next to the myometrium, consists of a mixture of decidualized stromal cells, bone marrow-derived macrophages and other types of cell, and contains low concentrations of both PGHS-1 and -2, and shows minimal PGDH staining in decidual stromal cells (Liggins *et al.*, 1977; Okazaki *et al.*, 1981; Casey and MacDonald, 1988; Cheung *et al.*, 1990; MacDonald *et al.*, 1991; Teixeira *et al.*, 1994; Hirst *et al.*, 1995b).

The fetus may contribute to the initiation of birth by secreting an active agent(s) that acts on the fetal membranes to stimulate PG production. PGHS activity and PGHS-2 mRNA concentrations are increased in amnion, in epithelial and fibroblast cells at term (Keirse and Turnbull, 1976; Mitchell *et al.*, 1978; Okazaki *et al.*, 1981; Bennett *et al.*, 1992; Economopoulos *et al.*, 1996; Gibb and Sun, 1996) and at preterm labour (Skinner and Challis, 1985; Teixeira *et al.*, 1993; Hirst *et al.*, 1995a; Slater *et al.*, 1995). The predominant role that the amnion plays in PG output at term is exemplified by the increase in PG content of the amniotic fluid as labour progresses and the cervix dilates (Mitchell, 1988; Keirse, 1990). PGHS-2 expression and output of PGE_2 increase at term and preterm labour within amnion epithelium and mesenchyme (Skinner and Challis, 1985; Lopez-Bernal *et al.*, 1987a; Strickland and Mitchell, 1987; Teixeira *et al.*, 1994; Hirst *et al.*, 1995a; Fuentes *et al.*, 1996; Gibb and Sun, 1996), although one early report failed to detect the increase in PGHS and PG output with labour in amnion (Satoh *et al.*, 1981). PGHS-2 mRNA expression also increases in chorion with the onset of labour (Slater *et al.*, 1995, 1998). Decidua may produce more PGF before labour than during labour (Harper *et al.*, 1983), although most groups report that decidual PGHS-2 mRNA and protein do not change with labour (Harper *et al.*, 1983; Casey and MacDonald, 1988; Fuentes *et al.*, 1996; Gibb and Sun, 1996). In short, amnion, chorion and decidua produce increasing amounts of PGs throughout gestation but only amnion and chorion PG output and PGHS-2 mRNA increase further at the onset of labour (Olson *et al.*, 1983; Skinner and Challis, 1985; Reddi *et al.*, 1990; Teixeira *et al.*, 1994; Freed *et al.*, 1995; Hirst *et al.*, 1995a; Slater *et al.*, 1995; Fuentes *et al.*, 1996).

Early studies indicated that PGDH protein and activity in the fetal membranes did not change significantly during spontaneous labour at full term (Skinner and Challis, 1985;

Lopez-Bernal *et al.*, 1987b; Casey *et al.*, 1989; Cheung and Challis, 1989; Germain *et al.*, 1994). However, current evidence indicates that mRNA expression and activity of chorionic PGDH decrease in human labour, at term and preterm (van Meir *et al.*, 1996, 1997a,b; Sangha *et al.*, 1994). PGDH mRNA concentrations in chorion obtained from patients at term during labour were lower than those obtained at term who were not in labour (Sangha *et al.*, 1994). A role for altered expression of PGDH in preterm labour has also been suggested. Fifteen to twenty per cent of patients in idiopathic preterm labour, in the absence of intrauterine infection, had decreased IR-PGDH protein in chorion trophoblast cells, which was correlated with a decrease in PGDH activity in these patients (Sangha *et al.*, 1994). In addition, there was low expression of IR-PGDH and PGDH mRNA in chorion collected from preterm deliveries associated with severe infection (van Meir *et al.*, 1996, 1997a) in which there was loss of trophoblast cells. This finding indicates that, in some patients in preterm labour without infection, a deficiency in chorion PGDH allows passage of PGs, generated in amnion or chorion, across the membranes, which may be involved in the initiation of preterm labour. In all of these studies, changes in PGDH activity in chorion correlated with changes in concentrations of PGDH mRNA in the tissue.

There may be a regional distribution of PGDH activity in human fetal membranes. At labour, there is a marked reduction in PGDH activity in chorion collected from the region over the internal os of the cervix compared with tissue taken adjacent to the placental plate or from the middle region of the chorioamniotic sac (van Meir *et al.*, 1996). This decrease in PGDH of cervical chorion at the time of labour is not associated with loss of trophoblast cells, indicating a potential role for altered expression of PGDH in the processes of cervical effacement and ripening. The active PGDH in decidua indicates that the PGs produced within this tissue are rapidly inactivated; however, uneven distribution of PGDH in decidua might allow areas of significant high local concentration.

