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15. Steroids in Parturition and Pregnancy

CONTROL OF PLACENTAL ENDOCRINE FUNCTION; ROLE OF ENZYME ACTIVATION IN THE ONSET OF LABOUR

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SUMMARY

The high levels of cortisol present in the fetal circulation during the last week of gestation in certain domestic animals appear to initiate labour by increasing placental production of oestrogens. This endocrine change may be brought about by the activation or induction of placental C_{21}-steroid 17α-hydroxylase and C-17,20 lyase. We review the evidence for this mechanism in the sheep and assess whether it could occur in other species.

During pregnancy the fetus influences the maternal endocrine environment by supplying to the placenta substances for conversion into steroid hormones. An example of this process is found in the feto-placental unit in women with the placental production of oestriol from fetal 16α-hydroxy-dehydroepiandrosterone sulphate. A different form of control of trophoblast metabolism has recently become evident in that some aspects of placental endocrine function may be influenced through the activation of enzymes or the induction of their synthesis. The concentration of cortisol in the fetal circulation, which rises dramatically towards the end of gestation in the sheep and the goat, activates or induces placental enzymes in the biosynthetic pathway from progesterone to oestrogens. If this process causes the maternal endocrine changes (decreasing progesterone and increasing oestrogens levels) which initiate parturition, then it is of major physiological importance. Furthermore, this control mechanism may be only one of several which affect placental endocrine function in different species, and perhaps at different gestational stages. In this paper we review the current state of our understanding of the control of placental endocrine function through changes in enzyme profiles. Since the occurrence of this phenomenon is best understood in relation to the onset of labour in domestic animals, this aspect will be dealt with in most detail.

ENDOCRINE CHANGES BEFORE PARTURITION

Pregnancy in the sheep, as in many species, is maintained by a high circulating progesterone concentration in the mother, and parturition is always preceded by a fall in the progesterone concentration. This fall occurs at about the time that the fetal level of cortisol rises, and it can be caused prematurely by administering glucocorticoids to the fetus. These endocrine changes in the fetus and mother, which have been reviewed recently [1], are thought to be the consequence of the changes in placental enzymes described below.

The changes in maternal concentrations of progesterone and oestrogens are important in controlling the onset of labour. Although the local concentrations of the steroids in the placenta and myometrium are probably more important than their circulating concentrations, uterine contractions can be blocked by giving high doses of progesterone systemically, and labour (often abnormal) can be induced prematurely with high doses of oestrogen. Since labour can be prevented with prostaglandin synthetase inhibitors [2], and uterine contractions can be caused by infusing prostaglandin $F_{2\alpha}$ [3], it is probable that, as in other species, the steroids control uterine contractility by modulating prostaglandin synthesis.

PLACENTAL ENZYME ACTIVITIES IN SHEEP

The methods used to measure the enzymes described below do not differentiate between increases in enzyme activities due to changes in enzyme concentration as opposed to activation of existing enzyme molecules. As we cannot yet exclude either mechanism, we use the term "activation" to include both possibilities.

That the maternal endocrine changes before parturition can be explained in terms of altered placental enzyme activities is indicated by observations made both *in vivo* and *in vitro*. Since the ruminant placenta is multicotyledonary, placentomes can be removed surgically throughout gestation for analysis *in vitro* without interrupting pregnancy, and this permits the demonstration of changes in the metabolism of C_{21}-steroids by cell-free extracts or minces, at the time of the fall in progesterone and rise in oestrogen. Using this approach, Anderson, Flint and Turnbull [4] showed that a rise in placental 17α-hydroxylase activity occurred before the onset of spontaneous parturition, or of parturition induced with exogenous glucocorticoid (Fig. 1). The main product of the in-

