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Endocrine Control of Human Parturition : a study of maternal and cord prolactin, progesterone, estradiol, 13, 14-dihydro 15-keto prostaglandin F2α and cord cortisol

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ENDOCRINE CONTROL OF HUMAN PARTURITION

A study of maternal and cord prolactin, progesterone, estradiol, 13,14-dihydro 15-keto prostaglandin $F_{2\alpha}$ and cord cortisol

by

Debra Ann Barrett

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submitted to the Yale University School of Medicine
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TABLE OF CONTENTS

ABSTRACT

To investigate possible endocrine relationships in human parturition paired maternal and cord bloods in select labor situations were obtained at delivery and assayed for cortisol, estradiol, progesterone, 13,14-dihydro 15 keto prostaglandin $F_{2\alpha}$ (PGFM), and prolactin. Correlations between these hormones, comparisons of material and cord blood levels, and relationships to spontaneous labor were evaluated.

No significant interrelationships were found between cortisol, estradiol, progesterone, PGFM, or prolactin. Significant correlations between maternal and cord levels of both estradiol and PGFM were noted. Progesterone and prolactin were significantly higher and estradiol was significantly lower in cord than in maternal blood. PGFM alone was significantly associated with the labor process.

The data provides evidence for involvement of $PGF_{2\alpha}$ in labor and suggests a dominant role. No endocrine relationships comparable to those in the sheep model of parturition were demonstrated. Examination of these results and the existing evidence in humans with comparison to the sheep model suggests significant differences and illustrates the need for an alternative hypothesis for the control of labor in humans.

INTRODUCTION

Speculation on the forces which control human birth is ancient (Gellius Aulus 130 A.D.) and continues to the present day.

In contrast to the advances made in recent years towards understanding the control of parturition in several mammalian species, most notably the sheep (Liggins 1969, Liggins et al. 1972, Liggins et al. 1973), the mechanism in humans remains enigmatic. Knowledge is fragmentary, controversial, and has not yet been synthesized into an accepted coherent model.

The body of comparative research on the physiology of initiation of labor in mammals is enormous (see review by Davies and Ryan 1972) and includes extensive work on the sheep, goat, rabbit, cow, and mouse as well as data on non-human primates, notably the chimpanzee, macaque, and marmoset. The pig, dog, cat, horse, guinea pig, armadillo, and many others have also been studied.

These data illustrate a striking diversity among otherwise closely related animals which is considered characteristic of mammalian reproduction in general and which far exceeds that of other organ systems (Lanman 1977). A fundamental distinction may be made between those animals in which luteolysis has an indispensable function in

parturition such as the goat (Currie et al. 1973), rabbit (Fraenkl 1905, Fuchs 1973), and mouse (Harris 1927) and that group of placental dependant mammals in whom parturition is independant of corpus luteum function which includes the sheep, cow, non-human primates (Davies and Ryan 1972) and humans (Csapo et al. 1973).

Although non-human primates may have provided intuitively the closest working model for the study of human parturition, analysis in these species has faced major technical obstacles (Lanman 1977) so that observations are far fewer and much more restricted in scope than in the sheep.

The "sheep model" has provided a working hypothesis for experimentation in humans. The basic elements of this model are: 1) The fetus plays a dominant role in initiating parturition via the fetal pituitary and fetal adrenal through the action of fetal cortisol (Binns et al. 1963, Liggins et al. 1966, Liggins et al. 1967, Liggins 1968, Drost and Holm 1968, Liggins et al. 1969). 2) Cortisol produced by the fetal adrenal (Nathanielsz et al. 1972) increases dramatically over the 7-10 days prepartum (Bassett and Thorburn 1969) and acts on placental steroidogenesis enzyme systems (Anderson et al. 1975) to acutely decrease progesterone production (Bassett et al. 1969, Bedford et al. 1972, Liggins et al. 1972, Thorburn et al. 1972) and to acutely increase estrogen production (Challis 1971, Liggins et al. 1972, Thompson and Wagner 1974, John and Pierrepoint

1975, Steele et al. 1975 and 1976). Both of these changes are readily measured in peripheral plasma. 3) The increase in estrogen and decrease in progesterone are thought to regulate $PGF_{2\alpha}$ through some combination of increased synthesis, release, and target organ sensitivity such that $PGF_{2\alpha}$ serves as the primary uterine stumulant and labor begins (Liggins et al. 1973, Schwartz 1974, Mitchell et al. 1976, Liggins et al. 1976).

