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INDUCTION OF PARTURITION IN FARM ANIMALS

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I. — INITIATION OF PARTURITION

The initiation of parturition is regulated by the complex interactions of endocrine, neural and mechanical factors. However, the exact sequence of the chain of events initiating the onset of labor is not known but is probably the result of many processes working together and reinforcing one another. The definition of the processes involved may be subject to great species variability but it is reasonable to postulate that certain general features are common to most farm animals.

There is now a considerable body of evidence which suggests that a functional hypothalamic-pituitary-adrenal axis in the fetus is a prerequisite for normal parturition. In cattle and in sheep several syndromes of prolonged gestation have been defined and are linked specifically to either anatomical or functional anomalies in the fetuses (ROBERTS, 1971; JUBB and KENNEDY, 1980). In cattle there are two well-defined syndromes, both caused by a homozygous autosomal recessive gene in the fetus. The first syndrome is found in the Holstein and Ayrshire breeds and is characterized by the presentation of a very large calf 60-90 days after the expected parturition date. The calves have normal proportions but show evidence of being postmature by the presence of very long hair and hooves, and the eruption of incisor teeth. Parturition is abnormal, with minimal relaxation of the pelvic ligaments and minimal filling of the udder; assistance with delivery is normally required. Hypoplastic adrenal glands are found in the calves upon post mortem examination.

In Guernsey, Jersey, and Swedish Red and White breeds a second syndrome of prolonged gestation has been observed. The affected calves are fetal monsters. They are developmentally immature and possess a variety of cranial and central nervous system anomalies including hydrocephalus, anencephalus, and cyclopia. Gestation is prolonged (mean of 120 days), and parturition is characterized by the delivery of a relatively immature dead fetus. Aplasia of the pituitary and/or hypoplasia of the adrenals are seen on post mortem examination of the calves.
In sheep the syndrome of prolonged gestation is caused by the ewe ingesting the weed *Veratrum californicum* on or about the 14th day of pregnancy. The ewe subsequently fails to initiate labor at term, and pregnancy may continue for weeks beyond term. In this syndrome of prolonged gestation the fetal lambs are usually giants, with severe cyclopean deformities, absence of the hypophysial stalk and the pituitary gland, adrenal hypoplasia, and an insufficiency of steroid production and metabolism (Bëns *et al.*, 1964).

In contrast, one would expect gestation to be abbreviated if there is hyper-activation of the fetal pituitary-adrenal axis. Such a naturally-occurring phenomenon has been documented in an early abortion syndrome described in Angora goats as a result of fetal adrenal hyperplasia (Van Rensburg, 1971).

In all of these naturally-occurring clinical syndromes there is some defect in the integrity or functional competence of the fetal pituitary-adrenal axis.

In addition, a series of specific experimental alterations of the ovine fetal pituitary-adrenal axis has confirmed the importance of the integrity of this axis in control of parturition in this species (Liggins *et al.*, 1967). These experiments were described by Liggins *et al.*, (1973), as follows:

1) Decapitation of the fetal lamb led to prolonged gestation and hypoplastic adrenal glands.

2) Electrocoagulation of the fetal ovine pituitary caused prolonged gestation.

3) Bilateral adrenalectomy caused prolonged gestation, but ablation of the adrenal medulla by formalin injection did not prolong gestation.

4) The fetal adrenal was found to be functional during gestation; and the rate of secretion and the plasma corticoid levels were found to increase significantly at term.

5) Administration of adreno-corticotrophic hormone (ACTH) or cortisol to fetal lambs during the last two months of gestation could induce parturition. Administration of the same dose of ACTH or cortisol to pregnant ewes was ineffective in inducing parturition. When larger doses of ACTH or cortisol were given to ewes, parturition could be induced.