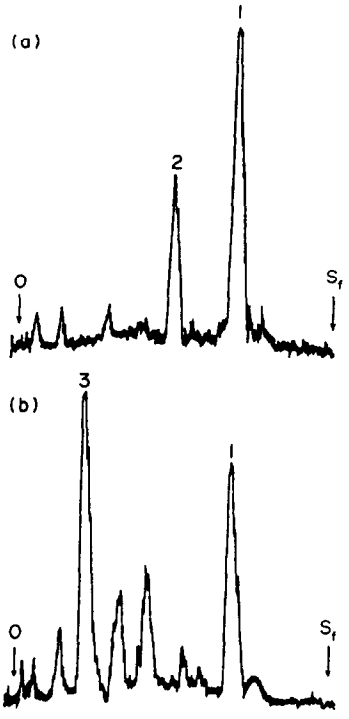

Fig. 1. Radiochromatogram scans illustrating metabolites formed from [^{3}H]-pregnenolone (2) by minced placenta. Origins are to left, solvent fronts to right. Placentomes were obtained (a) at approx. 120 days' gestation, before onset of labour; (b) 18 h after administering dexamethasone to the fetus. Steroids produced are: (1) progesterone and (3) 17,20α-dihydroxy-4-pregnen-3-one (17,20α-P). From [10].

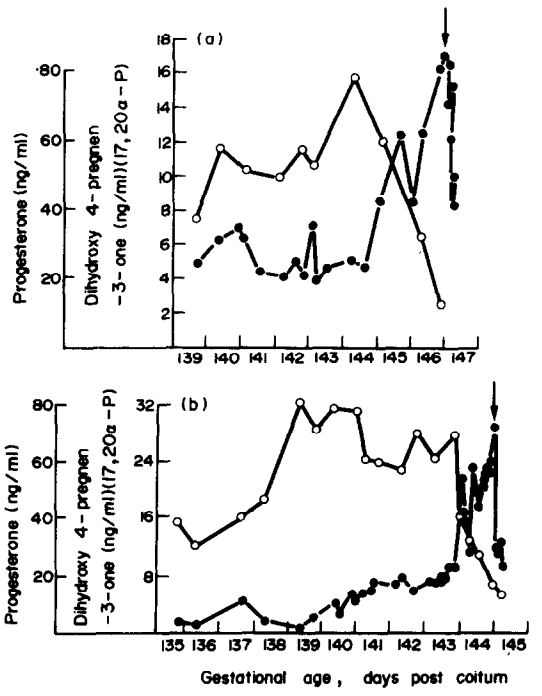

Fig. 2. Utero-ovarian venous concentrations of progesterone (○) and 17,20α-dihydroxy-4-pregnen-3-one (17,20α-P) (●) measured by radioimmunoassay during late pregnancy in two sheep lambing spontaneously at term (parturition is indicated by arrows). From [5].

creased 17α-hydroxylation *in vitro* was 17,20α-dihydroxy-4-pregnen-3-one (17,20α-P), presumably formed because of the high activity of 20α-hydroxysteroid dehydrogenase in the placenta. This increase in the activity of 17α-hydroxylase was not due to a change in precursor pool size and could not be achieved by adding glucocorticoid to cell-free extracts or minces *in vitro*. Subsequently, levels of 17,20α-P (measured by radioimmunoassay) were found to rise in the maternal circulation both at spontaneous and glucocorticoid-induced parturition [5] (Fig. 2). The activation of 17α-hydroxylase has recently been confirmed in fetuses treated with cortisol [6].

Using similar *in vitro* and *in vivo* techniques, an increase was later demonstrated in placental C-17,20 lyase activity [7]. The activity of this enzyme increases approx. 6-fold between 125 days' gestation and either spontaneous or glucocorticoid-induced parturition (Table 1) and its activation is accompanied by an increase in the maternal and fetal circulating concentrations of its product, androstenedione [8]. The observation that the rat testicular C-17,20 lyase is inhibited by progesterone [9] raises the possibility that this activation is a consequence of the falling level of progesterone in the tissue at this time. However, it is evident that as the fetal glucocorticoids rise, the enzymes 17α-hydroxylase and C-17,20 lyase are activated, the placenta becomes increasingly capable of synthesizing oestrogens from C_{21}-steroids, and the progesterone falls and oestrogens rise. This has led to the suggestion that the decrease in circulating maternal progesterone level occurs as a result of the metabolism of progesterone synthetized in the pla-

Table 1. Oestrone synthesis from 17α-hydroxy[^{3}H]-progesterone by microsomal fractions of ovine placentae

	No. of placental samples	Gestational age range (days)	Oestrone synthesis*	Peripheral plasma oestrogen concentration (pg/ml)†
Before labour	5	121–138	3.2 ± 0.20	89 ± 27
After spontaneous labour	5	142–146	20.6 ± 4.56	739 ± 210
After induced labour	4	127–130	24.4 ± 1.07	524 ± 126

Data from [7].

