BIOLOGY OF REPRODUCTION 16, 57–69 (1977)

The Regulation of Corticosteroids During Late Pregnancy and Their Role in Parturition

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INTRODUCTION

An increase in cortisol secretion by the fetal adrenal is a consistent feature of the endocrine milieu of late pregnancy in several animal species. In this paper we shall discuss some of the mechanisms by which fetal adrenal growth and steroidogenesis are stimulated during late pregnancy, and then consider some of the functions of this increase in cortisol production, particularly in relation to the initiation of parturition and to the maturation of organ systems necessary for extra-uterine life.

CONTROL OF FETAL ADRENAL FUNCTION

A considerable body of information concerning the control of fetal adrenal function has been gained from experimental studies in sheep. In this species, fetal adrenal weight doubles during the last 20 days of pregnancy (Comline and Silver, 1961). There is a gradual rise in the concentration of cortisol in fetal plasma beginning 10–15 days *prepartum*, which culminates in a more rapid increase during the last 2–3 days of gestation (Bassett and Thorburn, 1969). The increase in cortisol is abolished by fetal hypophysectomy, and thus depends upon the presence of the pituitary (Fig. 1). In the intact fetus, the rise in cortisol production at term appears to result both from maturational changes in the fetal adrenal, and from an increase in trophic drive reaching the adrenal from the fetal pituitary (Challis et al., 1977a).

The sheep fetal adrenal can be stimulated to secrete cortisol by the continuous infusion of ACTH for 2–5 days into the fetus. This treatment leads to premature parturition (Liggins et al., 1972; Thorburn et al., 1972). However, in chronically catheterized fetal lambs during normal pregnancy there is no clear increase in the concentration of ACTH in fetal plasma before the rise in fetal cortisol (Rees et al., 1975), although the sampling regimes employed in this and other studies may have been inadequate to detect small changes in the ACTH/cortisol relationship.

In contrast, the concentration of ACTH increases in fetal plasma during the last 1–2 days of intrauterine life, at a time when cortisol is elevated (Rees et al., 1975; see Challis et al., 1977a). This rise occurs despite convincing evidence for a negative feedback relationship between glucocorticoids and ACTH in the fetus (Fig. 2), and may relate to the stress of labour. From measurements of fetal plasma ACTH concentrations during the infusion of synthetic ACTH into intact and hypophysectomized fetal lambs, it has been suggested that there is a positive stimulus to endogenous ACTH secretion which overrides negative feedback (Johnson et al., 1975). This stimulus augments the drive to cortisol secretion by the fetal adrenal at a time when the gland's responsiveness to trophic hormone has already risen (see Challis et al., 1977a and below).

In man, a decrease has been reported in the concentration of ACTH in cord plasma during late pregnancy (Winters et al., 1974). However, in view of the rapid release of ACTH in response to hypoxemia, at least in animal studies (Boddy et al., 1974; see below), interpretation of these data should be made with caution. Indeed, it may prove exceedingly difficult to obtain from the human fetus the appropriate samples for ACTH determination.

A good correlation has been demonstrated in man between the concentration of prolactin in fetal plasma, and growth of the fetal adrenal (Winters et al., 1975). In fetal sheep, a similar

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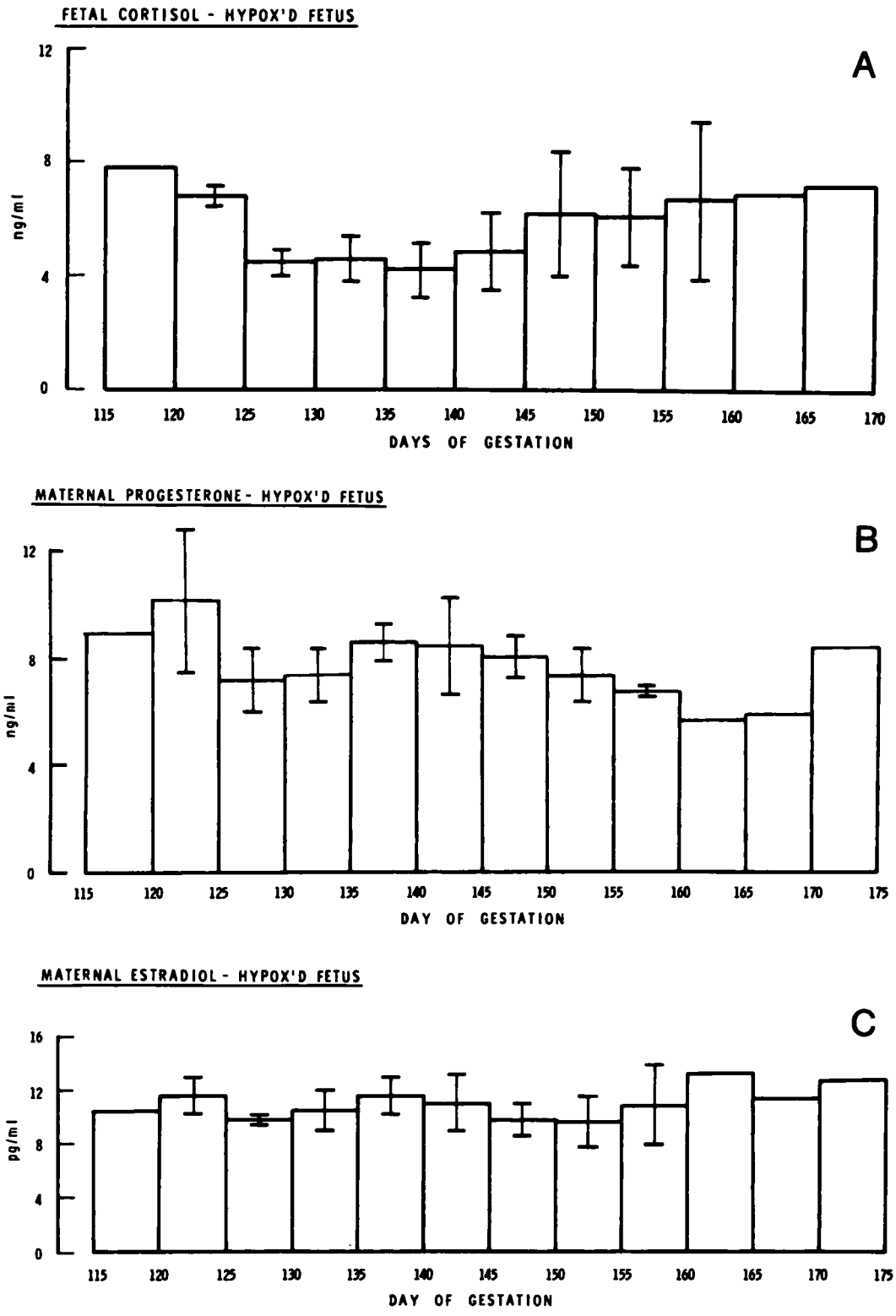

FIG. 1. Concentrations (mean ± S.E.M.) of a) fetal plasma cortisol, b) maternal plasma progesterone, c) maternal plasma estradiol during prolonged pregnancy in 3 sheep with hypophysectomized fetuses.