As stated earlier, there are several possible roles for PGs derived from the fetal membranes. Amnion PGs may play a role in fluid or ion balance as they are potent mediators of transmembrane ion flow (Ramwell and Shaw, 1970; Frazier and Yorio, 1992; Saunders-Kirkwood *et al.*, 1993). A role for amniotic PGs in cervical ripening, membrane rupture through effects on matrix metalloproteinases and myometrial contractility has also been postulated (Xu *et al.*, 2002). There are conflicting reports as to whether amnion-derived PGs can transfer across fetal membranes and play a role in the initiation of labour. Several reports indicate that there is very limited transfer of unmetabolized PG from amnion to decidua before and after labour at term (McCoshen *et al.*, 1987, 1990; Casey *et al.*, 1989; Roseblade *et al.*, 1990; Sullivan *et al.*, 1991, 1992, 1993; Collins *et al.*, 1992; Mitchell *et al.*, 1993; Kredentser *et al.*, 1995). In contrast, three studies using *in vitro* techniques have shown that small amounts of radioactive PGE_2 can cross the membranes from the amniotic side to the decidual–myometrial side (Nakla *et al.*, 1986; Bennett *et al.*, 1990; Johnston *et al.*, 1996) and Nakla *et al.* (1986) noted an increased rate of transfer or permeability of the membranes after spontaneous labour and demonstrated that arachidonic acid could also pass from amnion to decidua, potentially contributing to the substrate source for PGHS activity at that site. Similarly, Bennett *et al.* (1990) showed that lipoxygenase products (5-HETE) could pass across the membranes by diffusion through intercellular channels and remain largely unmetabolized.

Thus, the chorion, interposed between amnion and decidua, becomes an important PG metabolizing site and has been described as a protective barrier preventing the free transfer of primary PGs generated within amnion or chorion from passing unmetabolized to the underlying decidual tissue or myometrium (Nakla *et al.*, 1986; Sullivan *et al.*, 1992, 1993) and stimulating the onset of preterm or term delivery. Any reduction in the metabolizing capacity of the chorion may enhance PG transfer. In the presence of high PGDH activity in chorion during normal term labour, it is likely that PGs that are stimulating myometrial activity are derived from decidua or, locally, from the myometrium itself. However, in some circumstances of preterm labour, the PGDH metabolic barrier may break down, allowing PGs generated elsewhere within membranes to reach the underlying myometrium, and provoke premature delivery. Examination of the heterogeneous distribution of PGDH within the chorion (Cheung and Challis, 1989) indicates that protection of PG transfer across membranes by PGDH may not be uniform, allowing PGs produced in the amnion to pass through to the myometrium irrespective of changes in PGDH within the chorion (Challis *et al.*, 1990; Cheung *et al.*, 1990). Although several studies have examined PG transfer across the membranes at term and in the presence and absence of labour, studies to examine amnion- or chorion-derived PG transfer to the myometrium at preterm, when there are changes in PGDH activity and mRNA expression, and in correlation with concentrations of PGDH protein and PGDH activity at various sites within the uterus, have not been performed.

It is unclear whether there are changes in PGHS activity in human myometrium at the time of labour. In rats, both PGHS-1 and PGHS-2 were reported to increase with the onset of labour (Dong *et al.*, 1996; Tsuboi *et al.*, 2000), although other authors found increased mRNA expression of PGHS-2 but not PGHS-1 (Lye *et al.*, 1998). In women, concentrations of PGHS in myometrium are higher during the pregnant than during the non-pregnant state (Moonen *et al.*, 1984). PGHS-1 and PGHS-2 mRNA and protein have been reported to increase (Erkinheimo *et al.*, 2000), decrease (Zuo *et al.*, 1994) or remain unchanged (Myatt and Moore, 1994; Moore *et al.*, 1999; Sparey *et al.*, 1999) at the onset of labour at term and preterm. Ongoing studies have also failed to demonstrate changes in concentrations of PGHS-2 with labour at term in human myometrium collected from the lower uterine segment (Giannoulias *et al.*, 2002),

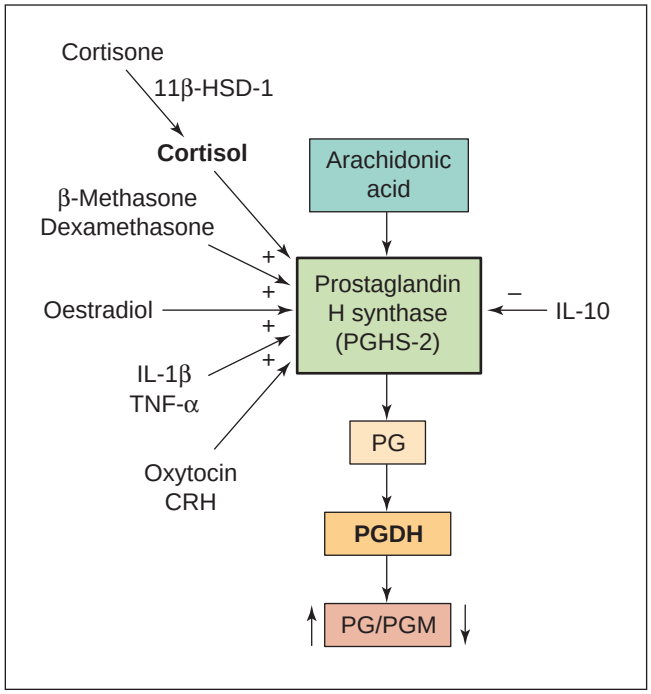

Fig. 2. Regulatory factors involved in the stimulation and inhibition of PGHS-2 (prostaglandin H synthase) in human intrauterine tissues. 11β-HSD: 11β-hydroxysteroid dehydrogenase; IL-1β: interleukin 1β; TNF-α: tumour necrosis factor α; CRH: corticotrophin-releasing hormone; PGDH: 15-OH prostaglandin dehydrogenase; PGM: prostaglandin metabolite. (Adapted from Challis *et al.*, 2000.)

although PGDH protein was lower in samples collected from women at term and preterm in labour.

