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Control of Parturition in Domestic Animals

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INTRODUCTION

In the past decade major advances in our understanding of the mechanism of the initiation of labor have originated from experimental studies in sheep. In this review we shall attempt to summarize these findings, but in addition, we shall consider how the sheep model applies to other domestic animals such as the goat, cow and pig. This will represent more than simply a cross-species comparison. We are demanding in these other species, in which the major site of progesterone production is the corpus luteum, that a signal from the fetus causes regression of the corpus luteum and thus parturition. As we shall see, the task is somewhat simpler in the sheep where the fetus only needs to modify placental steroidogenesis to effect its own delivery. In contrast, in the goat, cow and pig, the maintenance of pregnancy is dependent on the continued function of the corpus luteum. Delivery is dependent on regression of the corpus luteum. We shall attempt to explain how activation of the fetal hypothalamo-pituitary-adrenal axis causes luteal regression and the subsequent delivery of the fetus and placenta.

PROGESTERONE

Sheep

Progesterone production in the pregnant sheep is derived from the corpus luteum during the first 50 days of pregnancy (Denamur and Martinet, 1955) but there is a gradual decline in ovarian progesterone secretion thereafter (Edgar and Ronaldson, 1958). Thus ovariectomy after Day 50 does not cause abortion because placental progesterone production is adequate to maintain pregnancy (Linzell and Heap, 1968). Following ovariectomy the levels of progesterone necessary to maintain pregnancy between Days 50-90 are surprisingly low (0.5–1 ng/ml). Both in intact sheep and following ovariectomy, the plasma progesterone concentration (which directly reflects production rate; Bedford et al., 1973) increases steadily from Day 85-90 reaching maximum levels around Days 125-130 p.c. The concentration of progesterone in plasma decreases in a variable manner over the last 5-15 days of pregnancy (Bassett et al., 1969). This decrease in progesterone results from the increase in fetal plasma corticosteroids seen at normal term. A similar decrease is observed when premature parturition is induced by the administration of glucocorticoids to the fetus (Liggins et al., 1973; Currie et al., 1973). The mechanisms by which fetal corticosteroids influence placental steroidogenesis are discussed elsewhere in this Symposium (Challis et al., 1977).

Although progesterone withdrawal precedes normal or induced parturition, it is not clear whether this is an essential prerequisite. For instance, administration of progesterone fails to delay parturition when given at a daily dose of 80 mg for a week (Bengtsson and Schofield, 1963) and progesterone (50-150 mg/day) does not inhibit the premature delivery produced by the intra-fetal infusion of dexamethasone (1 mg/24 h) at 110-130 days of pregnancy (Liggins, 1973). In the earlier studies, Bengtsson and Schofield (1963) found that larger doses of progesterone (160 mg/day) blocked term labor in most sheep. With dexamethasone-induced parturition, Liggins (1973) found that larger doses of progesterone (150 mg/day) while not delaying the onset of labor did prevent cervical dilatation. Uterine activity was only blocked completely by the administration of progesterone at 200 mg/day. It has been calculated that the production rate of progesterone in the control animals given a fetal dexamethasone infusion, decreased from about 75 μg/min to 9 μg/min (Heap et al., 1977). Thus the administration of amounts of progesterone in the range of

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50-110 mg/day should be adequate to maintain the myometrial progesterone concentration and this was confirmed by Liggins et al. (1973). It is apparent that a decrease in the myometrial progesterone concentration is not a necessary prerequisite for delivery. However, the increased incidence of dystocia when progesterone levels remain elevated indicate that a decrease in progesterone concentrations to low levels is desirable for normal delivery.

Goat

In contrast to the sheep, in the goat the corpus luteum (CL) remains a major site of progesterone production throughout pregnancy. Ovariectomy at any stage in gestation results in abortion, and this can be prevented by replacement therapy with exogenous progesterone (Meites et al., 1951). In intact animals plasma progesterone concentrations are maintained at luteal phase levels until about Day 60 of pregnancy and then at higher levels until term (Thorburn and Schneider, 1972; Irving et al., 1972). Regression of the corpus luteum and a decrease in the plasma progesterone concentration precedes the evolution of uterine activity and normal delivery (Thorburn and Schneider, 1972; Currie, 1974; Umo et al., 1976). Thorburn and Schneider (1972) suggested that the placenta contributed some progesterone during late pregnancy but this was inadequate to prevent abortion in the absence of luteal function. Recently 3β-hydroxysteroid dehydrogenase activity has been demonstrated in goat placentae (Wiener, 1976).