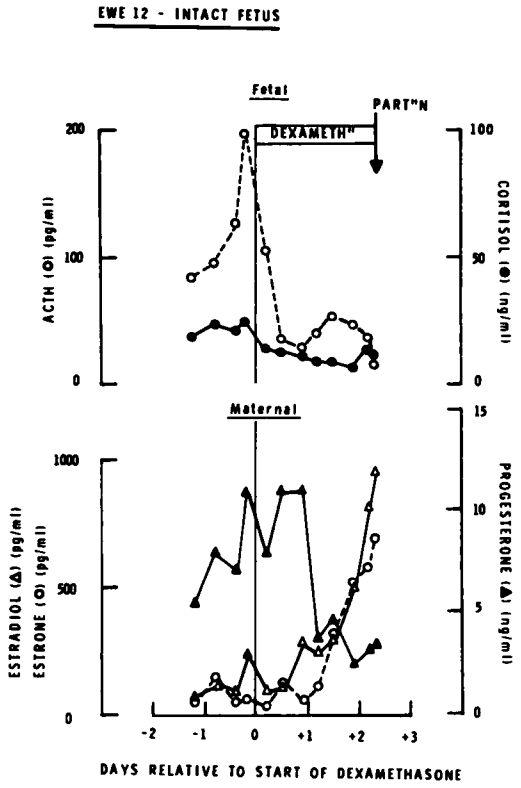

FIG. 2. Effects of intrafetal dexamethasone (1 mg/24 h) infusion on fetal plasma ACTH (o---o) and cortisol (●—●), and maternal peripheral plasma progesterone (▲—▲), estradiol (△—△) and estrone (o---o) concentrations in sheep. The dexamethasone infusion was begun on Day 128 of pregnancy. Premature delivery resulted in 56.5 h from the start of the infusion.

correlation has been found between the mean concentrations of prolactin and cortisol in plasma during the last 30 days of intra-uterine life (McMillen et al., 1976). These data raise the possibility that prolactin may be of importance in promoting the growth of the fetal adrenal and in stimulating steroidogenesis. In this regard, the importance of other pituitary hormones (GH, αMSH) cannot be excluded.

In the presence of 'basal' levels of ACTH (and/or other pituitary trophic hormones), the increase in fetal cortisol secretion may result from maturational changes in the fetal adrenal itself. *In vivo*, the intra-fetal infusion of ACTH (10 μg/h for 2–3 h) produces a greater increment in fetal cortisol after 135 days p.c. than earlier in pregnancy (Bassett and Thorburn, 1973). Hypoxemia is a potent stimulus to ACTH release by fetal sheep throughout the last 35 days of gestation, but it is only after 135–140 days that the increase in ACTH stimulates a significant increase in the cortisol concentration in fetal plasma (Boddy et al., 1974; see Challis et al., 1977a). Before this time, the resting ACTH levels in the fetus are similar to the values found in maternal plasma during hypoxemia. In the mother, these levels of ACTH elicit a large increase in cortisol secretion (Boddy et al., 1974) implying that in the fetus there is a marked reduction in the sensitivity of the adrenal to ACTH. This insensitivity may be of importance as a protective mechanism against premature labour. In sheep, there is little evidence for the transplacental transfer of ^{125}I-ACTH (Jones et al., 1975), nor is there yet evidence for a placental source of corticotrophin, as in man (Rees et al., 1975; Genazzani et al., 1975).

The development of fetal adrenal sensitivity to trophic stimulation has been demonstrated *in vitro* using a perifusion technique (Madill and Bassett, 1973; Bassett and Thorburn, 1973). Thus, the increase in cortisol secretion by slices of fetal adrenal in response to a constant amount of ACTH increased in tissue taken from older fetuses, and was highly correlated with the endogenous cortisol concentration in the plasma of the fetus from which the tissue had been removed. There was an increase in the ratio of cortisol:corticosterone produced, implying greater 17α-hydroxylating activity in the tissue from older fetuses. Perhaps surprisingly, information relating to the ontogeny, specificity and distribution of trophic hormone receptors in sheep fetal adrenals is not currently available. Recently, we have demonstrated that the intra-fetal infusion of PGE_2, but not $PGF_{2\alpha}$, at physiological concentrations, produced a rapid and significant increase in the concentration of cortisol in fetal plasma in fetuses of a mean gestational age of 128 days (Louis et al., 1976). At this stage of gestation, the fetal adrenal secretes little or no cortisol in response to short-term ACTH administration (Bassett and Thorburn, 1973; Boddy et al., 1974). This study demonstrates the presence of the pathway for cortisol production in these fetuses. It raises the possibility that if prostaglandins are involved in ACTH induced steroidogenesis (Warner and Rubin, 1975; Laychock and Rubin, 1976), a deficiency in their production may be a rate-limiting step in adrenal sensitivity. At term the concentration of PGE in fetal plasma increases (Challis et al.,

1976), and the prostaglandin may augment or complement the trophic drive from the pituitary to fetal adrenal steroidogenesis.

In sheep there is relatively little transplacental transfer of cortisol, whereas in primates the mother contributes a greater proportion of cortisol to the fetal cortisol pool (see Challis and Thorburn, 1976). In man, an increase in the concentration of cortisol in cord plasma (Murphy, 1973), and amniotic fluid (Murphy et al., 1975; Fencl and Tulchinsky, 1975) has been reported during late pregnancy. This may reflect an increase in the secretion of cortisol by the fetal adrenal (Leong and Murphy, 1976). In the rhesus monkey, a similar increase in the concentration of cortisol and other Δ_4 steroids has been measured in amniotic fluid during the 3–4 weeks before spontaneous term (Patrick et al., 1976; Challis et al., 1977). Evidence has been presented to show that these changes are not simply a reflection of a decrease in the volume of amniotic fluid.

In both man and *M. mulatta*, fetal ACTH appears necessary to maintain the structural integrity of the fetal adrenal cortex (Benirschke, 1956; Challis et al., 1974). ACTH has been demonstrated in human fetal pituitary tissue (Taylor et al., 1953) and cord plasma (Winters et al., 1974) by 10–12 weeks of pregnancy. The independence of ACTH levels in cord and maternal plasma in normal and complicated pregnancies (Allen et al., 1975) suggests that the ACTH present in the fetal circulation is, in large part, derived from the fetal pituitary. Similar conclusions may be derived from studies in the rhesus monkey (see Kittinger, 1973). In this species, ACTH stimulates cortisol release from fetal adrenals *in vivo* (Kittinger et al., 1972) and *in vitro* as early as 75 days of pregnancy (Kittinger, 1973).

CORTISOL AND PARTURITION

Field observations in sheep with prolonged pregnancy showed that this condition was associated with congenital malformations of the fetus, and fetal adrenal hypoplasia (see Liggins, 1969; Liggins et al., 1973). Fetal adrenal hyperplasia was found in habitually aborting Angora goats (van Rensburg, 1971). These findings led to the concept that the activity of the fetal pituitary-adrenal axis might determine the time of onset of parturition in animals. The observations supported a conclusion reached over 30 years previously in man by Malpas (1933). In man, anencephaly without associated polyhydramnios, congenital adrenal hypoplasia or adrenal hypoplasia may lead to a prolongation of gestation, or to a loss in the precision of the timing mechanism to parturition (see Anderson and Turnbull, 1973), although this is not invariably so (see Davies and Ryan, 1972).

The natural conditions were later reproduced experimentally in sheep with the demonstration that fetal hypophysectomy or adrenalectomy led to a prolongation of pregnancy (Liggins et al., 1967; Drost and Holm, 1968). Infusion of ACTH or of a glucocorticoid, but not mineralocorticoid hormone to the fetus precipitated premature delivery, whilst comparable infusions to the mother were ineffective in influencing the length of gestation (see Liggins, 1969; Liggins et al., 1973). Thus the fetal role appeared to be an active rather than permissive one. Further support for this role was provided in the observation of marked fetal adrenal hypertrophy in late pregnancy (Comline and Silver, 1961), and the increase in the concentration of cortisol in fetal plasma during the last 7–10 days *prepartum* (Bassett and Thorburn, 1969). This largely reflects an increase in the production rate of cortisol by the fetal adrenal (Nathanielsz et al., 1972). A similar increase in cortisol production is seen during premature parturition induced with intra-fetal ACTH infusion (Bassett and Thorburn, 1973; see below).