Techniques utilized in the sheep include in utero catheterization of the fetal lamb, ablation procedures, and a variety of drug infusions. Ethical human experiments, often by necessity less direct, have investigated the relevance of each aspect of the sheep model to human labor.

The dominant role of the fetus in initiating parturition in the ewe has encouraged investigations of the extent of fetal control in the human. In addition to scrutiny of the relatively rare human "experiments of nature" in which the effects of anencephaly (Comerford 1965, Milic and Adamsons 1969, Honnebeir and Swaab 1973) and adrenal hypoplasia (Roberts and Cowdry 1970, Liggins 1974) can be evaluated, the effects of glucocorticoid infusion in the human have been investigated (Liggins and Howie 1972, Mati et al. 1973, Ohrlander et al. 1975, Gamissans et al. 1975, Nwosu et al. 1976, Whitt et al. 1976, Genneser et al. 1976).

The predominant experimental approach and the one used

in this study has focused on fetal and maternal cortisol levels in the peripartum period and their relationship to spontaneous labor (Murphy and Diez d'aux 1972, Cawson et al. 1974, Leong and Murphy 1976, Goldkrand et al. 1976, Talbert et al. 1973, Nwosu et al. 1975, Pokoly 1973, Ohrlander et al. 1976, Sylbulski et al. 1976). The results of these studies are conflicting and controversial.

The changes in placental steroidogenesis documented in the sheep as decreased progesterone levels and increased estrogen levels in peripheral samples at the onset of labor have prompted experiments to document comparable changes in the human. The results of Turnbull et al. 1974 and Csapo et al. 1971 have shown some changes in progesterone and estrogen but these conflict with the preponderance of additional serial studies which do not (Eton and Short 1960, Grieg et al. 1962, Kumar et al. 1964, Llauro et al. 1968, Craft et al. 1969, Tulchinsky et al. 1972, Shagban and Klopper 1973).

There is abundant evidence that prostaglandins have an important place in the physiology of labor (Liggins et al. 1976). However the question of whether they are directly concerned with initiation of labor remains unresolved. Initial studies of $PGF_{2\alpha}$ showed values about 100-1000 times higher than those calculated by kinetic studies of prostaglandin metabolism (Granstrom 1972) and production rates (Samuelson 1973). As a consequence, results from the many studies using these methods are suspect.

Green et al. 1974 using a gas chromatographic technique demonstrated the superior reliability of measuring the major $PGF_{2\alpha}$ metabolite, 13,14-dihydro 15-keto prostaglandin $F_{2\alpha}$ (PGFM). PGFM is not formed during the collection of blood and can be expected to occur in considerably higher concentrations than its evanescent parent compound because of its longer half-life.

A new PGFM radioimmunoassay developed in this laboratory (Haning et al. 1977) was available for this study and facilitated a more reliable determination of the relationship between $PGF_{2\alpha}$ and the labor process.

One additional hormone, prolactin, which is not yet a part of any major parturition model, was examined in this study. The control of the fetal adrenal in sheep and humans has yet to be clarified. There is data (Winter et al. 1975, McMillan et al. 1976) to implicate prolactin as a trophic hormone for the human fetal adrenal. Prolactin's role in the initiation of labor, perhaps via the fetal adrenal, has not been demonstrated.

In order to investigate the endocrine control mechanisms of labor in the human, this study examined paired maternal and cord bloods obtained at the time of delivery in selected labor groups and assayed them for cortisol, estradiol, progesterone, PGFM, and prolactin. Statistical analyses were then made to examine the relationships of these hormones to each other and with spontaneous labor.

MATERIALS AND METHODS

Experimental Design

Under a protocol approved by the Yale University Human Investigation Committee, four major groups of patient volunteers were chosen for the study.

Group 1 were patients undergoing cesarean section after labor had begun spontaneously.

Group 2 were patients undergoing elective cesarean section prior to the onset of labor.

Group 3 were women delivering vaginally after completing spontaneous onset of labor who at no time received oxytocin.

Group 4 were women delivering vaginally after induction of labor with oxytocin prior to the onset of spontaneous labor.

All patients were at term between 38-41 weeks by dates (many also by ultrasound). All had normal pregnancies and produced healthy infants. Patients with rupture of the membranes without spontaneous labor (PROM), dysfunctional labor, or any obstetrical complication as well as patients with diabetes, hypertension, or other medical-high risk complications were excluded. No patient had taken aspirin within one month or non-aspirin anti-inflammatory agents including steroids at any time.