In the sheep, fetal cortisol probably induces 17α-hydroxylase and enhances $C_{17,20}$ lyase activity in the placenta and thereby decreases progesterone secretion at term. In the goat, any 'message' of fetal origin to initiate parturition must act by causing regression of the maternal corpus luteum, and there would appear to be little need for fetal cortisol to induce 17α-hydroxylase activity in the fetal placenta as a mechanism to reduce progesterone production.

Cow

In the cow, the corpus luteum is the major site of progesterone production, and regression of the corpus luteum occurs before the onset of parturition. Removal of the corpus luteum before Day 200 of pregnancy always causes abortion with delivery of a dead fetus. However, ovariectomy after Day 200 of gestation is compatible with the maintenance of pregnancy for up to 70 days (Estergreen et al., 1967; Edquist et al., 1973; Macdonald et al., 1958). It is of some interest that in these animals, premature delivery, dystocia and retained fetal membranes were observed. Following ovariectomy of cows between 140-240 days of gestation the plasma progesterone concentration decreased to 10 percent of the presurgical levels (Edquist et al., 1973). In the cow, as in the sheep, it may be that pregnancy can be maintained with relatively low circulating levels of progesterone. Under normal circumstances it is not possible to demonstrate a net production of progesterone by the cow placenta and uterine vein levels of the steroid were lower than jugular vein levels (Fairclough et al., 1975). However, this finding must be interpreted with the reservations that jugular vein progesterone levels would not reflect uterine artery concentrations if there is uptake across the head, and placental production cannot be calculated by subtracting arterial from venous concentrations if there is uptake by the uterus. Ainsworth and Ryan (1967) and Wiener (1976) have shown *in vitro* that bovine placental tissue is capable of synthesizing progesterone. Another possible site of progesterone production during late pregnancy in the cow is the maternal adrenal cortex (Balfour et al., 1957).

The concentration of progesterone in maternal blood plasma decreases gradually during the last 20 days of pregnancy and then falls more rapidly in the 2-3 days before parturition (Donaldson et al., 1970; Stabenfeldt et al., 1970). These progesterone concentrations correlate with the low levels of uterine activity up to 2-4 days *prepartum* (Gillette, 1966), and support the applicability of the progesterone block hypothesis (Csapo, 1956) to the cow. The importance of progesterone in the maintenance of pregnancy in this species is further illustrated by the failure to find a decrease in plasma progesterone concentration in animals with prolonged gestation associated with fetal abnormalities (Holm and Short, 1962) and with the ability of large amounts of exogenous progesterone to prevent the premature delivery induced by the glucocorticoids (Jöchle, 1971). However, it should be noted that large amounts of progesterone administered to cows in late pregnancy failed to delay the onset of parturition at term (Macdonald and Heys, 1958).

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Pig

In the pig, the major site of progesterone production is the corpus luteum and ovariectomy at any stage of pregnancy results in abortion. Although the progesterone concentration in the uterine vein is less than in the maternal artery indicating no net secretion into the maternal compartment, Barnes et al. (1974) found the concentration in the umbilical vein was consistently higher than in the umbilical artery suggesting a net secretion of progesterone into the fetal circulation. The progesterone concentration in the peripheral plasma of the sow remains relatively constant until 20-15 days before parturition. The concentration decreases gradually until about 2 days before delivery and then falls more rapidly. Progesterone withdrawal is not complete at delivery however and stable levels are found during the course of farrowing (Killian et al., 1973; Robertson and King, 1974). Exogenous progesterone administered to intact or ovariectomized pigs prevented delivery of the fetuses at normal term.