In addition, several other alterations occur rather consistently in the hormone system although there are obvious species differences. A wealth of recent data obtained from sheep and goats strongly suggest that the endocrine changes seen around the time of parturition reflect the complex interaction between the fetal and maternal compartments. Challis and Thorburn (1975) have summarized these complex interactions as follows:

1) Independence of maternal and fetal plasma concentrations of ACTH, growth hormone, and arginine-vasopressin indicates that the placenta is effectively impermeable to them and their presence in fetal plasma, therefore implies production of these peptide hormones within the fetus.

2) That the fetus may biochemically complement the maternal organism *e.g.*, by producing C₁₉ steroid precursors for subsequent placental aromatization.

3) The fetus may metabolize and reduce the biological activity of certain maternal or placental hormones, *e.g.* the conjugation or hydroxylation of placental estrogens in the fetal liver.

4) Depending upon the degree of placental permeability and metabolism the fetus may receive maternal hormones into its circulation. However, the increase
in size and function of the fetal adrenal, the induction of 17α-hydroxylase favoring production of cortisol over corticosterone, the increased response of the fetal adrenal, and the increased production of both fetal ACTH and cortisol as well as increased cortisol-binding globulin levels as term approaches suggest the independence of the fetal pituitary-adrenal axis from that of the maternal organism. Thus several changes on the fetal hypophysial-adrenal axis appear to be responsible for the increase in cortisol production that precipitates parturition. However, the controlling mechanisms of these maturational changes have not been fully elucidated (CHALLIS and THORBURN, 1975).

THORBURN and co-workers (1972) examined the levels of plasma progesterone in pregnant ewes and found that the levels fell from 7-11 mg/ml to 0.5-1.0 mg/ml during the last few days of pregnancy. Since other workers had previously established that the metabolic clearance of progesterone was constant during this time, the decrease in progesterone levels is probably related to decreased progesterone synthesis. Unlike the cow, where progesterone is primarily of luteal origin, the ewe is primarily dependent on placental progesterone synthesis in the later half of gestation.

In addition to increased fetal corticoid levels and a decrease in maternal progesterone levels, a third hormonal change seen at the time of parturition, at least in the sheep, is an increase in the maternal plasma levels of unconjugated estrogens. The unconjugated estrogen levels begin to rise at about day 120 of gestation and increase slowly to a peak value 16-24 hours prepartum (THORBURN et al., 1972). The role of the high levels of estrogens in the initiation of parturition has been investigated in several laboratories by stilbestrol administration to pregnant ewes (LIGGINS et al., 1973; HINDSON et al., 1967). Stilbestrol administration caused an increase in uterine myometrial contractility. This was evidenced by a decrease, measurable within twelve hours, of the dose of intravenous oxytocin required to initiate uterine contractions, and by the development of spontaneous uterine contractions within 24 hours. It is noteworthy that the time required to induce spontaneous uterine contractions is very similar to the latency between the estrogen peak and delivery of the fetus observed during normal parturition.

A fourth well-characterized endocrine change at the time of parturition is a sharp rise in plasma prostaglandin levels. The prostaglandin levels in both uterine venous blood and the myometrium increase markedly at the time of both normal and dexamethasone induced parturition (LIGGINS et al., 1973).

During the last eight years numerous scientific reports have confirmed that some of the glucocorticosteroid hormones are capable of inducing parturition in farm animals. JÖCHLE has presented an excellent detailed review of this subject (JÖCHLE, 1974).

Recent work in cows has shown that the administration of synthetic glucocorticoids (e.g. Dexamethasone and Flumethasone) to the pregnant cow during the latter part of pregnancy will induce premature labor (WAGNER, 1972).