Thus the activity of the fetal pituitary-adrenal axis and especially changes in cortisol secretion appeared intimately involved with the onset of parturition in sheep. In primates, the experimental evidence for a primary role of cortisol in determining the length of gestation is less convincing than in sheep. In part this is due to the appreciable contribution of the mother to the cortisol present in fetal plasma (Beitins et al., 1973; Kittinger, 1974). In the rhesus monkey, fetal hypophysectomy (Chez et al., 1970), but apparently not fetal adrenalectomy (Mueller-Heubach et al., 1971) leads to prolonged pregnancy. These studies perhaps indicate the importance of pituitary factors other than those solely responsible for cortisol production in determining gestation length.

As discussed, there is evidence in both man and the rhesus monkey for an increase in fetal cortisol production in late pregnancy. However, this is a more gradual change than described in the sheep, and is superimposed on a background of a greater maternal cortisol contribu-

tion. It is of note that the morning plasma cortisol concentration was significantly lower in postmature neonates than in normal term infants (Nwosu et al., 1975), suggesting a relationship between adrenal hypoactivity and prolongation of gestation. In contrast, Anderson and Turnbull (1973) have reported an association between fetal adrenal hyperactivity (increase in adrenal weight, and elevated estriol excretion) and otherwise unexplained premature labor. Observations such as these, which have been extensively reviewed by Davies and Ryan (1972) suggest that in primates the activity of the fetal pituitary-adrenal axis may influence the length of gestation, but in a manner which is less clearly defined than in the sheep. In primates, the fetal role appears to be one of providing precision to the timing of gestation length rather than activating the entire mechanism.

CORTISOL AND PLACENTAL STEROIDOGENESIS

In sheep, the increase in fetal cortisol production during the last 7–10 days of pregnancy is closely followed by a decrease in progesterone during the last 1–4 days, and by an increase in unconjugated estrogen during the last 24 h of gestation. The elevated levels of estrogen are associated with an increase in PGF production, and with the onset of active labor (Fig. 3; see Challis and Thorburn, 1975, 1976). Evidence is now accumulating that the increase in fetal cortisol may be responsible for both the decrease in progesterone, and increase in estrogen production rates. In the absence of an elevation in fetal cortisol, as in prolonged gestation after fetal hypophysectomy, the normal changes in maternal progesterone and estradiol do not occur.

Progesterone

In sheep, the fetal placenta is the major source of progesterone during late pregnancy (Linzell and Heap, 1968; Anderson et al., 1975). Progesterone production rates follow the plasma progesterone concentration (Bedford et al., 1973), and decrease before spontaneous or induced parturition. The factors responsible for this decrease in progesterone have been investigated by measuring enzyme activities in fetal placental homogenates before and after the intrafetal administration of glucocorticoids in amounts which suppress progesterone secretion and cause premature delivery. Whilst

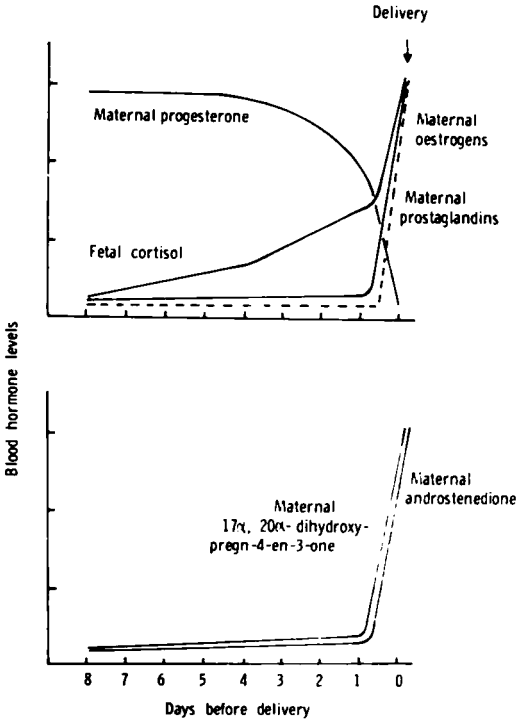

FIG. 3. Diagrammatic representation of maternal and fetal plasma hormone concentrations in relation to parturition (Day 0) in the sheep. For original references see text (courtesy of Dr. A. P. Flint).

the total activities of cholesterol side-chain cleavage and 3β-hydroxysteroid dehydrogenase enzymes were unchanged, there was a significant increase in 17α hydroxylase activity (Anderson et al., 1975). The sheep placenta possesses potent 20α-hydroxysteroid dehydrogenase activity during pregnancy, and thus after dexamethasone treatment *in vivo*, placental homogenates *in vitro* converted both [^{3}H]-progesterone and [^{3}H]-pregnenelone extensively to 17α,20α dihydroxypregn-4-en-3-one (17,20 diHP). The formation of this metabolite has been suggested as a mechanism by which progesterone production may be decreased (Anderson et al., 1975). Further support for this hypothesis has been the demonstration of an increase in the concentration of 17,20 diHP in utero-ovarian venous plasma which mirrors the decrease in progesterone concentration during both dexamethasone-induced and spontaneous delivery (Fig. 3).

Estrogens

The enhancement of placental 17α-hydroxylation may also be of potential signifi-

cance as the first step in the conversion, within the placenta, of progesterone to estrogen. *In vitro* incubation experiments have demonstrated the presence of a placental C_{17-20} lyase in sheep (John and Pierrepoint, 1975) the activity of which is increased after exposure to glucocorticoid (Steele et al., 1975). Although 17,20 diHP is not a substrate for the C_{17-20} lyase, progesterone may be converted to 17α-hydroxyprogesterone which can be used. Thus [^{3}H]-17α-hydroxyprogesterone is converted to estrogen, particularly estrone sulphate *in vitro* (John and Pierrepoint, 1975). *In vivo* the formation of the C_{19} intermediate is suggested by an increase in the concentration of androstenedione in utero-ovarian venous plasma occurring at the same time as the elevation in 17,20 diHP (Steele et al., 1976; see Fig. 3). Other workers have suggested that during late pregnancy, there may be an increase in aromatase activity, and a change in the relative activities of placental sulphatase and sulphotransferases under the influence of cortisol (Ash et al., 1973).

Further observations support the view that estrogen production in sheep at term results from the effects of fetal cortisol on placental enzymes rather than from an increase in the production of fetal adrenal C_{19} steroids. Both the maternal and fetal adrenals can provide C_{19} precursors for placental aromatization (Davies et al., 1970), but the increase in estrogen at delivery occurs after fetal (Flint et al., 1976) or maternal (Thompson and Wagner, 1974) adrenalectomy. Maternal ovariectomy has no effect on maternal plasma estrogens (Bedford et al., 1972). Suppression of the fetal pituitary-adrenal axis (as judged by a lowering of fetal plasma ACTH and cortisol) is achieved during the intra-fetal infusion of dexamethasone at amounts which precipitate premature delivery (Fig. 2). However, the changes in maternal progesterone and estradiol during dexamethasone-induced delivery resemble those seen at normal term, and are consistent with the increase in estrogen resulting from a direct effect of the glucocorticoid on placental enzymes. An increase in maternal estrogen is also seen during premature delivery induced by dexamethasone infusion to adrenalectomized fetal lambs (Flint et al., 1976). Finally, no increase has been found in the concentration of potential C_{19} estrogen precursors, androstenedione and testosterone in fetal plasma during spontaneous or ACTH-induced parturition (Strott et al., 1974; Liggins et al., 1977).