* Values are means ± SE for the per cent conversion of labelled substrate to [^{3}H]-oestrone (identified by recrystallization to constant specific activity).

† Mean ± SE.

centa to oestrone sulphate [10]. A rise also occurs in placental aromatase activity at the end of pregnancy [11, 12], but the significance of this change is uncertain, as *in vitro* studies suggest that C-17,20 lyase is rate-limiting in the synthesis of oestrogens from 17α-hydroxyprogesterone [7]. Observations *in vivo* on the ratio of oestrone sulphate to androstenedione in the uterine vein (which ranges from 18:1 to 64:1) support this [13].

An alternative hypothesis for the rise in maternal oestrogen levels during labour, that it may be dependent on increased secretion of androgens by the fetal adrenals [14, 15], was disproved by the observation that a rise of comparable magnitude was observed in oestrogen levels when ewes carrying bilaterally adrenalectomized lambs were induced to deliver by administration of glucocorticoid to the fetus [13]. Other maternal endocrine changes (in progesterone, 17,20α-P and androstenedione) were also normal in these animals. Although this finding does not rule out some contribution to the maternal oestrogen pool from androgens of fetal origin, it does show that a large proportion of the oestrogen formed at term arises by a pathway independent of the fetal adrenals.

OESTROGEN SYNTHESIS IN MID-PREGNANCY

The changes in placental enzymology described above may account for the fall in progesterone and rise in oestrogen occurring in maternal plasma during the last week of gestation, but they do not throw any light on the large rise in the production and excretion of oestrogens which occurs during the second half of pregnancy [16]. The origin of the oestrogen is presumably placental though, as shown above, the placenta appears to be deficient in C_{21}-steroid 17α-hydroxylase until the fetal cortisol level rises at term. The placenta is capable of aromatization, however [17], and contains some C-17,20 lyase [7, 18] in late pregnancy, and it is possible therefore that the high rate of oestrogen production depends on secretion of 17α-hydroxylated C_{21}-steroids or androgens by other steroidogenic organs of the mother or fetus. In order to assess the possible role of the adrenals in providing precursors, cortisol, 17,20α-P, androstenedione and oestrone sulphate were measured in maternal plasma after maternal adrenalectomy and oestrone sulphate was measured in fetal plasma after fetal adrenalectomy.

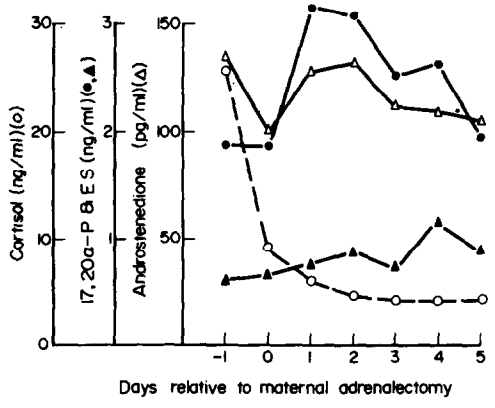

Fig. 3. Concentrations of cortisol (○), 17,20α-dihydroxy-4-pregnen-3-one (17,20α-P) (●), androstenedione (△) and oestrone sulphate (▲) in maternal jugular venous plasma, before and after bilateral maternal adrenalectomy. Values are means for daily samples in three animals. Adrenalectomy was performed between 98 and 104 days' gestation; replacement therapy (dexamethasone and deoxycorticosterone acetate) was started on the day before surgery. Unpublished data of A. P. F. Flint and A. B. M. Anderson.