Excitatory (FP, EP3, EP1) PG receptors, as well as the relaxant EP2 receptor, have been localized to human non-pregnant myometrial samples (Senior *et al.*, 1991, 1992). These receptor subtypes are also present in pregnant human myometrium in late pregnancy (Hofmann *et al.*, 1983; Adelantado *et al.*, 1988; Senior *et al.*, 1993; Erkinheimo *et al.*, 2000). There is no evidence for increased FP receptor density or increased coupling to phospholipase C (PLC) during pregnancy or parturition (Word *et al.*, 1992).

Regional controls of uterine contractility

Several studies in humans and other species have shown that expression of the oxytocin receptor, CRH receptor type 1 (CRH-R1), and PG receptors within the uterus differ spatially (Fuchs *et al.*, 1984; Moonen *et al.*, 1986; Adelantado *et al.*, 1988; Smith *et al.*, 1996; Lye *et al.*, 1998; Stevens *et al.*, 1998). Thus, it has been suggested that during labour the myometrium exhibits a regionalization of function that allows for the effective and forceful net expulsion of the fetus from the uterus (Lye *et al.*, 1998). The fundus increases expression of CAP genes in a manner similar to that in other species, whereas the lower segment expresses genes that contribute to relaxation (thus facilitating descent of the fetus during labour). In favour of this hypothesis, Wikland *et al.* (1984) demonstrated *in vitro* that $PGF_{2\alpha}$ stimulated the fundal myometrium during labour, but not before labour, whereas PGE_2 was able to stimulate fundal myometrium both before and during labour. In lower segment myometrium, $PGF_{2\alpha}$ stimulated contractility before labour but had no effect during labour, whereas PGE_2 induced a biphasic dose-dependent response (stimulation followed by inhibition) before labour but only inhibited contractility during labour (Wikland *et al.*, 1984; Senior *et al.*, 1993). Consistent with this finding, various groups have reported that EP2 expression in myometrium is higher preterm than at term (Molnar and Hertelendy, 1990). In rats, parturition is associated with downregulation of EP receptor subtypes and with upregulation of myometrial FP receptors, effecting a switch from inhibition to stimulation (Brodt-Eppley and Myatt, 1998, 1999; Dong and Yallampalli, 2000; Ou *et al.*, 2000).

These studies raise the possibility that PGHS and PGDH may also be spatially regulated in the myometrium. Higher concentrations of PGHS-1 and PGHS-2 were found in lower compared with upper segments of the uterus (Moonen *et al.*, 1986; Sparey *et al.*, 1999). Labour-associated decreases in PGDH mRNA were found in the fundus compared with the lower uterine segment in the myometrium of baboons (Wu *et al.*, 2000). However, the relative importance of autocrine control of myometrial contractility, versus paracrine control by PGs from amnion or chorion in relation to labour onset, remains unclear at present.

Regulation of prostaglandin synthesis

Regulation of PGHS-1 and PGHS-2 expression is multifactorial (Wang *et al.*, 1993; Goppelt-Struebe, 1995, 1997; Schaefers and Goppelt-Struebe, 1996) (Fig. 2). PGHS-2 can be increased rapidly up to 80-fold in response to cytokines (Romero *et al.*, 1989a,b,c, 1991), growth factors (EGF, PAF) (Mitchell, 1988; Romero *et al.*, 1989a,b,c), tumour promoters (for example, phorbol esters), bacterial endotoxins (Bennett *et al.*, 1987b; Lamont *et al.*, 1990), oxytocin (Zeeman *et al.*, 1997; Molnar *et al.*, 1999; Soloff *et al.*, 2000), agents that increase intracellular cAMP concentrations (Bleasdale and Johnston, 1984; Warrick *et al.*, 1985; Anteby *et al.*, 1997; Grammatopoulos and Hillhouse, 1999a), such as CRH (Jones and Challis, 1990a,b), and a variety of other factors, including, paradoxically in fetal membranes, glucocorticoids (Novy and Walsh, 1983; Mitchell *et al.*, 1988; Potestio *et al.*, 1988; Zakar and Olson, 1989; Gibb and Lavoie, 1990; Smieja *et al.*, 1993; Blumenstein *et al.*, 2000; Whittle *et al.*, 2000a). The PGHS-2 promoter region possesses several potential regulatory sequences including: TATA box, AP-2, SP1, nuclear factor κB (NF-κB), CRE, nuclear factor-interleukin 6 (NF-IL6), ETS-1 and glucocorticoid response element (GRE) sites (Tazawa *et al.*, 1994; Inoue *et al.*, 1995).