Whilst an increase in fetal cortisol stimulates changes in placental steroidogenesis, it is apparent that the magnitude of this increase need not be a critical factor. Further, if there are differences in the sensitivity of different placental enzyme systems to cortisol a change in progesterone need not invariably be associated with an increase in unconjugated estrogen. These possibilities have been examined in four intact and four hypophysectomized fetal lambs infused with Synacthen (β1-24 ACTH, 10 μg/h) until delivery occurred (Table 1). The results may be compared with other fetal lambs treated with dexamethasone (Kendall et al., 1975). Hypophysectomy was judged complete on the basis of macroscopic examination of the sella turcica, and the finding of levels of ACTH, GH and prolactin in fetal plasma of <10 pg/ml,

TABLE 1. Time to delivery induced by Synacthen or dexamethasone infusion in intact or hypophysectomized fetal sheep.

	Synacthen (β1-24 ACTH)** infusion		Dexamethasone infusion**	
	Intact fetus	Hypophysectomized fetus	Intact fetus	Hypophysectomized fetus
Time (hours) mean ± S.E.M.*	70.5 ± 8.3^{ab}	99.8 ± 8.0^{bcd}	49.8 ± 2.3^{ac}	52.8 ± 4.9^{d}

*n = 4 fetuses in each group. Significant differences (t test) between means with the same superscript are as follows: a, $P<0.05$, b, $P<0.05$; c, $P<0.01$; d, $P<0.01$.

**Synacthen (β1-24 ACTH, Ciba Ltd.; 10 μg/h) or dexamethasone (dexamethasone phosphate, Ciba Ltd.; 42 μg/h) were infused into a fetal vein commencing on days 124–129 of pregnancy, some 7–14 days after fetal surgery, and continued until delivery occurred.

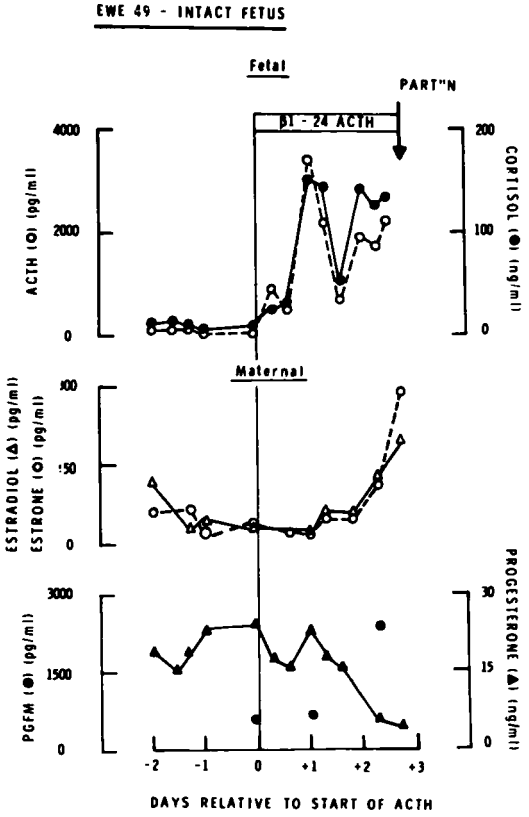

FIG. 4. Effects of Synacthen (β1-24 ACTH 10 μg/h) infusion into an intact fetal lamb on the concentrations of ACTH and cortisol in fetal plasma, and estrone, estradiol, progesterone and 13,14 dihydro 15-keto $PGF_{2\alpha}$ (PGFM) in maternal peripheral plasma. The ACTH infusion was started on Day 127 of pregnancy. Premature delivery occurred in 66 h.

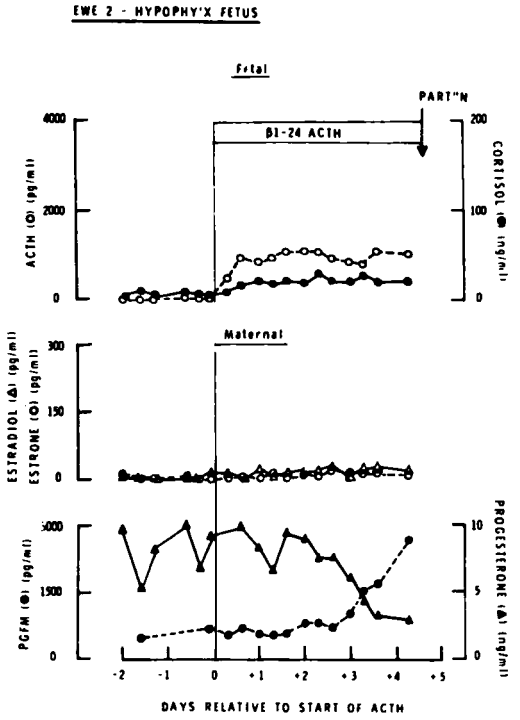

FIG. 5. Effects of Synacthen (β1-24 ACTH, 10 μg/h) infusion into a hypophysectomized fetal lamb on the concentrations of ACTH and cortisol in fetal plasma, and estrone estradiol, progesterone and 13,14 dihydro 15-keto $PGF_{2\alpha}$ (PGFM) in maternal peripheral plasma. Fetal hypophysectomy was performed on Day 110 p.c. The intra-fetal ACTH infusion was started on Day 126 p.c. Premature delivery occurred in 110 h.

<0.5 and <0.2 ng/ml respectively during the preinfusion control period, compared to levels of 50–200 pg/ml, 40–100 ng/ml, and 5–20 ng/ml respectively in intact fetuses. The hormone changes within the 4 fetuses in each group were similar, and representative animals are presented in Figs. 4 and 5 (Kendall et al., 1975).

The mean time taken to induce delivery by continuous ACTH infusion into intact fetuses was 70.5 h. This time interval was significantly prolonged after fetal hypophysectomy, or shortened by infusion of dexamethasone. Dexamethasone was equally effective in intact or hypophysectomized fetuses. These differences may be interpreted as indicating that the effect of ACTH on the placenta is an indirect one, mediated through the stimulation of the fetal adrenal. At present, it is not known whether the differences between intact and hypophysectomized fetuses relate to the absence of other pituitary hormones (prolactin, growth hormone), or relate to the loss of ACTH receptor after hypophysectomy.

During the continuous infusion of Synacthen at a constant rate to intact fetuses, large fluctuations in fetal plasma 'ACTH' have been found using an NH_2-terminal antibody to measure both endogenous ACTH and exogenous β1-24 ACTH (Johnson et al., 1975; *vide supra*). The identity of these different molecular species has been confirmed by gel filtration (Jones, 1975). In these previous reports, as in the present study, fetal cortisol fluctuated in parallel with the ACTH changes. This raises the possibility that although fetal adrenal weight occurs in response to intra-fetal ACTH (Liggins, 1969), the levels of cortisol achieved in fetal

plasma may relate directly to an unphysiologic level of trophic stimulus applied to the gland. The changes in maternal progesterone, estrone, estradiol and prostaglandin F (measured as jugular vein levels of 13,14-dihydro-15-keto $PGF_{2\alpha}$) production in this group of sheep was similar to those found at spontaneous term (Fig. 4).