Similarly, the administration of Dexamethasone to ewes during the last 5-10 days of pregnancy will also induce premature parturition. BASSETT and THORBURN (1973) reported that if the maternal cortisol concentrations are elevated to around 10-12 mg/100 ml, the fetal cortisol concentration increases to about
2.5 mg/100 ml. If this cortisol concentration were maintained in the fetus over about 48 hours, it is likely that it would induce premature parturition (Challis and Thorburn, 1975). In contrast to the cow, ewe and goat, the same dose levels of cortisol were ineffective in inducing parturition in both swine and horses (Jöchle, 1974), thus revealing a significant species difference. It is possible that some additional signal is required to trigger the onset of labor in these species or that the dose or routes of administration in the drugs tested were inappropriate. Jöchle (1974) observes that in cattle corticoid induced parturition is related to:

1) High plasma corticoid levels seeming to mimic a signal from the fetus.
2) A short, dramatic rise in urinary estrogen excretion followed by an equally sharp drop.
3) A sharp drop of plasma progesterone levels preceding the induction of labor.

He postulates that the corticoids shut off the source of progesterone from the corpus luteum thereby removing the blocking effect on myometrial contractility. The estrogen sensitized uterine musculature becomes capable of a response to oxytocin.

In sheep Liggins et al., (1972) demonstrated that dexamethasone-induced parturition is accompanied by a marked increase in prostaglandin F2α concentration in the uterine vein plasma. The same authors presented the hypothesis that the release of prostaglandin F2α may be the final step in the chain of events which triggers expulsion of the fetus.

Vandeplasche and co-workers (1974) have lent support to these hypotheses by observations on certain pathologic conditions in gravid cows. The corticoid effect in the induction of parturition appears to require a live fetus. They were able to induce parturition in 81% of cows with hydropsamnion or hydropsallantois between 7-9 months of gestation by one or two injections of dexamethasone (20-40 mg IM). However, the cows with mummified fetuses, which were unresponsive to dexamethasone, delivered between days 3 to 11 after repeated IM injection of stilbestrol (60-80 mg). Neither dexamethasone nor estrogen induced parturition in cows carrying a macerated fetus. Whereas, intrauterine infusion of prostaglandin F2α successfully induced parturition in cows carrying either macerated or mummified fetuses and was always accompanied by luteal regression. Since with mummification the uterine lining remains unimpaired, while it is severely damaged with maceration, estrogens work in the former situation, but not in the latter (Vandeplasche et al., 1974).

It is tempting to postulate that increased corticoid levels induce elevation in the levels of unconjugated estrogens and that the latter bring about luteal regression by stimulating the release of prostaglandins. Liggins et al., (1972) have postulated that, at term in the ewes, the fetal pituitary releases increasing amounts of ACTH which, in turn, causes an increased secretion of adrenal corticosteroids and C19 steroid precursors. The adrenal corticoids + C19 steroid precursors bring about a decrease in progesterone levels as a result of the increased levels of estrogens and prostaglandins. These changes cause a general increase in uterine excitability and are sufficient to initiate the uterine contractions required for parturition.

Although this scheme of cortisol induction of parturition in farm animals seems reasonably complete, it should be noted that even in the ewe and goat, the exact mechanism by which cortisol mediates the observed changes in hormone
levels is unknown. When other species are considered, the scheme becomes even less coherent. In the Cow, for example, although estrogen and progesterone levels change in a manner similar to that of the ewe, there is a smaller increase in fetal cortisol preceding changes in estrogen and progesterone and the response to exogenous glucocorticoids is frequently associated with retained placentas (Adams and Wagner, 1970). In the horse, little or no change in fetal cortisol levels is seen preceding parturition (Rossdale et al., 1973; Comline et al., 1972). But as opposed to moderate doses in the cow and the ewe, very high levels of corticosteroids given to the mare can induce parturition (Alm et al., 1974). On the other hand, in late gestation oxytocin alone is extremely effective in inducing labor (Purvis, 1972).

Wagner, cited by Jöchle (1974), saw no effects of large doses of corticoids on pregnant Sows or gilts. Perhaps some additional trigger is necessary in this species, as it appears to be in horses.

Despite certain general patterns observed in the early series of events surrounding the onset of parturition in farm animals it is apparent that many unanswered questions still remain. Control of the initiation of labor has obvious practical value to the livestock industry. However, more basic research is required before the potential can be realized.

REFERENCES