PLACENTAL LACTOGEN

Clearly the factors that regulate plasma progesterone levels are of importance in controlling the length of gestation in the cow, goat and pig. In the pregant goat, trophic support is necessary from the maternal pituitary since maternal hypophysectomy leads to abortion. It has been suggested (van Rensburgh, 1970) that a biological clock may exist in the maternal hypothalamus, and it may control the timing of corpus luteum regression and delivery through withdrawal of pituitary trophic support. However, after hysterectomy of pregnant goats, in which signals of fetal or placental origin were removed, Currie and Thorburn (1974) observed that the corpus luteum continued to function for a period of time ranging from 140-180 days. This observation would indicate that any maternal timing mechanism would be inadequate to account for the precise termination of progesterone secretion at term. A placental luteotrophin (Buttle et al., 1972; Thorburn and Schneider, 1972), may be necessary for full function of the corpus luteum because progesterone levels are markedly decreased after hysterectomy of pregnant goats (Currie and Thorburn, 1974). This luteotrophin may be a placental lactogen (PL), which first appears in the maternal circulation at around Day 60 and then increases up to Day 125 of pregnancy (see Currie and Thorburn, 1977).

Withdrawal of placental luteotrophic support could, in part, be responsible for regression of the corpus luteum at term (Currie and Thorburn, 1977). Placental lactogen levels fell progressively during the last 15 days of normal pregnancy when corticosteroid concentrations are rising in the fetal circulation. A similar change was observed when ACTH was infused into the fetal goat. It is possible that the decrease in the circulating levels of PL lead to a decrease in the trophic support to the corpus luteum and thus to a fall in progesterone concentration in the maternal plasma. Although removal of placental trophic support may be inadequate by itself to induce complete luteal regression, a partial decrease in progesterone may facilitate the release of $PGF_{2\alpha}$ which would then ensure irreversible luteolysis. However, it is still necessary to ascertain that PL is luteotrophic in the goat.

In the sheep, a temporal correlation between the plasma concentrations of PL and progesterone has been reported and the suggestion made that PL may be involved in progesterone production (Kelly et al., 1974). In the cow, there is little evidence for a luteotrophic function for prolactin (Karg and Shams, 1974) and LH does not change during late pregnancy (Hoffman and Karg, 1974; Arije et al., 1974). The possible importance of the bovine placental lactogen will have to await its identification and measurement during late pregnancy. Pituitary luteotrophic support is necessary for the continued function of the corpus luteum of pregnancy in the pig since maternal hypophysectomy results in abortion. Information is lacking on the placental lactogen in this species.

FETAL INFLUENCES

The classical experiments of Liggins (1969, 1973) clearly demonstrated the primary role of the fetal pituitary adrenal system in the initiation of parturition in sheep. The maturation of the fetal pituitary adrenal system in the lamb is the subject of another paper in this symposium and will not be discussed here. It was important to determine whether a similar mechanism involving the fetus was operative in a corpus luteum dependent species such as the goat. In this species an increase in the weight of the fetal adrenal (van Rensburgh, 1970) and elevated levels of cortisol in fetal plasma are seen at spontaneous delivery, (Currie and Thorburn, 1977). Infusion of ACTH into the goat fetus

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caused an increase in the fetal plasma concentration of corticosteroids. Subsequently there was an increase in both unconjugated and conjugated estrogens (estrone and estradiol-17α) in both fetal and maternal circulations which preceeded the pre-parturient decline in maternal plasma progesterone (Thorburn et al., 1972).

In the cow, early field observations implicated the fetus in the initiation of parturition and syndromes have been described in which prolonged pregnancy has been attributed to a single autosomal recessive gene in the fetus. In these calves the adenhypophysis may be absent and the fetal adrenals hypoplastic and unresponsive to ACTH (Holm, 1967; Kennedy, 1971). The corticosteroids in the plasma of the intact fetal calf rise from about 5 ng/ml at 20 days before parturition to levels around 70 ng/ml on the day of calving (Comline et al., 1974; Hunter et al., 1976). The degree of adrenal hypertrophy found in the fetal lamb before delivery has not been observed in the fetal calf (Comline and Silver, 1966). The infusion of corticotrophin to the fetal calf, caused parturition within 7 days (Welch et al., 1973; Comline et al., 1974), and the continuous administration of dexamethasone (3.3 mg/day) to the fetus induced calving within 72 ± 19 h (Hunter et al., 1976; Comline et al., 1974). When parturition was induced by the administration of dexamethasone to the fetal calf, the rise in estrogen and fall in progesterone was similar to that observed at normal term (Comline et al., 1974; Hunter et al., 1976). These observations suggest that activation of the fetal pituitary adrenal axis is responsible for the initiation of parturition in the cow.