Delivery could be induced in hypophysectomized fetuses treated with ACTH at levels of plasma cortisol of only 20–25 percent those seen at spontaneous term. These values are within the range found in some intact fetuses at this stage of gestation (Challis et al., 1976), unassociated with premature delivery. They illustrate that it may be a gross over-simplification to think of the stimulus to parturition in sheep simply in terms of the concentration of cortisol achieved in fetal plasma. A consistent finding (Kendall et al., 1975) was that despite a normal decrease in plasma progesterone, there was no rise in unconjugated estrone or estradiol in maternal plasma during Synacthen administration to hypophysectomized fetuses (Fig. 5). A similar result has been reported in intact fetuses infused with dexamethasone before 125 days (Liggins et al., 1972). Although there is no estrogen rise, prostaglandin F production increases (Fig. 5), and delivery occurs. This is consistent with the suggestion that providing basal estrogen is present, prostaglandin may be produced in response to progesterone withdrawal (Currie and Thorburn, 1973).

These studies show that ACTH or dexamethasone will induce delivery when administered directly to the hypophysectomized fetus on about Day 130 p.c. At this stage of gestation maternally administered glucocorticoids have little effect on the length of pregnancy (Liggins, 1969), and Bosc (1972) showed that even at term, when maternal administration of dexamethasone is normally effective, it is not so if the fetus has been hypophysectomized. An explanation for these findings may be that an intact fetal pituitary-adrenal axis is necessary for occurrence of the normal changes in placental permeability. If the primary site of action of glucocorticoids is on the fetal placenta, such a mechanism may explain their relative ineffectiveness in inducing parturition when administered to the mother, until close to normal term (see Challis and Thorburn, 1976). This may be of value as protection against premature labour.

Cortisol and Placental Steroidogenesis in Primates

In primates there is a greater degree of permeability to cortisol than in domestic animals, and there is no evidence for placental enzyme induction or activation. In particular, exhaustive studies have shown the inability of the primate placenta to 17α hydroxylate C_{21} steroids, and have pointed to a requirement for the provision of C_{19} steroids of fetal adrenal origin as precursors for placental estrogen production (see Diczfalusy and Mancuso, 1969; Ryan, 1969; Ryan and Hopper, 1974). Thus in primates glucocorticoids reduce maternal estrogen levels as a result of suppression of the fetal pituitary-adrenal axis, but are without effect on placental progesterone production (Simmer et al., 1974; Challis et al., 1974). This situation is in marked contrast to that described in the sheep, and is a major point of divergence between the different species. Cortisol is extensively metabolized in the primate placenta (Murphy et al., 1974; Kittinger, 1974). It seems unlikely to have significant effects on placental sulphatase, 3β-hydroxysteroid dehydrogenase, or aromatase activities.

CORTISOL AND LUNG SURFACTANT

Fetal lambs, delivered by caesarean section before Days 125–130 of gestation are unable to establish satisfactory respiration. However, Liggins (1969) observed that when premature parturition was induced at that age with intrafetal glucocorticoid, the lambs were able to expand their lungs, suggesting that the glucocorticoid had accelerated lung maturation and pulmonary surfactant production. Subsequently many investigators have demonstrated the possibility of accelerating lung maturation in animals and in man by the use of glucocorticoids (see Avery, 1975; Liggins and Howie, 1972). In the fetal lamb, surface active material (S.A.M.) is first present in tracheal fluid collections on about Day 120–122 of gestation (Platzker et al., 1975) and increases thereafter. Intrafetal administration of glucocorticoid to one of a pair of twin lambs (DeLemos et al., 1970; Platzker et al., 1975) or one of a litter of rabbits (Kotas and Avery, 1971) accelerates lung maturity in the treated fetus, as judged by measurements of S.A.M. in tracheal and lung fluid, differentiation of alveolar type II cells, and the concentration of osmiophilic inclusions within these cells. In the rabbit fetus, glucocor-

ticoid injections increased the activity of lung choline phosphotransferase, one of the enzymes involved in lecithin synthesis through the cytidine diphosphate-choline pathway (Farrell and Zachman, 1973). In both rabbit and human the increase in lecithin content in fetal lung is brought about through preferential accelerated activity of the CDP-choline pathway over the methylation pathway (see Gluck and Kulovich, 1973).

Further evidence that these effects relate to cortisol has been the demonstration of cytosol and nuclear binding sites for glucocorticoids in fetal lung tissue before the normal appearance of surfactant in alveolar spaces. In the rabbit, cortisol receptors in the nuclear fraction of fetal lungs appear on Day 21, and reach their maximum concentration about Day 28, when unbound cortisol is at its maximum in fetal plasma, and surfactant production is demonstrable (Giannopoulos et al., 1972). Glucocorticoid receptors have been demonstrated in human fetal lung by 9 weeks gestation (see Giannopoulos, 1975). The mechanism of glucocorticoid uptake in rabbit fetal lung is a multi-step mechanism involving association with extranuclear receptor protein, activation, and then binding to nuclear chromatin, through acceptor sites which appear to involve DNA (Giannopoulos, 1975). The rabbit fetal lung also actively converts cortisone to cortisol, with the reverse inactivation pathway of only minor importance. After incubating either cortisol or cortisone with fetal lungs at 37°C, similar amounts of cortisol are recovered in association with nuclear receptors (Giannopoulos, 1975). Both cortisone and cortisol enhance the conversion of [^{3}H]-choline into lecithin by rabbit fetal lung cells in tissue culture. 11-Ketoprogesterone, which blocks the conversion of cortisone to cortisol, inhibits the effect of cortisone on [^{3}H]-choline incorporation into lecithin. In the human fetal lung, cortisone may be converted to cortisol. The inhibitory effect of 11-ketoprogesterone may be of physiological importance if the steroid is present in the fetal circulation in high concentrations (Torday et al., 1975).

Although some investigators (Murphy, 1974) have presented evidence for a decrease in glucocorticoid production in human infants developing respiratory distress syndrome, the results of other workers have not supported this conclusion (Reynolds, 1973; Baden et al., 1972). In the fetal lamb it is clear that the increase in surfactant production precedes the increase in both total and unbound cortisol concentrations in fetal plasma (Mescher et al., 1975). There is therefore a need for caution in interpreting the relationship between blood levels of glucocorticoids and maturation of lung function especially if the latter is expressed as the appearance of S.A.M. or a change in the L/S ratio in amniotic fluid or tracheal fluid. Consideration must be made of differences between receptor activities and steroid interactions in the fetal lung, and information is still required on the temporal relationship between S.A.M. synthesis and its appearance in amniotic fluid. The above relationships demonstrate that cortisol need not be present in high concentrations for normal maturation of the fetal lung; although clearly elevated cortisol levels will accelerated maturation. It has been pointed out that situations in which the fetus is 'stressed' *in utero* (such as infection and perhaps intrauterine growth retardation) may give rise to precocious cortisol secretion and an enhancement of lung maturation. It should be noted that other substances may influence S.A.M. production. In the fetal rabbit, both thyroxine and heroin were shown to stimulate lung maturation, although whether the action of these compounds is a direct one, or is mediated through cortisol has not been established (see Avery, 1975).

Exogenous glucocorticoids have been used in an antepartum attempt to prevent respiratory distress in man. In the original series of premature infants, Liggins and Howie (1972) used either alcohol or salbutamol to delay labor, since it is apparent that exposure to the glucocorticoid for greater than 24 h *in utero* is required. Protection from RDS was apparent in the group of infants presenting at 26–32 weeks gestational age, treated with betamethasone. After 32 weeks there was no benefit from the treatment.

