FETAL CORTISOL AND LABOUR IN HUMAN:

Physiological Considerations and Clinical Implications)

by

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Labour is a coordinated rhythmic uterine activity that accomplishes progressive cervical dilatation and effacement. The uterus contracts throughout pregnancy, but it is usually only at term that contractions achieve the coordination necessary for cervical change and descent of the fetus through the birth canal. The precise etiology of labour is unknown. It is in all probability a combination of factors being expressed by both the maternal and fetal organisms (Quilligan, 1973).

The concept that the fetus influences its own destiny by initiating labour has been discussed for a long time. While many divergent factors are concerned in this complex mechanism which precisely controls the onset of human labour, endocrine factors appears to be of vital importance. Evidence in experimental animals, primarily sheep, suggests that within this complex regulatory process, the fetus makes a major contribution to the timing of its own delivery. In the sheep, the central feature of the initiation of parturition is a rapid increase in the secretion of cortisol by the fetal adrenal gland in the final days of pregnancy. After this, there occur in the mother other changes, notably a decrease in the plasma concentration of progesterone and increases in the plasma concentration of oestrogens and prostaglandins, resulting in myometrial contractions.

There is a large body circumstantial evidence to suggest that the fetal adrenal gland is involved in the timing of the onset of human labour, although there are obvious difficulties in establishing whether this comes about through increased hormone secretion. Some of the indirect evidences linking fetal adrenal weight with disorders of gestation length are as follows:

1. In the absence of hydramnios, anencephaly (a fetal malformation with varying degree of adrenal hypoplasia) is frequently but not invariably associated with prolonged gestation (Malpas, 1933; Comerford, 1965). The extent of the prolongation of pregnancy in anencephaly has been shown to be inversely related to fetal adrenal weight at birth (Anderson *et al*, 1971).

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2. Fetal adrenal hypoplasia without gross pituitary abnormality may be associated with postmaturity (O'Donohoe and Holland, 1968).

3. Fetal adrenocortical hyperplasia, with increased adrenal weight, has been found in babies delivered as a result of 'unexplained' preterm labour (Anderson *et al*, 1971), in keeping with the high urinary excretion of the fetal adrenal steroid hormone, dehydroepiandrosterone sulphate (DHEAS), in babies born prematurely (Lauritzen and Lahmann, 1967).

4. Fetal adrenal weight increases rapidly towards the end of gestation, both in absolute terms and relative to body size (Winters *et al*, 1974) so that at birth the fetal adrenals weigh 10-20 times more than the adult adrenals, relative to body weight. Much of this increased size is due to the 'fetal' zone of the cortex which comprises some 80% of the gland at term but regresses soon after birth, thus suggesting an intrauterine role for this tissue and for the steroid hormones synthesized there.

Although the evidence is inconclusive and some times controversial, taken as a whole it points to the fetal adrenal gland having a regulatory role, direct or indirect, in the onset of labour. The most likely way in which the human fetal adrenal would influence gestation length is through secretion of either corticosteroids (cortisol being quantitatively the most important of these) or the oestrogen precursor, dehydroepiandrosterone (DHEAS).

Fetal adrenal activity is increased at the end of gestation, as evidenced by the raised maternal concentration of oestriol. The increased maternal urinary excretion of corticosteroid sulphates (Klein *et al*, 1971) and the rising cortisol concentration in amniotic fluid during last trimester (Murphy *et al*, 1975; Gennser *et al*, 1976) have been interpreted as being due to an increased fetal production of steroids.

It seems established that cortisol from the fetal adrenal serves as a link in the mechanism, triggering parturition in species such as sheep and goat (Liggins *et al*, 1973; Thorburn *et al*, 1972). The regulation of the events terminating pregnancy in the human is far less clear, due in part to the obvious limitations to experimental studies on women. Several studies have pointed out to an increased occurrence of postmaturity in cases with congenital hypoplasia with or without concomitant anencephaly (O'Donohoe and Holland, 1968; Anderson *et al*, 1969). A relation has also been suggested between adrenal hyperplasia and premature labour (Anderson *et al*, 1971). This is, however, circumstantial evidence for the role played by the human fetal adrenal in the initiation of labour. Support for such a role would be demonstration of a surge of circulating cortisol during a few days' preceding spontaneous labour, as found in sheep (Liggins *et al*, 1973). The cortisol levels in the cord blood have been shown to be higher after spontaneous than after induced labour by some investigators (Murphy, 1973; Cawson *et al*, 1974; Smith and Shearman, 1974) but not by others (Pokoly, 1973; Ohrlander *et al*, 1976).

Several workers pointed out that plasma cortisol concentration in the fetus are higher after vaginal delivery than after caesarean section (Krauer, 1973; Kauppila *et al*, 1972). A difference in cord blood cortisol after labour was noted between cases with spontaneous onset of parturition and those with induced parturition (Murphy, 1973; Cawson *et al*, 1974; Smith and Shearman, 1974). A

role for fetal circulating cortisol in the initiation of parturition in man was suggesed in these studies.

Fetal cortisol is supposed to be synthesized in the permanent and the fetal zone of the adrenal cortex, from placental progesterone and from 17-alpha-hydroxyprogesterone of fetoplacental as well as of ovarian origin. A de novo synthesis of cortisol seems possible in the permanent adrenocortical zone (Oakey, 1970), provided that a 3-beta-hydroxysteroid dehydrogenase system is active. It is not clear at present whether the permanent cortex can respond to stimulation with corticotropin during late pregnancy.