As the study progressed, samples from two additional minor groups became available. Many patients in spontaneous labor who volunteered for the study required oxytocin stimulation following epidural anesthesia. This group (Group 5) was included for comparison to the major groups. Likewise a group of patients with PROM who received oxytocin induction (Group 6) was also added to the study.

All the patients in this study underwent epidural anesthesia to control for this variable especially in view of evidence that maternal hormone levels may be affected (Buchan et al. 1973).

Collection of Samples

Maternal blood samples were obtained from the antecubital fossa by fresh venipuncture after full cervical dilatation and within one hour before delivery.

Cord blood samples were obtained from the umbilical vein by clean venipuncture immediately following clamping and cutting of the cord and delivery of the placenta.

All samples were collected into glass vacutainer tubes containing 143 units of heparin and immediately chilled in ice then centrifuged with supernatant plasma stored at -20C.

Assays

The cortisol assay was performed on aliquots of plasma as described by Tan et al. 1976. Cortisol was determined only in cord samples.

Prolactin was determined in aliquots of plasma by the method of Sinha et al. 1973 in the laboratory of Dr. Richard Donabedian.

An extraction protocol was developed for determination of progesterone, estradiol, and PGFM in one sample. A 4 ml. aliquot of plasma was placed in a 15 by 125 mm glass tube with teflon lined cap along with 10,000 cpm of each of the three recovery indicators in buffer. Progesterone was extracted with 6 ml. of ligroin petroleum ether. Estradiol was extracted with 4 ml. of diethyl ether. The sample was then acidified with 0.1 ml. of 1N HCl per ml. of sample and PGFM was extracted with 2 x 8 ml. of redistilled ethyl acetate. The tube was centrifuged for 5 minutes at 4 C to 1000 g to effect phase separation after each extraction.

Following phase separation the organic phases were handled as described for each hormone. Recoveries were determined for each sample and were approximately as follows: Progesterone 50 percent, estradiol 60 percent, and PGFM 65 percent overall including column chromatography. Less than 0.75 percent of any recovery indicator appeared in the inappropriate chromatographic fraction.

Estradial was determined by radioimmunoassay as previously described (Haning et al. 1979) with 0.25 percent charcoal and 0.025 percent dextran for dextran coated charcoal.

Progesterone was determined by radioimmunoassay as previously described (Orczyk et al. 1979) except that the system was modified for use with minicolumns.

PGFM was determined by radioimmunoassay following column chromatography as described by Haning et al. 1977. This method includes use of ^{3}H-internal recovery standard and mathematical correction for procedural losses, the effect of the added counts on the logit/log transformation, and the mass of the recovery indicator.

Statistical Analysis

The group design of this study is well suited to the statistical analysis of variance and correlation. Four maternal-cord pairs were included in each group. A total of 24 maternal-cord pairs were analyzed.

Assignment to row and column of the two-way analysis of variance was made prior to sample assay. Two sets of assays were performed for this study. Each cord sample was assayed in the same set as the corresponding maternal sample. All samples compared as a replication in the two-way analysis of variance were included in a single assay. Between assay variance was corrected for by the two-way analysis of variance. The test was used to test between group differences with the pooled variance derived from the two-way analysis.

With regard to the four major groups the following orthogonal comparisons were planned for both maternal and cord samples.

1) Spontaneous labor controlled for cesarean section (Group 1 vs. Group 2)

2) Spontaneous labor controlled for vaginal delivery (Group 3 vs. Group 4)

3) Labor vs. no labor (Groups 1, 3, 4 vs. Group 2)

4) Vaginal delivery vs. cesarean section (Groups 1, 2 vs. Groups 3, 4)

One additional orthogonal comparison was planned: comparison of maternal vs. cord hormone levels (maternal groups 1-6 vs. cord groups 1-6).

Correlation coefficients were computed for each of hormone parameters with each of the others as well as with duration of labor. It was fully realized that computation of all correlations might lead to false correlations which would not represent physiologic relationships and the results should be viewed in that light.

All calculations were performed on a Hewlett Packard 9830 with programs prepared by Dr. Ray Haning, Jr. Log transformation was found to be necessary due to heterogeneity of variance as determined by Bartlett's test for homogeneity of variance. All statistical analyses were performed on log-transformed data.

RESULTS

The results of all measurements appear in Table I.

Cortisol

There were no significant differences in cord cortisol between the clinical groups.