CORTISOL AND OTHER ENZYME SYSTEMS IN THE FETUS

Glucocorticoids are known to be involved in the maturation and biochemical differentiation of other tissues in the fetus. Among the clearest examples is that of glycogen deposition in the liver. In the rat fetus it has been shown that following production of adrenocortical insufficiency by decapitation on Day 17 or 18 of pregnancy, liver glycogen storage was reduced by 35–50 percent on Day 21. If the mother

was also adrenalectomized, liver glycogen was reduced even further, indicating that maternal adrenal hormones can cross the placenta and substitute for the fetal hormones to a certain extent. Restoration of glycogen uptake was accomplished by administration of ACTH to the fetus, or corticosteroids to the mother or fetus (see Jost, 1969). In the rabbit fetus, suppression of liver glycogen uptake was maximal after fetal decapitation alone, and could not be restored by ACTH or glucocorticoid. However addition of GH or prolactin restored glycogen storage, pointing to a possible dual control mechanism. In the guinea pig the increase in liver glycogen storage closely parallels the increase in the concentration of cortisol in fetal plasma (Jones, 1975). In the rat, glucocorticoid receptors can be demonstrated in the fetal liver on Day 18 of gestation, and the concentration increases after birth to reach mature levels by the fifth postnatal day. In the fetal rat liver, there appears to be only one class of high affinity receptors, with different specificity characteristics for cortisol and corticosterone than the receptors in adult liver (Giannopoulos, 1975).

Studies on fetal sheep induced to deliver prematurely with ACTH or cortisol seem likely to provide further important information on the role of cortisol in fetal organ maturation. Thus the release of insulin in response to glucose normally begins to increase just before birth, and the adult pattern is achieved in the few days immediately postpartum (Bassett et al., 1973). This switch to the adult secretory response can be hastened in lambs born prematurely after intra-fetal ACTH infusion, raising the possibility that it may be related to the increase in glucocorticoid titres at this time. Whether cortisol directly affects β-cell function in the fetal pancreas is presently unknown.

Finally, we (Pierce et al., 1976) have recently investigated the role of glucocorticoids in the switch from fetal to adult hemoglobin in sheep by measuring the proportions of β chain synthesis. In this species the switch begins about 130 days and is complete by 5 days postnatally. Since the timing of the switch appears to coincide with the cortisol rise in the fetus and red cells contain glucocorticoid receptors (Golde et al., 1976), dexamethasone was infused into fetuses at 110 days and premature switching observed. After fetal hypophysectomy the switch started at the same time although the time for complete switching was much greater. However, this may be explained by the low basal cortisol levels observed in these fetuses (Fig. 1).

COMMENT

Development of the functional activity of the fetal adrenal axis can in many species be considered a key process in the maturation of other organ systems. In the sheep, the active principle appears to be cortisol, but in species where corticosterone is the main fetal glucocortocoid, these roles could be reversed. In some species, e.g., man, cortisone produced in the placenta may function as a pre-hormone in the fetus, being converted locally to the active form, cortisol, in the fetal lung. Such a mechanism could serve as a useful safeguard against inhibiting fetal ACTH secretion, and suppressing the activity of the fetal adrenal axis *in utero*.

It is also apparent that many of the changes attributed to cortisol will proceed albeit at a slower rate, in the absence of a *prepartum* glucocorticoid surge. In this sense, cortisol may function as the 'tuner' that synchronizes and coordinates those maturational processes required for extra-uterine life.

ACKNOWLEDGMENTS

We are indebted to our colleagues Drs. J. W. K. Ritchie, P. Johnson and C. T. Jones who have collaborated in aspects of this work; to Dr. A. P. F. Flint for his help and comments on this manuscript. The work was supported in part by a Grant from the M.R.C. (U.K.).

REFERENCES

Allen, J. P., Cook, D. M., Kendall, J. W. and McGilvra, R. (1973). Maternal-fetal ACTH relationships in man. J. Clin. Endocr. Metab. 37, 230-234.

Anderson, A. B. M. and Turnbull, A. C. (1973). Comparative aspects of factors involved in the onset of labor in ovine and human pregnancy. Mem. Soc. Endocr. 20, 141-162.

Anderson, A. B. M., Flint, A. P. F. and Turnbull, A. C. (1975). Mechanism of action of glucocorticoids in induction of ovine parturition: effect on placental steroid metabolism. J. Endocr. 66, 61-70.

Ash, R. W., Challis, J. R. G., Harrison, F. A., Heap, R. B., Illingworth, D. V., Perry, J. S. and Poyser, N. L. (1973). Hormonal control of pregnancy and parturition; a comparative analysis. In: *Foetal and Neonatal Physiology*; Eds. R. S. Comline, K. W. Cross, G. S. Dawes and P. W. Nathanielsz. London, Cambridge University Press, pp. 551-561.

Avery, M. E. (1975). Pharmacological approaches to the acceleration of fetal lung maturation. Br. Med. Bull. 31, 13-17.

Baden, M., Bauer, C. R., Colle, E., Klein, G., Taeusch,

H. W. and Stern, L. (1972). A controlled trial of hydrocortisone therapy in infants with respiratory distress syndrome. Pediatrics 50, 526-532.

Bassett, J. M. and Thorburn, G. D. (1969). Foetal plasma corticosteroids and the initiation of parturition in the sheep. J. Endocr. 44, 285-286.

Bassett, J. M. and Thorburn, G. D. (1973). Circulating levels of progesterone and corticosteroids in the pregnant ewe and its foetus. In: *Endocrinology of Pregnancy and Parturition Experiment Studies in the Sheep*. Ed. C. G. Pierrepoint. Cardiff. Alpha Omega Alpha Publishing, pp. 126-140.

Bassett, J. M., Thorburn, G. D. and Nicol, D. H. (1973). Regulation of insulin secretion in the ovine fetus *in utero*. Effects of sodium valerate on secretion and of adrenocorticotrophin-induced premature parturition on the insulin secretory response to glucose. J. Endocr. 56, 13-25.

Bedford, C. A., Challis, J. R. G., Harrison, F. A. and Heap, R. B. (1972). The role of oestrogens and progesterone in the onset of parturition in various species. J. Reprod. Fert. Suppl. 16, 1-23.

Bedford, C. A., Harrison, F. A. and Heap, R. B. (1972). The metabolic clearance rate and production rate of progesterone and the conversion of progesterone to 20α-hydroxypregn-4-en-3-one in the sheep. J. Endocr. 55, 105-118.

Beitins, I. Z., Bayard, F., Ances, I. G., Kowarski, A. and Midgeon, C. J. (1973). Metabolic clearance rate, blood production, interconversion and transplacental passage of cortisol and cortisone in pregnancy near term. J. Pediat. Res. 7, 509-519.

Benirschke, K. (1956). Adrenals in anencephaly and hydrocephaly. Obstet. Gynecol. 8, 412-425.

Boddy, K., Jones, C. T., Mantell, C., Ratcliffe, J. G. and Robinson, J. S. (1974). Changes in plasma ACTH and corticosteroid of the maternal and fetal sheep during hypoxia. Endocrinology 94, 588-591.

Bosc, M. J. (1972). The induction and synchronization of lambing with the aid of dexamethasone. J. Reprod. Fert. 28, 347-357.

Challis, J. R. G., Davies. I. J., Benirschke, K., Hendrickx, A. G. and Ryan, K. J. (1974). The effects of dexamethasone on plasma steroid levels and fetal adrenal histology in the pregnant rhesus monkey. Endocrinology 95, 1300-1305.

Challis, J. R. G., Dilley, S. R., Robinson, J. S. and Thorburn, G. D. (1977a). Development of fetal pituitary-adrenal function. J. Steroid Biochem. (in press).

Callis, J. R. G., Dilley, S. R., Robinson, J. S. and Thornburn, G. D. (1976). Prostaglandins in the circulation of the fetal lamb. Prostaglandins 11, 1041-1052.