As shown in Fig. 3, there was no decrease in the level of 17,20α-P, androstenedione or oestrone sulphate after maternal adrenalectomy, although the maternal cortisol level dropped dramatically; in fact in some animals the 17,20α-P, androstenedione and oestrone sulphate concentrations increased (possibly because the dexamethasone given as replacement therapy activated 17α-hydroxylase). Similarly there was no change in fetal oestrone sulphate levels after fetal adrenalectomy; the mean level in intact lambs (16 samples obtained from 6 lambs between 127 and 136 days' gestation) was 3.6 ± 1.2 ng/ml (±SD); the level after bilateral adrenalectomy (in 7 samples from 3 lambs obtained during the same period) was 3.8 ± 1.5 ng/ml. The sensitivity of the oestrone sulphate assay was equivalent to 230 pg/ml. One explanation for these findings is that the *in vitro* analysis of placental extracts or minces underestimates 17α-hydroxylase activity, and that some conversion of C_{21}-steroids to androgens is occurring throughout pregnancy, accounting for the basal levels of oestrogens produced. This is supported by the presence of relatively high levels of 17,20α-P and androstenedione in the maternal circulation [5, 8] and their rapid disappearance *post partum*.

An alternative explanation is that placental aromatase is normally saturated by the available androgen so that when the maternal adrenals are removed the rate of aromatization, using fetal androgens, is unchanged; the same may apply after fetal adrenalectomy, utilizing androgens produced by the mother. Attempts to assess this possibility by maintaining bilaterally adrenalectomized fetuses in bilaterally adrenalectomized mothers have been unsuccessful. A contribution from the maternal ovaries has not been excluded in these experiments, though this seems unlikely on the basis of data previously obtained by ourselves and others [13, 19, 20]. It should be noted that the observation that maternal adrenalectomy has no effect on circulating oestrogen levels is not in agreement with the findings of Thompson and Wagner[19], who found lower uterine venous oestrone levels in adrenalectomized ewes in late gestation.

PLACENTAL ENZYMES IN CULTURE

The activation of 17α-hydroxylase, C-17,20 lyase and aromatase is readily demonstrable *in vivo*, but

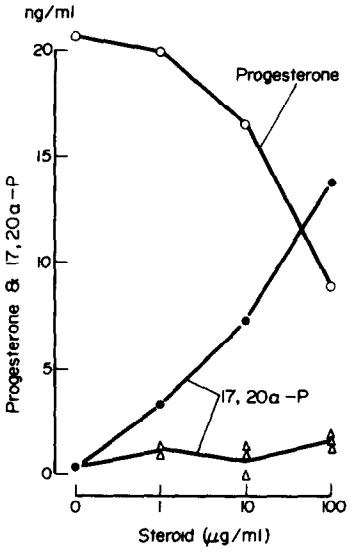

Fig. 4. Production of progesterone and 17,20α-dihydroxy-4-pregnen-3-one (17,20α-P) by explants of ovine placenta in culture. Tissue fragments from a placenta on Day 133 p.c. were cultured for 24 h in the presence of varying concentrations of cortisol, aldosterone, deoxycorticosterone or corticosterone (0–100 μg/ml in TC 199). Mean concentrations are given of progesterone (○) and 17,20α-P (●) in the medium for duplicate cultures with cortisol; values for 17,20α-P produced in presence of the other steroids are also presented (△). Unpublished data of A. P. F. Flint, A. K. A. Galil and R. B. Heap.

it is not certain whether the effect of cortisol is exerted directly on the placenta, or whether it may be mediated by another fetal, or maternal factor. It is also possible that another substance in the fetal circulation plays a permissive role in the process. The enzymes can be shown to be activated after fetal adrenalectomy, so it seems unlikely that products of the fetal adrenal cortex other than cortisol are involved; on the other hand factors of fetal pituitary origin have been implicated in the development of placental oestrogen production [21], as well as in binucleate cell migration in the placenta [22] and it was of interest therefore to determine whether isolated placental explants maintained in organ culture would respond to cortisol with activation of the enzymes of oestrogen synthesis.

High levels of cortisol or dexamethasone (up to 100 μg/ml) reduce production of progesterone by placental explants, and induce the formation of a compound cross-reacting in the radioimmunoassay for 17,20α-P (Fig. 4). However, 17α-hydroxylase has not been demonstrated in explants homogenized after culture in the presence of cortisol. The C-17,20 lyase has not been investigated in culture, but aromatase can also be shown to be activated in the presence of cortisol [23].