It is more difficult to acquire definitive experimental data in a polytocous species such as the pig for the fetal involvement in the initiation of parturition. Nevertheless, Bosc et al. (1974) showed that premature delivery could be achieved by the administration of ACTH to a sufficient number of fetuses. Furthermore, fetal decapitation between Days 40-50 (Striker and Dziuk, 1975) or fetal hypophysectomy around Day 50 (Bosc et al., 1974) prolonged the length of gestation to 120 days. Parturition was not delayed if more than one intact fetus remained in the litter (Striker and Dziuk, 1975). After fetal hypophysectomy, fetal adrenal weight was reduced compared to non-operated litter mate controls and the concentration of cortisol in the plasma was significantly lower than in intact fetuses of the same age (Bosc et al., 1974). We can conclude from these studies that in the pig as in the sheep and goat, the onset of parturition depends on the presence of the fetal pituitary and an active fetal pituitary adrenal axis.

PROSTAGLANDINS AND LUTEOLYSIS

In considering the mechanisms by which the fetus can produce regression of the maternal corpus luteum, Thorburn et al. (1972) considered that in the goat PGF release into the uterine vein may have been responsible for luteolysis. Subsequent studies have shown that PGF is released into the uterine vein draining the pregnant horn of the uterus at the time of, or up to 24 h before, the decrease in progesterone levels (Currie et al., 1973; Currie and Thorburn, 1977; Umo et al., 1976). Currie and Thorburn (1977) also noted that during the induction of premature parturition by the infusion of synthetic ACTH into the fetus, PGF appeared in the utero-ovarian vein ipsilateral to the infused fetus some 24 h before delivery. Confirmation of the luteolytic effect of PGF at these concentrations was obtained by infusing $PGF_{2\alpha}$ into a tributary vein ipsilateral to the corpus luteum. As little as 2-5 ng/ml of PGF maintained in the uterine vein for 5-6 h caused luteolysis, and initiated delivery. However if $PGF_{2\alpha}$ was used to induce delivery before 139 days of gestation, the newborn kids failed to initiate breathing and died. In addition, placental delivery was delayed and lactogenesis failed to occur. It was considered that because the fetal adrenals were probably not activated by this procedure, the normal changes in fetal cortisol and feto-placental estrogen did not occur (Currie and Thorburn, 1977). Lack of these changes may explain the respiratory incompetence of the immature fetuses, the placental retention and agalactia.

In the cow, prostaglandin F levels in the utero-ovarian venous plasma remain relatively constant (<0.5 ng/ml) up to 5-7 days before term and then increase gradually to around 1.5 ng/ml 24-48 h before delivery (Fairclough et al., 1975). Utero-ovarian PGF concentrations increased sharply during the last 24-48 h of pregnancy to a maximum of 5.5–9 ng/ml during labor. The elevated levels of PGF were closely related in time with the sharp decrease in plasma progesterone concentrations. It was concluded that PGF may be the luteolytic factor in the cow.

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In the pig, measurements of primary prostaglandins in the uterine vein or of circulating metabolites in the peripheral plasma around the time of parturition are not currently available. However $PGF_{2\alpha}$ is luteolytic during the estrous cycle of the pig (Gleeson et al., 1974) and a synthetic analogue of $PGF_{2\alpha}$ (I.C.I. 79939) has been used to induce parturition in late pregnancy (Ash and Heap, 1973). It seems reasonable to suggest that $PGF_{2\alpha}$ will prove to be the luteolytic factor responsible for luteal regression preceding parturition in the pig.

ESTROGENS

Goat

From the foregoing discussions it seemed likely that $PGF_{2\alpha}$ was the luteolytic factor in the goat, cow and pig. Evidence will be presented that in the goat, as in the sheep, the stimulus to PG production normally arises from an increase in estrogen production. In the goat, maternal unconjugated estrogen levels are higher than in the sheep and increase steadily throughout pregnancy before rising rapidly during the 4-5 days preceding delivery (Challis and Linzell, 1971; Thorburn et al., 1972; Currie et al., 1973; Umo et al., 1976). The major estrogens in fetal and maternal plasma are estrone and estradiol-17α. Detailed information on the changes in estradiol-17β is lacking at the present time.