The ability of pro-inflammatory cytokines, particularly interleukin 1β (IL-1β), to upregulate PGI_2 and PGE_2 synthesis in primary cultures of human myometrial cells has been well established (Hertelendy *et al.*, 1993; Gomez *et al.*, 1995). IL-1β rapidly induces PGHS-2 mRNA expression and PGE_2 production in primary human amnion cells, chorion and decidua (Mitchell *et al.*, 1993a,b, 1994; Tahara *et al.*, 1995; Trautman *et al.*, 1996) and in an amnion-derived cell line (WISH cells) (Xue *et al.*, 1995). Dexamethasone inhibited IL-1β-induced PGHS-2 mRNA and protein expression, and activity (Xue *et al.*, 1996). Goodwin *et al.* (1998) reported that IL-1β and tumour necrosis factor α (TNF-α), but not TGF-β, stimulate PGE_2 production in cultured placental trophoblast cells. In contrast, Pomini *et al.* (1999) found that, although IL-1β stimulates PGHS-2 expression and PGE_2 output by cultured villous and chorion trophoblast, TNF-α had no effect. These effects of IL-1β were reversed by co-incubation with the anti-inflammatory cytokine, IL-10, in placenta and chorion, although IL-10 alone produced a modest stimulation of PGE_2 output and PGHS-2 mRNA concentrations in chorion explants. This finding is consistent with IL-10 stimulating rather than inhibiting PG production in amnion explants (Dudley *et al.*, 1993; Mitchell *et al.*, 1994). IL-1β appears to increase not only the rate of transcription of the PGHS-2 gene (Mitchell *et al.*, 1993b, 1994), but also the stability of PGHS-2 mRNA (Ristimaki *et al.*, 1994). p50 and p65, key members of the NF-κB *Rel* family of proteins, are present in trophoblast cells and probably serve as mediators of cytokine-induced upregulation of PGHS-2 expression (Kniss, 1999). It has been suggested that the stimulation of PG synthesis caused by cytokines is greater than the increase due to PGHS activity alone (Edwin *et al.*, 1996), implying that cytokines have multiple sites of action, including effects on phospholipase, PG synthases and PGDH, all of which contribute to the net stimulation of PG output. Indeed, IL-1β has been shown to induce cPLA2 mRNA expression in WISH cells (Xue *et al.*, 1996). IL-1β, IL-10 and TNF-α also downregulate PGDH activity and expression (see below). Thus, *in vivo*, it appears that the relative amounts of eicosanoids and cytokines produced from an interactive cytokine–eicosanoid cascade are critical in regulating the final response of the tissue and the amount of PG produced (Keelan *et al.*, 1997). These results also raise the possibility that anti-inflammatory cytokines might be used therapeutically to modulate the action of compounds such as IL-1. Regulation of enzymes in the PG metabolic pathway by cytokines is likely in preterm patients with infection; however, regulation of these enzymes in term patients and in preterm patients without infection may be related to a different set of regulators.

Normally, PGHS-2 is induced under conditions of inflammation. Glucocorticoids inhibit PGHS-2 transcription and reduce PGHS-2 mRNA stability (DeWitt and Meade, 1993; Evett *et al.*, 1993), representing one pathway of anti-inflammatory action. However, several studies have shown that PG production in cultured amnion and chorion is stimulated by cortisol and the synthetic glucocorticoid dexamethasone (Novy and Walsh, 1983; Mitchell *et al.*, 1988; Potestio *et al.*, 1988; Zakar and Olson, 1989; Gibb and Lavoie, 1990; Smieja *et al.*, 1993; Economopoulos *et al.*, 1996; Patel *et al.*, 1999; Blumenstein *et al.*, 2000; Whittle *et al.*, 2000b). The amnion consists of a single layer of epithelial cells and a subepithelial mesenchymal layer. At term, the basal output of PG by amnion mesenchymal cells exceeds that of amnion epithelial cells (Whittle *et al.*, 2000a). Glucocorticoids may have dual effects in different types of cell within amnion. Glucocorticoids appear to inhibit PGE_2 output in amnion epithelial cells (Blumenstein *et al.*, 2000), whereas in mesenchymal fibroblast cells, they upregulate PGHS-2 mRNA expression and increase PGE_2 output (Potestio *et al.*, 1988; Economopoulos *et al.*, 1996). However, Whittle *et al.* (2000a) reported that glucocorticoids stimulate PG production in amnion epithelial cells but that there was no significant change in the already increased output of PG from mesenchymal fibroblast cells. Glucocortocoid receptors have been localized to amnion epithelium, amnion mesenchymal fibroblasts, chorion trophoblast cells, and placenta in human pregnancy tissues at term and preterm (Giannopoulos *et al.*, 1983; Karalis *et al.*, 1996; Sun *et al.*, 1996; Weisbart and Huntley, 1997). In mixed amnion cell cultures, the action of glucocorticoids is dependent upon interaction with GR and apparently requires activation of protein kinase C (PKC). Furthermore, the glucocorticoid regulation of PG output in amnion cells can be inhibited by addition of a GR antagonist (Alvi *et al.*, 1999), and this finding is in agreement with a role for receptor mediation.