Challis, J. R. G., Jones, C. T., Robinson, J. S. and Thornburn, G. D. (1977a). Development of fetal pituitary-adrenal function. J. Steroid Biochem. (In press).

Challis, J. R. G., Robinson, J. S. and Thorburn, G. D. (1977b). Fetal and maternal endocrine changes pituitary-adrenal function. J. Steroid Biochem. (in press).

Challis, J. R. G., Robinson, J. S. and Thorburn, G. D. (1977). Fetal and maternal endocrine changes during pregnancy and parturition in the rhesus monkey. In: *Fetus and Birth*. Ciba Fdn. Symp. Ed. M. O'Connor and J. Knight. Excerpta Medica, Amsterdam (in press).

Challis, J. R. G. and Thorburn, G. D. (1975). Pre-natal endocrine function and the initiation of parturition. Br. Med. Bull. 31, 57-62.

Challis, J. R. G. and Thorburn, G. D. (1976). The fetal pituitary-adrenal axis and its functional interactions with the neurohypophysis. In: *Fetal Physiology and Medicine*. Ed. R. Beard and P. W. Nathanielsz. London, Saunders (in press).

Chez, R. A., Hutchinson, D. L., Salazar, H. and Mintz, D. H. (1970). Some effects of fetal and maternal hypophysectomy in pregnancy. Am. J. Obstet. Gynec. 108, 643-650.

Comline, R. S. and Silver, M. (1961). The release of adrenaline and noradrenaline from the adrenal glands of the foetal sheep. J. Physiol. 156, 424-444.

Currie, W. B. and Thorburn, G. D. (1973). Induction of premature parturition in goats by prostaglandin $F_{2\alpha}$ administered into the uterine vein. Prostaglandins 4, 201-214.

Davies, I. J. and Ryan, K. J. (1972). Comparative endocrinology of gestation. Vitam. Horm. 30, 223-278.

Davies, I. J., Ryan, K. J. and Petro, Z. (1970). Estrogen synthesis by adrenal-placental tissues of the sheep and the Iris monkey *in vitro*. Endocrinology 86, 1457-1459.

DeLemos, R. A., Shermeta, D. W., Knelson, J. H., Kotas, R. and Avery, M. E. (1970). Acceleration of appearance of pulmonary surfactant in the fetal lamb by administration of corticosteroids. Am. Rev. Respir. Dis. 102, 459-461.

Diczfalusy, E. and Mancuso, S. (1969). Oestrogen metabolism in pregnancy. In: *Foetus and Placenta*. Eds. A. Klopper and E. Diczfalusy. Oxford. Blackwell, pp. 191-248.

Drost, M. and Holm, L. W. (1968). Prolonged gestation in ewes after foetal adrenalectomy. J. Endocr. 40, 293-296.

Farrell, P. M. and Zachman, R. D. (1973). Induction of choline phosphotransferase and lecithin synthesis in the fetal lung by corticosteroids. Science (N.Y.) 179, 297-298.

Fencl, M. and Tulchinsky, D. (1975). Concentrations of cortisol in amniotic fluid during pregnancy. New Eng. J. Med. 292, 133-136.

Flint, A. P. F., Anderson, A. B. M., Goodson, J. D., Steele, P. A. and Turnbull, A. C. (1976). Bilateral adrenalectomy of lambs *in utero*: effects on maternal hormone levels at induced parturition. J. Endocr. 69, 433-444.

Genazzani, A. R., Fraioli, F., Hurlimann, J., Fioretti, P. and Felber, J. P. (1975). Immunoreactive ACTH and cortisol plasma levels during pregnancy. Detection and partial purification of corticotrophin-like placental hormone: the human chorionic corticotrophin (HCC). Clin. Endocr. 4, 1-14.

Giannopoulos, G. (1975). Early events in the action of glucocorticoids in developing tissues. J. Steroid Biochem. 6, 623-631.

Giannopoulos, G., Mulay, S. and Solomon, S. (1972). Cortisol receptors in rabbit fetal lung. Biochem. Biophys. Res. Commun. 47, 411-418.

Gluck, L. and Kulovich, M. W. (1973). Surfactant production and foetal maturation. In: *Foetal and neonatal physiology*. Eds. R. S. Comline, K. W.

Cross, G. S. Dawes and P. W. Nathanielsz. Cambridge. Cambridge University Press, pp. 638-641.

Golde, D. W., Beisch, N. and Cline, M. J. (1976). Potentiation of erythropoesis *in utero* by dexamethasone. J. Clin. Invest. 57, 57-62.

John, B. M. and Pierrepoint, C. G. (1975). Demonstration of an active C_{17}-C_{20} lyase in the sheep placenta. J. Reprod. Fert. 43, 559-562.

Johnson, P., Jones, C. T., Kendall, J. Z., Ritchie, J. W. K. and Thorburn, G. D. (1975). ACTH and the induction of parturition in sheep. J. Physiol. (Lond.) 252, 64-66P.

Jones, C. T. (1975). Adrenocorticotrophic hormone secretion during foetal life. In: *Radioimmunoassay Techniques in Clinical Biochemistry*. Ed. C. A. Pasternak. van Heyden & Son, pp. 253-260.

Jones, C. T., Luther, E., Ritchie, J. W. K. and Worthington, D. (1975). The clearance of ACTH from the plasma of adult and fetal sheep. Endocrinology 96, 231-234.

Jost, A. (1969). The extent of foetal endocrine autonomy. In: *Foetal Autonomy*. Ciba Fdn. Symp. Ed. G. E. W. Wolstenholme and M. O'Connor. London. Churchill, pp. 79-89.

Kendall, J. Z., Challis, J. R. G., Jones, C. T., Ritchie, J. W. K. and Thorburn, G. D. (1975). Steroid changes associated with the induction of premature parturition in intact and hypophysectomized fetal lambs. Acta Endocrinologica Suppl. 199, Abst. no. 33.

Kittinger, G. W. (1973). The regulation of cortisol levels in fetal plasma. Primate News 11, 2-5.

Kittinger, G. W. (1974). Feto-maternal production and transfer of cortisol in the rhesus *(Macaca mulatta)*. Steroids 23, 229-243.

Kittinger, G. W., Beamer, N. B., Hagemenas, F., Hill, J. D., Baughman, W. L. and Ochsner, A. J. (1972). Evidence for autonomous pituitary-adrenal function in the near-term fetal rhesus *(Macaca mulatta)*. Endocrinology 91, 1037-1044.

Kotas, R. V. and Avery, M. E. (1971). Accelerated appearance of pulmonary surfactant in the fetal rabbit. J. Appl. Physiol. 30, 358-361.

Laychock, S. G. and Rubin, R. P. (1976). Indomethacin-induced alterations in corticosteroid and prostaglandin release by isolated adrenocortical cells of the cat. Br. J. Pharmac. 57, 273-278.

Leong, M. K. H. and Murphy, B. E. P. (1976). Cortisol levels in maternal venous and umbilical cord arterial and venous serum at vaginal delivery. Am. J. Obstet. Gynec. 124, 471-473.

Liggins, G. C. (1969). The foetal role in the initiation of parturition in the ewe. In: *Foetal Autonomy*. Ciba Fdn. Symp. London, Churchill, pp. 218-231.

Liggins, G. C., Fairclough, R. J., Grieves, S. A. Forster. C. S. and Knox, B. S. (1977). Parturition in the Sheep. In: *The Fetus and Birth*. Ciba Fdn. Symp. Ed. M. O'Connor and J. Knight. (In press.)

Liggins, G. C., Fairclough, R. J., Grieves, S. A., Kendall, J. Z. and Knox, B. S. (1973). The mechanism of initiation of parturition in the ewe. Rec. Prog. Horm. Res. 29, 111-150.