During the intra-fetal infusion of ACTH (Thorburn et al., 1972) there is an increase in the estrogen concentration of both maternal and fetal plasma. The mechanism of this increase is as yet uncertain. In sheep, fetal glucocorticoids enhance placental 17α-hydroxylase and $C_{17,20}$ lyase activity (see Challis et al., 1977) leading to an increase in placental estrogen biosynthesis. However, in the goat, there is no evidence at the present time for a similar mechanism. It is possible that the progressive increase in estrogen levels in maternal plasma is due to the provision of increasing amounts of fetal adrenal precursors. These questions should be resolved by the intra-fetal infusion of dexamethasone into the goat fetus.

Currie and Thorburn (1977) showed that infusion of physiological amounts of estradiol-17β but not estradiol-17α into pregnant goats increased the levels of PGF in the utero-ovarian vein. Luteolysis and premature delivery subsequently occurred. The release of PGF was greater in the vein draining the pregnant than the non-pregnant uterine horn. Currie and Thorburn (1977) suggested that there may be an increased receptor population for estradiol in the maternal cotyledon. The mechanism by which estrogens increase PGF levels is not clear, but may involve changes in the stability of lysosomal membranes in the maternal placenta. An action on the lysosomes with the release of hydrolases would be consistent with the idea that estrogen causes separation of the placenta and membranes.

In contrast to the effects of $PGF_{2\alpha}$, when premature parturition was induced with estradiol-17β, the placenta and membranes were delivered with 12 h of the fetus (Currie and Thorburn, 1977). Furthermore, lactogenesis was evident within 24 h after beginning an infusion of estradiol into the mother, but fetuses of gestational age less than 139 days failed to survive (Currie and Thorburn, 1977). The lungs of these lambs were immature presumably since the fetal adrenals had not been activated.

Sheep

In pregnant sheep the concentration of unconjugated estrogens in maternal blood remains low throughout pregnancy increasing only during the last 24 h before delivery (Challis, 1971; Thorburn et al., 1972; Bedford et al., 1972). The ratio of estrone:estradiol-17β:estradiol-17α in maternal plasma is approximately 2:1:1 with the level of sulphoconjugates greater than those of free steroids (Thorburn et al., 1972). This is due partly to rapid sulphoconjugation in the placenta (Findlay and Seamark, 1973). Conjugated estrogens increase in both maternal and fetal plasma *prepartum*. Since the infusion of dexamethasone into the fetus causes an increase in estrogen biosynthesis, it seems unlikely that the prepartum increase in estrogens is due to an increase in precursors from the fetal adrenal but may relate to glucocorticoid induction of placental enzymes (see Challis et al., 1977).

Permeability of the placenta appears to increase with gestational age. This may explain why the induction of labor in sheep and cattle by the maternal injection of synthetic glucocorticoids becomes progressively more reliable the closer treatment is to normal term, if the primary action of exogenous glucocorticoids is on the fetal placenta. Bosc (1972) failed to

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induce premature delivery of a hypophysectomized fetus by administering glucocorticoids to the mother. This is possibly due to the failure to achieve the normal changes in placental permeability in the presence of the hypophysectomized fetus since when the glucocorticoid is infused directly into the hypophysectomized fetus, parturition was induced (Kendall et al., 1975).

Cow

In the cow, the urinary excretion of estrogens increases progressively during the last month of gestation. A major site of estrogen production is likely to be the placenta, since this contains an active aromatase system (Ainsworth and Ryan, 1966) and the concentrations of unconjugated estrogens in the utero-ovarian vein are greater than those in the jugular vein (Comline et al., 1974; Peterson et al., 1975). Plasma estradiol levels increase linearly from about 30 pg/ml over the last 30 days of pregnancy to about 300 pg/ml at −2 days. The concentration decreased to about 50 pg/ml at 1 day *postpartum*. The concentration of unconjugated estrone was approximately 10 times higher than that of estradiol (Smith et al., 1973; Peterson et al., 1975). The estrogen changes after the administration of synthetic glucocorticoids to the mother also vary with different reports. The injection of dexamethasone (20 mg) 8-14 days before the expected calving date caused premature parturition but failed to cause an increase in plasma estrogen values (Garverick et al., 1974). However, Osinga (1970) found a rapid increase in urinary estrone excretion after the administration of flumethasone to pregnant cows. When parturition was induced by the infusion of dexamethasone to the fetus, there was an increase in the estrogen concentrations and a fall in progesterone levels (Comline et al., 1974; Hunter et al., 1976). The mechanism by which this is accomplished requires elucidation.