Prostaglandin metabolism

Biologically active concentrations of PG appear to depend not only on rates of synthesis, but also on the rates of metabolism (Challis *et al.*, 1999). Normally, high concentrations of PGDH expressed in chorion trophoblasts would be expected to metabolize effectively PG generated within amnion or chorion. However, patients in preterm labour with an underlying infective process have markedly reduced numbers of trophoblasts in the chorion layer and markedly reduced PGDH activity (Sangha *et al.*, 1994). In addition, approximately 15% of patients with idiopathic preterm labour have diminished expression of PGDH but normal numbers of trophoblasts. PGDH activity is reduced modestly in chorion from patients at term, but is markedly diminished in myometrium and cervix of patients presenting in preterm labour. Thus, reduced PG metabolism appears to be an effective way of increasing PGs that may then reach agonist PG receptors in a paracrine fashion. Furthermore, concentrations of matrix metalloproteinase 9 (MMP-9) in chorion are increased with term and preterm labour. Since this gelatinase enzyme contributes to the controlled degradation of collagen within the fetal membranes, and MMP-9 activity is increased by PGE_2, this feed-forward cascade may help explain the mechanism of

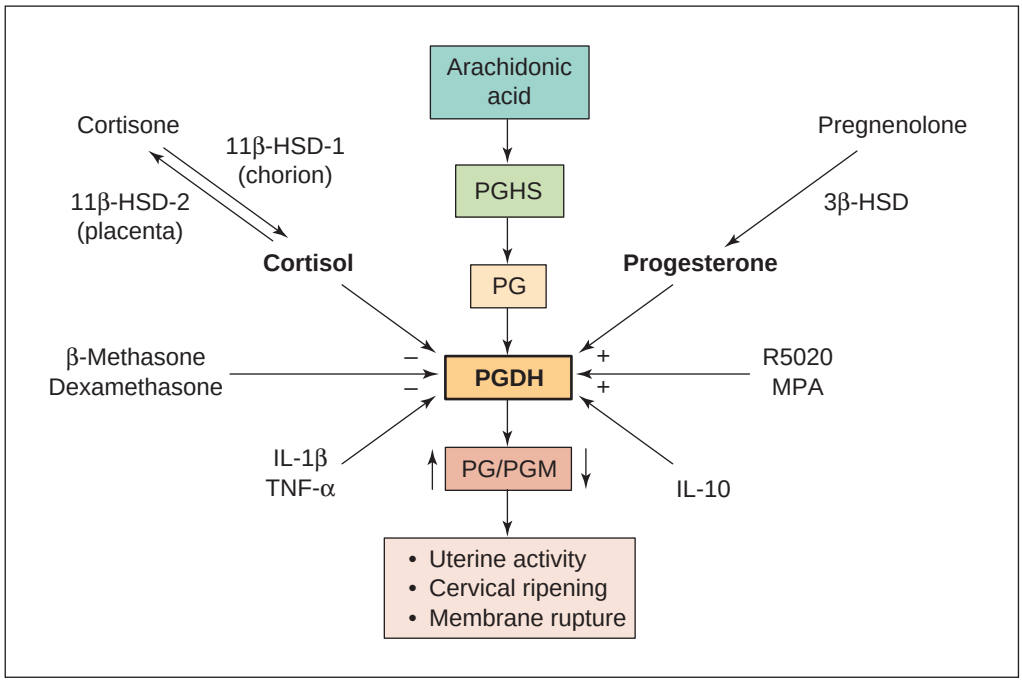

Fig. 3. Schematic representation factors that regulate 15-OH prostaglandin dehydrogenase (PGDH) activity and expression in human fetal membranes and placenta. Progestins (produced intracellularly from pregnenolone conversion to progesterone by 3β-hydroxysteroid dehydrogenase (3β-HSD) or from the maternal circulation) stimulate PGDH acting to maintain prostaglandin concentrations throughout pregnancy. Glucocorticoids, either from the maternal circulation or produced locally via 11β-HSD activity, inhibit PGDH activity and expression. Pro-inflammatory cytokines such as interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α) inhibit PGDH, whereas anti-inflammatory cytokines such as IL-10 stimulate PGDH activity and expression. A downregulation of PGDH would lead to a higher prostaglandin (PG) to prostaglandin metabolite (PGM) ratio at term, which may result in increased uterine activity, cervical ripening or rupture of the fetal membranes. MPA: medroxyprogesterone acetate; PGHS: prostaglandin H synthase.

preterm premature rupture of the membranes, with MMP-9 providing the predominant gelatinolytic activity.