Observed trends were as follows: Babies delivered by cesarean section whose mothers experienced spontaneous onset of labor (Group 1) had a slightly higher mean cord cortisol concentration than those babies delivered prior to the onset of labor by cesarean section (Group 2).

Babies delivered vaginally following spontaneous onset of labor (Group 3) had a mean cord cortisol slightly higher than babies delivered by cesarean section prior to the onset of labor (Group 2).

However, babies delivered vaginally after induced labor (Group 4) had a slightly higher mean cord cortisol than any of the other three major groups. Addition of oxytocin stimulation to patients with spontaneous labor (Group 5) produced a 50 percent elevation of the cord cortisol mean Group 1-4 ($p > 0.05$).

The highest mean cortisol was that of the patients with PROM and oxytocin induction (Group 6). The mean reflected the single high value of 257.3 ng/ml in one sample

TABLE I

Hormone Levels in Maternal and Cord Blood Groups 1-6
(mean ± standard deviation)

Category and Group No.	Venous blood	Cortisol (ng./ml.)	Estradiol (ng./ml.)
Cesarean section, major groups:			
Spontaneous labor (Group 1)	Maternal		28.2 ± 11
	Cord	45.5 ± 29.2	6.5 ± 2.3
No labor (Group 2)	Maternal		25.3 ± 7.4
	Cord	37.7 ± 12.4	8.7 ± 2.9
Vaginal delivery major groups:			
Spontaneous labor (Group 3)	Maternal		17.8 ± 4.1
	Cord	43.6 ± 9.8	5.8 ± 2.0
Induced labor (Group 4)	Maternal		26.1 ± 6.1
	Cord	46.4 ± 17.0	7.7 ± 5.7
Vaginal delivery, minor groups:			
Spontaneous labor with oxytocin supplement after epidural (Group 5)	Maternal		28.4 ± 14
	Cord	63.0 ± 36.6	9.9 ± 6.1
Abnormal categories (Group 6)	Maternal		19.6 ± 15
	Cord	119.5*±119.4	9.7 ± 8.4

N = 4 except where noted by *, where N - 3.
†13,14-Dihydro-15-keto-prostaglandin $F_{2\alpha}$.

TABLE I--continued

Progesterone (ng./ml.)	Prolactin (ng./ml.)	PGFM † (pg./ml.)	Labor duration (hr.)
253 ± 106	146 ± 78	400 ± 200	11.7 ± 5.8
1,906 ± 357	306 ± 122	330 ± 130	
221 ± 53	164 ± 20	120 ± 50	0 ± 0
1,340 ± 715	341 ± 122	135 ± 30	
216 ± 68	141 ± 99	910 ± 340	10.7 ± 2.5
2,399 ± 1587	288 ± 207	870 ± 600	
277 ± 54	278 ± 144	530 ± 230	16.5 ± 5.2
1,856 ± 1077	330 ± 144	630 ± 290	
419 ± 242	234 ± 119	282* ± 49	14.7 ± 1.4
1,156 ± 525	288* ± 78	503 ± 48	
164* ± 47	199 ± 78	430 ± 200	11.0 ± 6.1
1,695 ± 577	345 ± 73	740 ± 390	

from a patient with low grade fever and a question of amnionitis. In all other respects this group was comparable to the induced patients (Group 4).

Prolactin

There were no significant differences in cord prolactin levels between any of the clinical groups.

Among women who delivered vaginally, maternal prolactin values were significantly higher in those women whose labor was induced (Group 4) than in those women with spontaneous labor who received no oxytocin (Group 3) ($p < 0.05$).

The administration of oxytocin to women with spontaneous labor (Group 5) led to prolactin levels without significant difference from those in the induced group (Group 4).

Cord prolactin levels were significantly higher than maternal prolactin levels in all groups ($p < 0.005$).

Estradiol

There were no significant differences between the clinical groups for either maternal or cord estradiol.

In all groups the maternal values were significantly higher than the cord values ($p < 0.001$).

Maternal and cord estradiol concentrations were highly correlated ($p < 0.01$).

Progesterone

There were no significant differences in progesterone levels between any of the clinical groups.

Cord progesterone was significantly higher than the corresponding maternal level in all groups ($p < 0.001$).

However there was no correlation between maternal cord levels.

PGFM

Significant differences between groups were found for both maternal and cord PGFM.

The PGFM concentrations found in patients without labor (Group 2) were significantly lower than those of any labor group for both maternal and cord samples ($p < 0.005$).