In the cow, it appears that estradiol-17β plays an important role in the initiation of parturition and particularly in the delivery of the placenta and membranes, and the initiation of lactogenesis. Further estrogen biosynthesis may only be stimulated by exogenous glucocorticoids during the last 30 days of pregnancy, when plasma estrogen levels are already increasing. Thus, if placental separation is dependent on a good estrogen response to the exogenous glucocorticoid, administration of glucocorticoid earlier in pregnancy may fail to induce estrogen biosynthesis and therefore fail to cause placental separation. The results of Garverick et al. (1974) and Jöchle (1971) would suggest that placental separation occurs more readily when exogenous estrogen is administered together with exogenous glucocorticoids. In this regard, it has been found that natural estrogens or diethylstilbestrol will themselves provoke premature parturition and will even terminate pregnancy in the presence of a dead fetus when synthetic glucocorticoids are ineffective (see Jöchle, 1971).

Pig

It has long been recognized that there is an increase in urinary estrogen excretion in the pig during pregnancy (Raeside, 1963), which is not abolished by ovariectomy (Fèvre et al., 1968). In maternal plasma, there is a progressive increase in the concentration of estrone sulphate and unconjugated estrogens, especially estrone, during late pregnancy. The levels are maintained through parturition, and do not decline until *postpartum* (Robertson and King, 1974).

PROSTAGLANDINS AND UTERINE ACTIVITY

Recent work has clearly established that prostaglandins play a major role in the mechanism of parturition. In sheep, Liggins and Grieves (1971) showed that during an intrafetal infusion of dexamethasone there was an increase in the concentration of $PGF_{2\alpha}$ in the maternal cotyledons and myometrium. Suppression of uterine activity with large doses of progesterone (200 mg/day) failed to prevent the increase in the $PGF_{2\alpha}$ levels in the myometrium and maternal cotyledons, but did block PGF release into the utero-ovarian vein. This release may require the stimulus of estrogen and/or withdrawal of progesterone. At term in sheep there is a parallel increase in estrogen, PGF and uterine activity (Challis et al., 1972; Thornburn et al., 1972; Rawlings and Ward, 1973), and the administration of stilbestrol to pregnant ewes elevates the levels of PGF in the maternal placenta. myometrium, and utero-ovarian vein within 24 h (Liggins, 1973). These changes result in a 90 percent decrease in the myometrial threshold response to oxytocin, without any concomitant change in peripheral or utero-ovarian venous proges-

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terone. However, high circulating levels of progesterone appear to inhibit the release of $PGF_{2\alpha}$, and the decrease in progesterone levels before parturition probably facilitates the synthesis and release of $PGF_{2\alpha}$. Currie (1974) found that treatment of sheep in late pregnancy with amounts of estradiol which produced physiological concentrations in the maternal circulation (150–800 pg/ml), initiated labor and delivery in 3 of 4 animals. PGF release and parturition occurred in the absence of any changes in circulating progesterone. However, the infusion of similar amounts of estradiol a few weeks earlier failed to induce parturition.

In the pregnant goat, there is a gradual increase in utero-ovarian venous PGF during the last 4-5 days before delivery. Superimposed on this pattern are intermittent peaks of PGF release, reminiscent of those seen at luteolysis during the estrous cycle (Thorburn et al., 1972, 1973; Umo et al., 1976). The peaks of PGF coincided with or preceded the *prepartum* decline in utero-ovarian venous progesterone. However, as progesterone fell, a further increase in PGF was found, with a striking increase during second stage labor, associated with entry of the fetus into the cervix and vagina, and accompanied by maternal abdominal straining, (Currie et al., 1973; Currie, 1974). Oxytocin release is known to occur at this stage of labor (Fitzpatrick and Walmsley, 1965) and may account for the massive release of PGF (Currie et al., 1973) and the potentiation of uterine activity (Umo et al., 1976). Currie (1974) noted that PGF was released in association with suckling, and Flint et al. (1975) demonstrated in sheep that utero-ovarian PGF was elevated in response to cervical or vaginal distension. Because vaginal distension is known to stimulate the release of oxytocin, the temporal relationship was examined between changes in oxytocin levels in the jugular plasma and prostaglandin levels in the utero-ovarian venous plasma in response to vaginal distension, and a close association was found (Flint et al., 1975). Moreover, infusions of oxytocin caused the release of PGF into the utero-ovarian vein (Mitchell et al., 1975). The results therefore support the hypothesis that vaginal distension increases PGF levels through a reflex release of oxytocin. The release of oxytocin in response to vaginal distension is enhanced by estradiol and inhibited by progesterone (Roberts and Share, 1969), and the hormonal changes at term would tend to facilitate the release of both oxytocin and PGF. Some of the massive release of PGF during labor escapes metabolism (Currie and Thorburn, 1977) and significant levels appear in the arterial plasma. The arterial PGF may act directly on the myometrium. Since PGF is believed to stimulate oxytocin release (Gillespie, 1973), a positive feedback cascade effect may exist between these substances. These data suggest that PGF production may be a prerequisite to parturition, and that under normal conditions oxytocin plays an important augmenting role in second stage labor. Because oxytocin and PGF are released in association with suckling, their elevated levels after delivery of the fetus may also facilitate expulsion of the placenta and uterine involution (Flint et al., 1974).