Many factors, including drugs (Flower, 1974), protein-modifying agents, zinc and copper metal ions (Sakuma *et al.*, 1990, 1996), hyperoxia (Parkes and Eling, 1975; Chaudhari *et al.*, 1979; Vader *et al.*, 1981; Pisarello *et al.*, 1997), fatty acids, cAMP (Lennon *et al.*, 1999), calcium, bacterial endotoxins (lipopolysaccharide) (Alam *et al.*, 1973; Nakano and Prancan, 1973; Blackwell *et al.*, 1976; Harper *et al.*, 1980; Hahn *et al.*, 1998), 1,25-dihydroxy-vitamin D3 (Pichaud *et al.*, 1997), vitamin E (Chan *et al.*, 1980), thyroid hormones (Tai *et al.*, 1974; Moore and Hoult, 1978), cytokines (Brown *et al.*, 1998) and steroid hormones, have been implicated in the regulation of PGDH activity in a variety of species and types of cell (Nakano and Prancan, 1973; Andersen and Ramwell, 1974; Lee and Levine, 1975; Hansen, 1976; Tai and Hollander, 1976; Pace-Asciak and Smith, 1983; Krook *et al.*, 1992; Okita and Okita, 1996). The 1.6 kb promoter region of the PGDH gene contains two TATA boxes and a number of potential regulatory elements, including Sp1, CRE, GRE, AP1, AP2, NF-IL6, C-MYC and a putative oestrogen receptor binding site (Matsuo *et al.*, 1996, 1997).

The presence of an NF-IL6 regulatory element in the promoter region of the PGDH gene indicates that PGDH may be regulated by cytokines (Matsuo *et al.*, 1997) (Fig. 3). Indeed, cytokines such as IL-1β and, to a lesser extent, TNF-α, have been reported to decrease PGDH mRNA and PGDH activity in intact fetal membrane disks and in cultured chorion and placental trophoblast cells (Brown *et al.*, 1998; Pomini *et al.*, 1999; Mitchell *et al.*, 2000). In accordance with their effect on PGHS expression, anti-inflammatory cytokines such as IL-10 reverse IL-1β and TNF-α inhibition of PGDH.

Studies directed towards understanding the mechanism by which steroid hormones might regulate PGDH (Patel *et al.*, 1999) (Fig. 3) have also revealed a mechanism for local progesterone withdrawal within the human fetal membranes. Human chorionic PGDH gene expression and activity are inhibited by glucocorticoids (cortisol, betamethasone and dexamethasone) and maintained in a tonic fashion by progesterone (Patel *et al.*, 1999). Chorion trophoblasts express 3β-hydroxysteroid dehydrogenase (3β-HSD)

and have the capacity to produce their own progesterone from pregnenolone (Bloch, 1945; Gibb *et al.*, 1978; Challis and Vaughan, 1987; Mitchell and Challis, 1988; Riley *et al.*, 1992). Inhibition of endogenous 3β-HSD activity with the drug trilostane inhibited progesterone output from chorion trophoblast cells, and reduced PGDH mRNA. Replacement of progesterone or a synthetic progestagen restored PGDH activity. This effect could be blocked, in part, by a progesterone receptor antagonist. However, the action of progesterone to restore PGDH could also be blocked by a specific GR antagonist. This observation implies that progesterone, produced locally within chorion, acts throughout pregnancy to maintain chorionic PGDH activity through interacting with GR. At term, increased availability of endogenous cortisol would displace progesterone from GR, resulting in loss of the stimulation to PGDH, and also a direct inhibitory effect on PGDH expression. This interaction, whereby the effects of progesterone are mediated through GR but can be opposed by increased output of glucocorticoid, may provide a mechanism for producing local progesterone withdrawal in the human uterus. This activity may be greater in the fundal area, thereby contributing to regionalized changes in uterine contractions (Sparey *et al.*, 1999; Challis *et al.*, 2000).

The biologically inactive corticosteroid, cortisone, was almost as effective as cortisol in inhibiting PGDH in chorion cells, but not in placental trophoblast cells (Challis *et al.*, 1999). In chorion, the action of cortisone could be blocked by a GR antagonist, and was completely attenuated in the presence of the drug carbonexolone. This drug, an active ingredient of liquorice, inhibits the enzyme 11β-hydroxysteroid dehydrogenase 1 (11β-HSD-1). 11β-HSD-1 is abundantly expressed in chorion trophoblasts, and predominantly converts cortisone to cortisol. Thus, chorion trophoblasts have the potential to form cortisol locally from cortisone, in addition to forming progesterone locally from pregnenolone. In theory, therapeutic regulation of PGDH could be accomplished by steroid hormones, or by drugs that alter the concentration of 11β-HSD-1.

CRH and preterm labour

It is now well established that the concentrations of CRH in maternal blood increase progressively during human pregnancy (Linton *et al.*, 1993; Petraglia *et al.*, 1996). This increase correlates with increased CRH mRNA and CRH peptide in placental tissue (Frim *et al.*, 1988). In the circulation, CRH is largely associated with a high-affinity circulating CRH-binding protein (CRH-BP) produced in the liver, placenta and other sites including the brain. CRH-BP effectively blocks the action of placental CRH on the maternal pituitary and on the myometrium. Near term, and in association with preterm labour, CRH-BP concentrations decrease, coincident with the increase in circulating CRH (Linton *et al.*, 1993). Thus, it has been suggested that the substantial increase in free CRH concentrations in systemic plasma is a component of the trigger to the labour process.