The data of Kendall *et al.*[21], which support the hypothesis that a fetal pituitary factor was required for full activation of the pathway from progesterone to oestrogens, was interpreted by the authors as implying activation of 17α-hydroxylase (since glucocorticoid or Synacthen would elicit a fall in progesterone levels after administration to a fetus hypophysectomized *in utero*) but not of C-17,20 lyase (since the unconjugated oestrogens failed to rise under these circumstances). This conclusion is consistent with the findings so far made in culture, which indicate that 17α-hydroxylase and aromatase can be activated in isolated tissue, but which do not relate to C-17,20 lyase.

PLACENTAL ENZYME CHANGES IN OTHER DOMESTIC ANIMALS

In the sheep, progesterone of placental origin is capable of maintaining pregnancy after ovariectomy from about Day 50 p.c. [24], whereas in the goat, the cow and the sow the bulk of the progesterone required for pregnancy maintenance is secreted by the corpora lutea. Yet in these species a reduction in progesterone levels and a rise in oestrogen precedes parturition, and a rise in fetal cortisol appears to trigger these maternal endocrine changes, as in the sheep [25–28]. It is of interest therefore to determine whether placental endocrine function is altered in these species late in pregnancy and, if so, how the message triggering parturition is transferred from the placenta to the maternal corpus luteum.

Most work in these animals has been done on the goat. Studies on progesterone metabolism reveal that (unlike that of the sheep) the placenta of the goat metabolizes progesterone to 5β-pregnanediol compounds in late pregnancy; and that (as in the sheep) a more polar, 17α-hydroxylated-C_{21}-metabolite is formed after exposure to cortisol or dexamethasone in the fetal circulation [29]. Thus the spontaneous onset of parturition at term, and premature labour induced with glucocorticoid, is associated with increased 17α-hydroxylation (Fig. 5). Induction of labour with prostaglandins, on the other hand, is not accompanied by a rise in 17α-hydroxylase, since the prostaglandins are directly luteolytic, by-passing increased placental oestrogen synthesis.

With the appearance of placental 17α-hydroxylase at term the placenta becomes capable of synthesizing oestrogens from C_{21}-steroids; it already contains C-17,20 lyase and aromatase [29, 30]. Oestrogens are luteolytic in the goat in late pregnancy, and parturition can be induced by small doses of oestradiol-17β (though not by oestradiol-17α) [31]; it seems probable therefore that fetal cortisol exerts its luteolytic effect through the enhancement of placental oestrogen synthesis [27]. However, neither the increase in circulating concentrations of oestradiol-17β [29], nor the rise in other oestrogens [32–34] has been attributed to increased placental synthesis. There is little increase in arterio-venous difference across the uterus for oestrone or oestradiol-17α [32] and no evidence for an increase in the blood production rate of oestrone [35]. Recently a large increase in mammary oestradiol-17β production has been demonstrated near term