In the cow, a major release of PGF into the uterine vein occurs after progesterone levels have fallen, and this is consistent with observations in the pregnant goat and the non-pregnant sheep of progesterone withdrawal facilitating PGF release (see Thorburn et al., 1976). Exogenous $PGF_{2\alpha}$ does cause luteolysis and abortion when administered to cows during early pregnancy (Lamond et al., 1973), and PGE or $PGF_{2\alpha}$ provoke abortion when administered during the last trimester (Zerobin et al., 1973). At this time a major effect of the prostaglandins—whether they are administered intravenously or directly into the uterine lumen—is to increase myometrial activity and delivery of the fetus. In spite of sustained myometrial activity there is a high incidence of retained placentae, which are eventually delivered spontaneously 2-10 days later. Prostaglandins of the E or F series also initiate parturition in instances of prolonged gestation where flumethasone is ineffective.

Prostaglandin $F_{2\alpha}$ is luteolytic during the estrous cycle of the pig (Gleeson et al., 1974) and a synthetic analogue of $PGF_{2\alpha}$ (I.C.I. 79939) has been used to induce parturition in later pregnancy (Ash and Heap, 1973). However, measurements of primary prostaglandins in the uterine effluent, or of circulating metabolites in the peripheral plasma throughout the course of late pregnancy are currently not available.

RELAXIN

A recent report has described changes in the concentration of relaxin in the maternal plasma of the sow during late pregnancy. Peak values

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were reached 14 h before parturition and this increase could be stimulated with $PGF_{2\alpha}$ (Sherwood et al., 1975, 1976). Relaxin is, at least in part, of ovarian origin and may be involved in dilation of the cervical canal. In addition, in laboratory animals relaxin inhibits myometrial activity (for discussion see Finn and Porter, 1975), and the possibility that it may exert "fine control" over uterine activity at the time of changing progesterone concentration during late pregnancy cannot be ignored.

Induced Parturition

Exogenous glucocorticoids administered to the mother can be used to precipitate delivery in the cow, sheep and goat; glucocorticoids appear to be without effect in the mare, sow, bitch (and man). In species where CL progesterone secretion continues throughout pregnancy, parturition can be induced with prostaglandins (Ash and Heap, 1973), and in the cow, sheep and goat parturition can be induced with exogenous estrogens (see Bosc, 1974). Because normal parturition involves a dequence of integrated processes leading to surfactant production, enzyme induction in the fetus, labor and lactation, some of the above treatments have resulted in unacceptable side-effects. Results of trials using synthetic glucocorticoids have been summarized by Jöchle (1974) and Bosc (1974). In the cow, calving can be successfully induced with glucocorticoids but the high incidence of calf mortality (see also Welch et al., 1973) and retained placentae are unacceptable and the onset of milk production may be slower. These problems may be overcome by injecting estradiol at the same time as dexamethasone administration. This combined treatment has been used successfully, and the incidence of retained placentae was similar to that in the control (spontaneously calving) group (Garverick et al., 1974). Artificial means of inducing labor may not achieve this full complement of effects (eg. estrogen or prostaglandin administered to pregnant goats may lead to delivery but do not stimulate surfactant production). Furthermore, it is apparent that the stress response of the newborn at induced labor may not be normal, and premature lambs delivered with Synacthen may have a poor response to cold stress (see Thorburn et al., 1976).

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