Regulation of placental CRH output is multifactorial, and has been reviewed extensively (Petraglia *et al.*, 1996). Paradoxically, CRH gene expression and CRH output by placental trophoblast cells are increased by glucocorticoids. CRH output from placenta and fetal membranes also increases in response to PGs, cytokines and catecholamines, and is decreased by nitric oxide and progesterone. Karalis *et al.* (1996) suggested that the inhibitory effect of progesterone is exerted through binding to GR in trophoblast cells. At term, increased cortisol may displace progesterone bound to GR and this is reflected as an increase in CRH output. Thus, the mechanism of interaction between progesterone and cortisol in the regulation of CRH is similar to that proposed for the regulation of PGDH.

The action of CRH on the intrauterine tissues and myometrium is effected through an extensive network of high affinity CRH receptors with different specificities. There are two main classes of CRH receptor, CRH-R1 and CRH-R2. In myometrium, CRH acts by binding to CRH-R1, which is coupled to $G_{\alpha}s$, leading to stimulation of cAMP output. Thus, the primary effect of CRH throughout pregnancy is likely to be one of uterine relaxation. The binding affinity of the CRH receptor in human myometrium increases during pregnancy, but then decreases before parturition. Grammatopoulos *et al.* (1999b,c) suggested that oxytocin effects this change by upregulating a PKC that phosphorylates the CRH receptor protein, resulting in desensitization and loss of the inhibitory influence of CRH on myometrium. Therefore, the peptide CRH may act as an inhibitor or stimulant to the myometrium, depending upon the affinity and second messenger of the different receptor species (Spaziani *et al.*, 2000; Karteris *et al.*, 2001).

The differential effects of CRH on the myometrium may also contribute to the regionalization of myometrial activity at term and in the preterm period. Stevens *et al.* (1998) showed that the expression of CRH-R1 in myometrium collected from the lower uterine segment was higher in patients in labour compared with those not in labour. Furthermore, expression of CRH-R1 was substantially higher in lower segment compared with fundal myometrium when paired samples of tissue from individual patients were examined. Thus, during labour, CRH may promote relaxation of the lower segment but stimulate activity in the body of the uterus. This stimulatory action could be direct or indirect, as CRH stimulates output of PGs by upregulating PGHS-2 and downregulating PGDH in human fetal membranes.

It is possible that increasing maternal plasma CRH concentration may be used to predict women destined to enter preterm labour. McLean *et al.* (1995) demonstrated increased maternal plasma concentrations of CRH as early as weeks 14–16 of pregnancy in women who subsequently delivered preterm, and lower concentrations of CRH in the plasma of women who delivered post term. Korebrits *et al.* (1998) found that maternal plasma CRH concentrations were higher in patients at weeks 28–32 of pregnancy with an initial diagnosis of threatened preterm labour, who

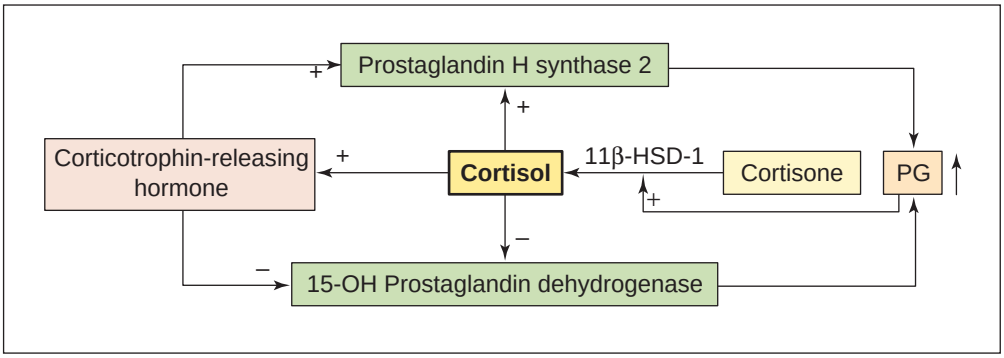

Fig. 4. Cortisol and prostaglandin (PG) interactions in the human fetal membranes. 11β-HSD-1: 11β-hydroxysteroid dehydrogenase 1. (Adapted from Challis *et al.*, 2000.)

delivered within 48 h. However, CRH concentrations were within the normal range in patients with the same initial diagnosis who proceeded to delivery at term. At present, it seems unlikely that a single measurement of maternal plasma CRH will provide an adequate means of predicting the patient who is at risk of preterm labour. However, a combination of biochemical tests including CRH and salivary oestriol, combined with measurements of fibronectin, may be of sufficient sensitivity and specificity to be used clinically.

Birth – an integrated series of autocrine–paracrine loops?

From the preceding discussion, it should be apparent that birth, at term and preterm, results from processes leading to increased PG output. Glucocorticoids have a central role in those processes, stimulating CRH output within placenta and fetal membranes. Similarly, CRH upregulates PGHS-2 and downregulates PGDH. The effects of CRH may be modulated by the state of the CRH receptor. Oxytocin appears to play a key role in changing the affinity of CRH receptor interaction. Oxytocin may be derived from the systemic circulation, and also locally from chorion or decidua.