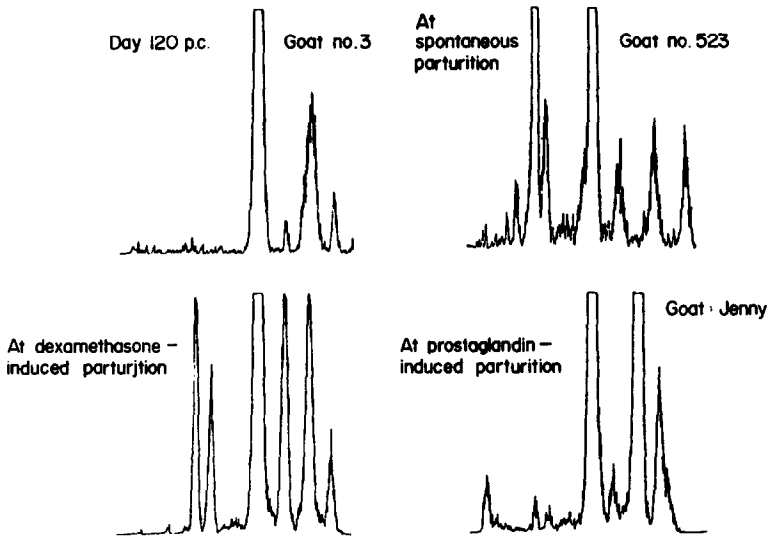

Fig. 5. Radiochromatogram scans illustrating the metabolism of [^{3}H]-progesterone. Origins are to left, solvent fronts to right. Homogenates were prepared from placentae obtained before labour at 120 days' gestation; from the same goat after parturition induced on Day 130 by intrafetal administration of dexamethasone; at spontaneous parturition, Day 153; and at parturition induced with 15-methyl-prostaglandin $F_{2\alpha}$ on Day 144. In the trace obtained at dexamethasone-induced parturition (bottom left) the 6 peaks of radioactivity correspond to (numbering from left): 1 and 2, pregnanetriols; 3 and 4, pregnanediols; 5, unidentified; 6, progesterone. The major pregnanetriol has been tentatively identified as 5β-pregnane-3β,17,20α-triol [29].

[36]; but whether this represents *de novo* synthesis or formation from precursors supplied by the placenta is not known.

Although no direct measurements of C-17,20 lyase have been made in the goat placenta around parturition, any change in the activity of this enzyme at term appears to be smaller than in the sheep (A. P. F. Flint, unpublished observations). There is a rise in maternal circulating androstenedione level before parturition (Table 2), but much less than that in sheep. One explanation for this might be that androstenedione is converted to epitestosterone in the placenta, and that as a result any activation of C-17,20 lyase may cause a larger rise in epitestosterone than in androstenedione. A high rate of 17α-reduction is consistent with the high level of circulating oestradiol-17α in the goat [32]. To test this possibility, epitestosterone was measured by a specific radioimmunoassay, in maternal plasma both at spontaneous and glucocorticoid-induced parturition (Fig. 6). By measuring arteriovenous differences across the uterus, epitestosterone was shown to be present, and its site of production localized within the pregnant uterus. The level dropped rapidly after kidding, consistent with it being a placental product. Although there was a rise in the maternal circulating level in both spontaneous and induced kidding, the rise was small compared to that in total unconjugated oestrogens, and it was concluded that epitestosterone levels provided little evidence for activation of C-17,20 lyase.

Changes in levels of cortisol in the fetal circulation and of progesterone and oestrogens in the maternal circulation are similar in the goat, cow and sow, but little is known of any placental enzyme changes in late pregnancy in the latter two species. Preliminary data suggest that in many respects placental enzymology in the cow is similar to that in the goat; both species are currently under investigation.

Table 2. Concentrations of androstenedione in maternal peripheral plasma in goats in late pregnancy and during the 6 h preceding parturition

	No. of samples	No. of animals	Gestation age range (days)	Androstenedione concentration (pg/ml)*
In late pregnancy	12	4	116–127	182 ± 4
At spontaneous parturition	6	5	146–153	402 ± 72
At dexamethasone-induced parturition	11	4	126–136	423 ± 38

Data from [27].
* Mean ± SEM.

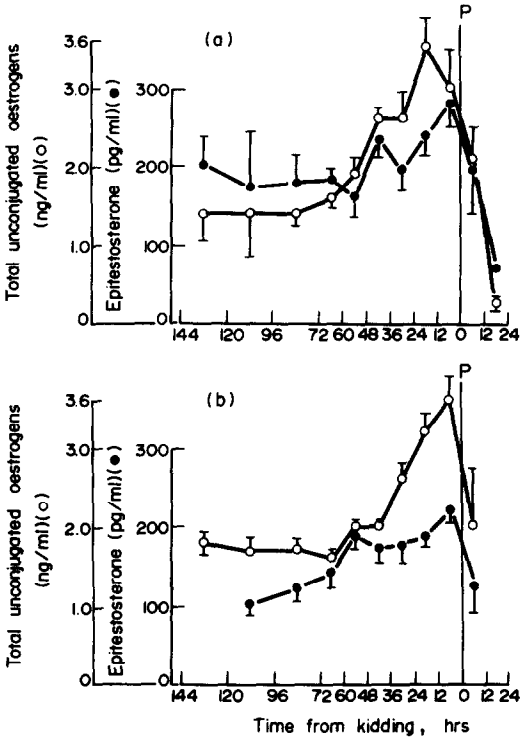

Fig. 6. Maternal peripheral plasma concentrations of epitestosterone (●) and total unconjugated oestrogens (mainly oestradiol-17α) (○) before (a) spontaneous ($n = 11$) and (b) dexamethasone-induced ($n = 4$) parturition. Both steroids were measured by radioimmunoassay. Vertical bars represent SEM. Unpublished data of A. P. F. Flint and P. Burrow.