Several workers have shown that corticotrophin and chorionicgonadotropin are poor stimulators of fetal adrenal function. Therefore, it is doubtful whether the fetus can produce specific increases in cortisol concentration by the action of these hormones (Ciba Symposia 47, 1977).

The issue as to whether adrenocorticotropic hormone (ACTH) is the tropic hormone of the provisional zone of the fetal adrenal cortex had remained controversial. Because the provisional zone is hypertropic in utero, and exhibits rapid involution postpartum, it was postulated at one time that this zone may be dependent on continued human chorionicgonadotrophin (HCG) stimulation during pregnancy (Jones, 1955; Bernirschke, *et al*, 1956). More recently, prolactin has been suggested as playing a role in the tropic stimulation of this zone, since fetal prolactin secretion (but not ACTH) was found to parallel the growth pattern of the fetal adrenal glands (Winter *et al*, 1975). Morever, ACTH binding to minces from provisional zones of second trimester abortuses could not be demonstrated (Seron-Ferre *et al*, 1975). On the other hand, although the adrenal cortex of the anencephalic newborn is presumed to lack the provisional zone, daily administration of ACTH to an anencephalic infant was found to cause adrenocortical hypertrophy indistinguishable from the provisional zone (Lanman, 1961).

Maternal administration of steroids during pregnancy has previously been shown to cause mild to moderate suppression of oestriol excretion (Charles *et al*, 1971). Nwosu *et al* (1976) observed an acute severe oestriol suppression by direct instillation of hydrocortisone into the amniotic fluid, thereby demonstrating an association between biosynthetic pathway of the oestriol and hydrocortisone in the fetal adrenal cortex. According to them, the declining oestriol excretion is thought to be a reflection of rising plasma cortisol levels in the fetus with consequent inhibition of the fetal hypothalamus and reduction in pituitary ACTH secretion. Since ACTH acts in the conversion of cholesterol to pregnenolone and since this reaction is known to occur in the fetal zone, the declining oestriol excretion provides additional evidence in favour of ACTH as the tropic hormone of the provisional zone.

The mechanism of cortisol induced labour is not fully understood. In the sheep, Liggins *et al* (1972) have proposed that the cortisol shower released by the fetal lamb near term increases the levels of placental prostaglandin F-2-alpha as well as oestrogens. The increasing concentrations of both these agents are thought to prime the uterus, increasing its sensitivity to endogenous oxytocin (Nwosu *et al*, 1976). Whether a similar mechanism is applicable to the human remains to be defined.

The role of maternal corticosteroids in parturition is rarely considered although

maternal adrenal activity may affect gestation length, women with Addison's disease tending to have prolonged pregnancies, while cases of Cushing's syndrome deliver early (Osler, 1962). In addition, the marked circadian rhythm in the spontaneous onset of labour (Smolensky *et al*, 1972) could relate to a rhythmic variation in adrenal function. The initiation of labour occurs most frequently between midnight and 0.3.00 hours, but infrequently around midday; labours beginning at night are shorter than those starting during the day (Malek, 1952). A relationship between these findings and maternal or possibly fetal endocrine rhythms is merely speculative.

Clinical Implications

The concept of postmaturity is as old as it is controversial, the possibility of prolongation of pregnancy beyond term first having been proposed in approximately 130 A.D. by Gellius Aulus (Nwosu *et al*, 1976). Postmaturity is one of the several prenatal conditions which may subject the fetus to distress during labour (Nwosu *et al*, 1975).

Certainly the most inappropriate statement regarding prolonged pregnancy is that when the fruit is ripe, it will drop! Apparently in this case, it not only does not drop, it spoils!

The fetal adrenal cortex has recently been implicated in the etiology of postmaturity in the light of low cortisol levels in the plasma of postterm neonates. These findings suggested that labour could be initiated in prolonged pregnancy by iatrogenic elevation of fetal plasma cortisol (Nwosu *et al*, 1976).

Liggins and his coworkers have been largely responsible for developing the concept that the secretion of cortisol by the fetal adrenal is a key factor in the initiation of labour (Liggins, 1968; Liggins and Kennedy, 1968; Liggins, 1969). Mati *et al* (1973) reported successful induction of labour in patients with postterm pregnancy after intra-amniotic injection of betamethasone but the same treatment failed to induce labour with anencephalic fetus. Nwosu *et al* (1976) reported the successful induction by intra-amniotic injection of hydrocortisone. In contrast, similar patients receiving water failed to go in labour. Liggins (Ciba symposia 47, 421, 1977) observed results as that of Mati *et al* (1973) in an incomplete study of 45 women beyond term. In India, mid-trimester abortion has been effectively induced by intra-amniotic injections of either hydrocortisone (Parikh *et al*, 1978) or betamethasone (Baveja *et al*, 1979).

Following infusions of radiolabelled cortisol into the amniotic fluid, Migeon *et al*, (1961) noted a disappearance rate of 10% per hour and found high concentrations of radioactivity in the fetal circulation. Although it is possible that access into the fetal circulation may be via the skin of the fetus during mid-trimester, this route is less likely in the term or postterm fetus in whom the skin is less permeable. It is therefore reasonable to conclude that intra-amniotic cortisol reaches the fetal circulation by fetal deglutition, followed by intestinal absorption (Nwosu *et al*, 1976).

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