Liggins, G. C., Grieves, S. A., Kendall, J. Z. and Knox, B. S. (1972). The physiological roles of progesterones, oestradiol-17β and prostaglandin $F_{2\alpha}$ in the control of ovine parturition. J. Reprod. Fert. Suppl. 16, 85-103.

Liggins, G. C. and Howie, R. N. (1972). A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 50, 515-525.

Liggins, G. C., Kennedy, P. C. and Holm, L. W. (1967). Failure of initiation of parturition after electrocoagulation of the pituitary of the fetal lamb. Am. J. Obstet. Gynecol. 98, 1080-1086.

Linzell, J. L. and Heap, R. B. (1968). A comparison of progesterone metabolism in the pregnant sheep and goat: sources of production and an estimation of uptake by some target organs. J. Endocr. 41, 433-438.

Louis, T. M., Challis, J. R. G., Robinson, J. S. and Thorburn, G. D. (1976). Rapid increase of fetal corticosteroids after prostaglandin E_2. Nature (submitted).

McMillen, I. C., Jenkin, G., Robinson, J. S., Challis, J. R. G. and Thorburn, G. D. (1976). The relation between plasma prolactin and cortisol in fetal sheep. J. Endocr. (in press).

Madill, D. and Bassett, J. M. (1973). Corticosteroid release by adrenal tissue from foetal and newborn lambs in response to corticotrophin stimulation in a perifusion system *in vitro*. J. Endocr. 58, 75-87.

Malpas, P. (1933). Postmaturity and malformation of the foetus. J. Obstet. Gynaec. Br. Emp. 40, 1046-1053.

Mescher, E. J., Platzker, A. C. G., Ballard, P. L., Kitterman, J. A., Clements, J. A. and Tooley, W. H. (1975). Ontogeny of tracheal fluid, pulmonary surfactant, and plasma corticoids in the fetal lamb. J. Appl. Physiol. 30, 1017-1021.

Mueller-Heubach, E., Myers, R. E. and Adamsons, K. (1972). Effects of adrenalectomy on pregnancy length in the rhesus monkey. Am. J. Obstet. Gynec. 112, 221-226.

Murphy, B. E. P. (1973). Does the human fetal adrenal play a role in parturition? Am. J. Obstet. Gynec. 115, 521-525.

Murphy, B. E. P. (1974). Cortisol and cortisone levels in the cord blood at delivery of infants with and without the respiratory distress syndrome. Am. J. Obstet. Gynec. 119, 1112-1120.

Murphy, B. E. P., Clark, S. J., Donald, I. R., Pinsky, M. and Vedady, D. (1974). Conversion of maternal cortisol to cortisone during placental transfer to the human fetus. Am. J. Obstet. and Gynec. 118, 538-541.

Murphy, B. E. P., Patrick, J. and Denton, R. L. (1975). Cortisol in amniotic fluid during human gestation. J. Clin. Endocr. Metab. 40, 164-167.

Nathanielsz, P. W., Comline, R. S., Silver, M. and Paisey, R. B. (1972). Cortisol metabolism in the foetal and neonatal sheep. J. Reprod. Fert. Suppl. 16, 39-59.

Nwosu, U., Wallach, E. E., Boggs, T. R., Nemiroff, R. L. and Bongiovanni, A. M. (1975). Possible role of the fetal adrenal glands in the etiology of postmaturity. Am. J. Obstet. & Gynec. 121, 366-370.

Patrick, J. E., Challis, J. R. G., Johnson, P., Robinson, J. S. and Thorburn, G. D. (1976). Cortisol in amniotic fluid of rhesus monkeys. J. Endocr. 68, 161-162.

Pierce, K., Clegg, J., Dawes, G. S., Robinson, J. S., Thorburn, G. D., Weatherall, D. and Wood, B. (1976). Unpublished observations.

Platzker, A. C. G., Kitterman, J. A., Mescher, J., Clements, J. A. and Tooley, W. H. (1975). Surfactant in the lung and tracheal fluid of the fetal lamb and acceleration of its appearance by dexamethasone. Pediatrics 56, 554-561.

Rees, L. H., Burke, C. W., Chard, T., Evans, S. W. and Letchworth, A. T. (1975). Placental origin of ACTH in normal human pregnancy. Nature (Lond.) 254, 620-622.

Rees, L. H., Jack, P. M. B., Thomas, A. L. and Nathanielsz, P. W. (1975). Role of foetal adrenocorticotrophin during parturition in sheep. Nature (Lond.) 253, 274-275.

van Rensburg, S. J. (1971). Reproductive physiology and endocrinology of normal and habitually aborting Angora goats. Onderst. J. Vet. Res. 38, 1-62.

Reynolds, J. W. (1973). Serum total corticoid and cortisol levels in premature infants with respiratory distress syndrome. Pediatrics 51, 884-890.

Ryan, K. J. (1969). Theoretical basis for endocrine control of gestation—a comparative approach. In *Feto-placental Unit*. Ed. A. Pecile and C. Finzi. Excerpta Medica Foundation, Amsterdam, p. 120-131.

Ryan, K. J. and Hopper, B. R. (1974). Placental biosynthesis and metabolism of steroid hormones in primates. Contrib. Primatol. 3, 258-283.

Simmer, H. H., Tulchinsky, D., Gold, E. M. and Frankland, M. (1974). On the regulation of estrogen production by cortisol and ACTH in human pregnancy at term. Am. J. Obstet. Gynec. 119, 283-296.

Steele, P. A., Flint, A. P. F. and Turnbull, A. C. (1975). Evidence of steroid $C_{17,20}$ lyase activity in ovine foetal placental tissue. J. Endocr. 64, 41P.

Steele, P. A., Flint, A. P. F. and Turnbull, A. C. (1976). Increased utero-ovarian androstenedione production before parturition in sheep. J. Reprod. Fert. 46, 443-445.

Strott, C. A., Sundel, H. and Stahlman, M. T. (1974). Maternal and fetal plasma progesterone, cortisol, testosterone and 17β-estradiol in preparturient sheep: response to fetal ACTH infusion. Endocrinology 95, 1327-1339.

Taylor, N. R. W., Loraine, J. A. and Robertson, H. A. (1953). The estimation of ACTH in human pituitary tissue. J. Endocr. 9, 334-341.

Thompson, F. N. and Wagner, W. C. (1974). Plasma progesterone and oestrogens in sheep during late pregnancy: contribution of the maternal adrenal and ovary. J. Reprod. Fert. 41, 57-66.

Thorburn, G. D., Nicol, D. H., Bassett, J. M., Shutt, D. A. and Cox, R. I. (1972). Parturition in the goat and sheep: Changes in corticosteroids, progesterone, oestrogens and prostaglandin F. J. Reprod. Fert. Suppl. 16, 61-84.

Torday, J. S., Smith, B. T. and Giroud, C. J. P. (1975). The rabbit fetal lung as a glucocorticoid target tissue. Endocrinology 96, 1462-1467.

Warner, W. and Rubin, R. P. (1975). Evidence for a possible prostaglandin link in ACTH-induced steroidogenesis. Prostaglandins 9, 83-95.

Winters, A. J., Colston, C., MacDonald, P. C. and Porter, J. C. (1975). Fetal plasma prolactin levels. J. Clin. Endocr. Metab. 41, 626-629.

Winters, A. J., Oliver, C., Colston, C., MacDonald, P. C. and Porter, J. C. (1974). Plasma ACTH levels in the human fetus and neonate as related to age and parturition. J. Clin. Endocr. Metab. 39, 269-273.