CONTROL OF PLACENTAL ENDOCRINE FUNCTION IN PRIMATES

From the point of view of the steroid hormones, the endocrinology of pregnancy in primates differs radically from that in the domestic animals dealt with above. The existence of a "fetal zone" in the fetal adrenal, which in man secretes large amounts of 5-ene-steroids, particularly dehydroepiandrosterone sulphate, accounts for the high rate of oestrogen production characteristic of human pregnancy. However, in man, high plasma oestradiol-17β concentrations do not of themselves cause parturition. Administration of glucocorticoids to primates during pregnancy suppresses the fetal pituitary–adrenal system, thereby decreasing oestrogen production, rather than increasing it as in the sheep [37]. Although it has been suggested that high doses of glucocorticoids will induce labour in cases of post-maturity [38, 39] this has not been found to apply in normal pregnancy before term either in women or in non-human primates [40, 41]. This striking contrast between the domestic animals and the primates may be understood in terms of the patterns of changes in fetal cortisol concentrations in the two groups. Whereas fetal cortisol levels rise dramatically before parturition in the former species, they rise much more gradually, and over a longer period, in the latter [42].

Aromatase and C-17,20 lyase are present in the human placenta, the former in high activity [43]. 17α-Hydroxylase has been reported to be present [44, 45], but this remains controversial; the human placenta produces large amounts of 17α-hydroxyprogesterone but this is synthesized from precursors, mostly 17α-hydroxypregnenolone, supplied to it by the fetal adrenals [46]. It has not been suggested that these enzymes are activated at term, though it does appear that the concentration of aromatase may alter in certain pathological conditions [47].

Although changes in these enzyme activities are not implicated in the mechanisms underlying parturition, the endocrine function of the primate placenta is controlled in several ways. An important form of control is through the supply of substrates to the placenta (for instance of androgens from the fetal adrenal); this accounts for the low maternal oestriol excretion rate in fetal growth retardation or distress. However, there is some evidence that placental endocrine function may also be influenced through the activation (or induction) of enzymes. Placental 3β-hydroxy-steroid dehydrogenase activity is reduced after fetal hypophysectomy in rhesus monkeys [48], though it is not known why. Furthermore, Salbutamol (a β-adrenergic drug administered intravenously in cases of preterm labour) reduces the maternal circulating progesterone and oestrogen levels, presumably through an effect on placental steroidogenesis [49]; whether this reflects a mechanism which normally controls placental endocrine function is yet to be determined.

CONCLUSION

The activation of placental enzymes by fetal cortisol has so far been demonstrated only in species in which fetal cortisol levels are known to rise rapidly at term. A high fetal concentration of cortisol before parturition induces a variety of enzyme systems (for instance in the lung, liver and gut) necessary for neonatal survival [42]. The rôle of fetal cortisol in some species may therefore be viewed as not only preparing the fetus for extra-uterine life, but also ensuring its delivery into it.

The mechanisms outlined above by which placental endocrine control may be achieved in ruminants, that is mechanisms involving activation of enzymes, constitutes a biochemical process whereby the fetus may control the onset of labour in these animals. Furthermore, the demonstration that hormone production by the placenta may be under some form of control before parturition implies that there may be other occasions on which this may occur, and other ways in which it may be exercized. For instance we do not know the mechanism underlying the dramatic increase in placental progesterone production which occurs in mid-pregnancy in sheep [50, 51] and why it does not occur in goats. Nor is it understood why the ability of the pig trophoblast to secrete oestrogens increases during the first month of pregnancy and

then almost disappears, before rising again during the last two months [52]. The significance of the effect of β-adrenergic compounds on utero-ovarian progesterone levels [53] is not known; nor are the modes of action of Synacthen and dopaminergic drugs on placental lactogen levels in the goat and sheep [27, 54]. The elucidation of these observations may provide further insights into the control of placental function.

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