The mean maternal PGFM concentration in patients with cesarean section after spontaneous labor (Group 1) was significantly higher than the mean concentration in patients with cesarean section without labor (Group 2).

Among women delivered vaginally those in spontaneous labor (Group 3) had a higher mean PGFM level than women with induced labor (Group 4); however, the difference was not statistically significant.

Women with spontaneous labor requiring subsequent oxytocin stimulation (Group 5) had a mean PGFM significantly lower than that of women with spontaneous labor without oxytocin (Group 3).

Cord PGFM levels from patients with cesarean section after spontaneous labor (Group 1) were significantly higher than those from patients with cesarean section not in labor (Group 2) ($p < 0.01$).

Among women delivered vaginally, cord PGFM levels from patients with spontaneous labor (Group 3) were slightly higher than those from patients with induced labor (Group 4) but this difference was not statistically significant.

In addition, maternal and cord PGFM concentrations were highly correlated ($p < 0.01$).

Duration of Labor

Duration of labor was defined as the time from contractions at a frequency of 0.2 per minute to the time of delivery of the infant.

There were no significant between group differences when the group with labor was excluded from the two-way analysis of variance.

The duration of labor was negatively correlated with both maternal and cord estradiol concentrations but only the correlation with cord estradiol is significant ($p < 0.05$). No other hormone was significantly correlated with duration of labor.

Correlation Coefficients

A summary of all correlation coefficients is presented in Table II.

No significant correlations were made between

TABLE II

Correlation Coefficients for the Parameters Studied

Log/log transformation correlation coefficient and degrees of freedom	Maternal estradiol	Maternal progesterone	Maternal $PGF_{2\alpha}M$	Maternal prolactin
Estradiol, maternal	1 (26)			
Progesterone, maternal	0.33 (25)	1 (25)		
$PGF_{2\alpha}M$, maternal	0.1 (25)	0.1 (24)	1 (25)	
Prolactin, maternal	0.05 (26)	0.32 (25)	-0.186 (25)	1 (26)
Duration of labor	-0.27 (22)	0.096 (21)	-0.06 (21)	-0.08 (22)
Estradiol, cord	0.67** (26)	0.36 (25)	-0.04 (25)	0.08 (26)
Progesterone, cord	-0.17 (26)	-0.15 (25)	0.34 (25)	0.04 (26)
$PGF_{2\alpha}M$, cord	-0.02 (26)	0.24 (25)	0.716** (25)	0.03 (26)
Prolactin, cord	-0.01 (25)	0.29 (24)	0.20 (25)	0.33 (25)
Cortisol, cord	0.041 (25)	-0.152 (24)	0.230 (24)	-0.155 (24)

*Denotes nominal significance at the 5 percent level and ** denotes nominal significance at the 1 percent level.

TABLE II--continued

Duration of labor	Cord estradiol	Cord progesterone	Cord $PGF_{2\alpha}M$	Cord prolactin	Cord cortisol
1 (22)					
-0.40* (22)	1 (26)				
-0.14 (22)	0.10 (26)	1 (26)			
-0.09 (22)	0.20 (26)	0.29 (26)	1 (26)		
0.27 (21)	0.08 (25)	-0.06 (25)	-0.05 (25)	1 (25)	
-0.210 (21)	0.017 (25)	0.035 (25)	0.056 (25)	-0.158 (24)	1 (25)

prolactin, cortisol, estradiol, progesterone, or PGFM in maternal or cord blood.

Highly significant correlations were noted between maternal and cord estradiol ($p < 0.01$) and between maternal and cord PGFM ($p < 0.01$). Duration of labor was correlated with cord estradiol ($p < 0.05$).

DISCUSSION

No significant interrelationships were found between cortisol, progesterone, estradiol, or PGFM which in the sheep model represent a closely linked control system. PGFM alone was significantly correlated with the labor process without any significant differences between groups for prolactin, cortisol, estradiol, or progesterone.

This data provides indirect evidence for involvement of $PGF_{2\alpha}$ in labor and suggests a dominant role. No endocrine relationships comparable to those in the sheep model of parturition were demonstrated for PGFM. There is a growing body of data and speculation which supports these findings and rejects the sheep model for human parturition (Liggins et al. 1977).

Examination of the specific results of this experiment and the existing evidence in humans with comparison to the sheep model suggests significant differences and illustrates the need for an alternative hypothesis for the control of labor in humans.

Cortisol

No association between cortisol and labor is demonstrated in this study and the data does not demonstrate any correlation with prolactin, progesterone, estradiol, or PGFM.