Increased concentrations of cortisol may be derived from the maternal circulation, for example in association with a maternal stress response, or from the fetus after precocious activation of the fetal HPA axis. In addition, cortisol can be formed locally within chorion trophoblast cells from the inactive precursor cortisone. The expression of 11β-HSD-1, which effects this conversion, increases in chorion trophoblasts progressively during human gestation. Alfaidy and Challis (2000) have demonstrated that PGE_2 and $PGF_{2\alpha}$ act to increase local cortisol concentrations in chorion (Fig. 4). PGE_2 and $PGF_{2\alpha}$ increase 11β-HSD-1 activity in chorion via a Ca^{2+}-dependent mechanism, which also results in increased production of cortisol derived either from circulating cortisone or from increased cortisone in the amniotic fluid owing to a developing fetal HPA axis. Furthermore, PGE_2 and $PGF_{2\alpha}$ decrease 11β-HSD-2 activity in placenta, which also results in an increase in local cortisol concentrations. This cortisol can then act on PGDH, PGHS, and CRH to further increase PG concentrations. These feed-forward loops serve to increase both local cortisol and local PG concentrations. The increase in intracellular cortisol at term may facilitate withdrawal of progesterone effects at the GR as a result of increased cortisol concentrations and a higher affinity of cortisol for its own receptor. Where there is infection, other agents such as cytokines can intercede in this series of autocrine–paracrine loops by stimulating PGHS-2 and downregulating PGDH expression. In the presence of such complex intracellular feed-forward loops, it is not surprising that the prevention of preterm labour has eluded us. Current tocolytic therapies have been designed to block one part of this complex pathway by treating a symptom of labour such as uterine contractility rather than the underlying cause, and clearly this approach has been unsuccessful.

It is also apparent that the mechanisms that predispose to preterm labour almost certainly vary at different stages of gestation. The incidence of preterm birth in association with chorioamnionitis is higher earlier in pregnancy. Later in gestation, the fetal stress response may predominate. In this situation, fetal HPA activation increases fetal cortisol output which, in turn, upregulates placental CRH expression. This contention is consistent with the higher concentrations of CRH in the umbilical cord plasma of fetuses with intrauterine growth restriction (IUGR). Placental CRH also drives fetal adrenal steroidogenesis, leading to increased production of dehydroepiandrosterone (DHEA) from the fetal zone of the fetal adrenal. DHEA, in turn, is aromatized in the placenta to oestrogen, thereby contributing to myometrial activation.

An additional concern is the excessive use of synthetic glucocorticoids to promote fetal lung maturation in women

who are at threat of preterm labour (Ballard and Ballard, 1995). Although there are many beneficial effects of endogenous glucocorticoids, such as maturation of fetal organ systems required for extrauterine life (Liggins, 1977; Ballard and Ballard, 1995), exogenous corticosteroids given to pregnant women at risk of preterm labour (Elliott and Radin, 1995; Yeshaya *et al.*, 1996) and to animals (Liggins, 1968; Liggins *et al.*, 1973), have been shown to increase uterine activity. The effects of exogenous corticosteroids on labour and delivery problems and neonatal outcomes in asthmatic women have been well researched. Perlow *et al.* (1992) showed that preterm delivery and premature rupture of membranes are more common among asthmatic women with data demonstrating a preterm delivery incidence of 54.8% for corticosteroid-dependent women and 14% for non-corticosteroid-dependent women. Other groups have also found that corticosteroid-dependent asthmatic women have significantly higher risks of premature rupture of membranes, preterm labour and delivery, Caesarean delivery and other maternal complications (Perlow *et al.*, 1992; Doucette and Bracken, 1993; Demissie *et al.*, 1998). Furthermore, corticosteroid-dependent women had a significantly higher incidence of low birth weight babies (Schatz *et al.*, 1990; Perlow *et al.*, 1992; Jana *et al.*, 1995; Demissie *et al.*, 1998).

Since the diagnosis of preterm labour cannot be made with accuracy because of a lack of any clear quantifiable marker, some patients may receive repeated corticosteroids unnecessarily (Ballard and Ballard, 1995). Risks of steroid exposure include adrenal insufficiency, growth retardation and immune suppression (Reinisch *et al.*, 1978; Uno *et al.*, 1990; Seckl and Meaney, 1993; Bakker *et al.*, 1995; Barbazanges *et al.*, 1996; Ikegami *et al.*, 1997; Seckl and Miller, 1997) and the risks of repeated steroid exposure are unknown. Exposure to corticosteroids *in utero* may program the fetus for altered stress responses after birth that may predispose to adult onset diseases such as diabetes mellitus, hypertension and coronary heart disease (Seckl and Miller, 1997; Dodic *et al.*, 1998). An additional risk of exogenous corticosteroids may be to precipitate preterm labour. Therefore, it is crucial that care is taken in the dose and repetition of corticosteroids given to women who appear to be threatened with preterm labour. The ability to predict or diagnose the patient in preterm labour will be invaluable in selecting those women for whom prenatal corticosteroids should be administered.

Work in the authors' laboratories has been supported by the Canadian Institute of Health Research (CIHR) Group in Fetal and Neonatal Health and Development. The authors gratefully acknowledge support from the Parke-Davies Fellowship Trust of the University of Cambridge.

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