These findings are consistent with the analyses of several major reviewers (Davies and Ryan 1972, Liggins et al. 1977) who argue that the human fetal pituitary-adrenal axis may provide "precision" for timing but probably does not initiate or control labor.

Initial support for a relationship between the human fetal pituitary-adrenal axis and initiation of labor was based almost entirely on cases of congenital abnormality in which prolonged pregnancy was observed. Comerford 1965 described prolonged pregnancy in anencephalics. Roberts and Cowdry 1970 described prolonged pregnancy in babies with adrenal hypoplasia. These infrequent "experiments of nature" were the counterpart of classic field observations in cattle (Holm 1960) and sheep (Binns et al. 1963; Liggins 1969) with congenital lesions of the pituitary or adrenal which prompted the ablation experiments of pituitary (Liggins et al. 1966, Liggins et al. 1967) and adrenal (Drost and Holm 1968) and established the dominant role of the fetal pituitary-adrenal axis in parturition in the ewe.

The fact that premature delivery in human anencephalics is as common as post-term delivery has been noted more recently (Milic and Adamsons 1969). Honnebier and Swaab 1973 show that in pregnancy complicated by anencephaly mean pregnancy length in patients without polyhydramnios and without obstetrical interference is approximately 40 weeks but the range is very wide. Likewise other investigators (Anderson and Turnbull 1973, Davies and Ryan 1972) remark on a loss of

precision of timing with some cases of prolongation but not invariably so.

Liggins (1974) demonstrated that human fetuses with adrenal hypoplasia are born at or close to term. Hypophysectomy in rhesus monkey fetuses (Novy 1976) produced one-third early, one-third late, and one-third term deliveries.

These results demonstrate that labor occurs spontaneously in the absence of normal fetal pituitary or adrenal function and indicate that the fetal pituitary-adrenal axis may influence length of gestation but in a manner less direct than in sheep.

Major evidence that fetal lamb cortisol plays a dominant role in parturition came from experimental infusion of ACTH or glucocorticoids into the fetus which produced premature delivery while comparable maternal infusions were ineffective (Liggins 1968).

Administration of large intraamniotic doses of glucocorticoids to pregnant women does not induce premature labor (Liggins and Howie 1972). Numerous other experiments using a variety of glucocorticoid preparations, routes of administration, and doses have also failed to produce premature labor (Ohrlander et al. 1975, Gamissans et al. 1975, Whitt et al. 1976, Genneser et al. 1976). Walsh and Novy 1977 could not induce premature labor in the rhesus macaque by direct fetal infusion.

In human pregnancy one week or more beyond term,

intramniotic injection of 20 mg. dexamethasone (Mati et al. 1973) or 500 mg. cortisol succinate (Nwosu et al. 1976) was followed by labor within 120 hours in more treated women than controls. However Gamissans 1975 using 20 mg. betamethasone found no difference.

Even in the successful trials it is extremely doubtful that the mechanism of labor initiation was comparable to that of the sheep. All the cited studies of glucocorticoid treatment found plasma and urinary estrogens markedly depressed. This dramatic decrease displays a major point of divergence between the human and sheep model in which ACTH or glucocorticoid treatment induces placental steroidogenesis to markedly increase estrogen levels (Anderson et al. 1975).

There is no evidence of placental enzyme induction or activation by cortisol in humans (Challis et al. 1977). Maternal pregnandiol excretion is not lowered by steroid treatment and estrogen levels are depressed rather than elevated (Oakey 1970, Ohrlander et al. 1975). The cause for the estrogen decrease is diminished secretion of dehydroepiandosterone by suppression of the fetal adrenal, a major source of this precursor. Placental metabolism of steroids is unaffected (Simmer et al. 1974). This study demonstrates no correlation between cortisol and estradiol or progesterone.

The major approach to the investigation of the role of cortisol in human labor, and the one taken in this study,

has been measurement of fetal and often maternal cortisol levels. There is a progressive rise in maternal cortisol during pregnancy (Gemzell 1954, Mukherjee and Swyer 1972). In the fetus there is a progressive rise in plasma total corticosteroid (Smith and Shearman 1974) and cortisol (Murphy and Diez d'aux 1972) with advancing gestational age at birth during the last month of pregnancy with a similar rise in cortisol levels in amniotic fluid (Murphy et al. 1975, Fencl and Tulchinsky 1975).

It is less certain that a rise in fetal cortisol levels in the human preceeds the onset of labor comparable to the sharp rise in fetal lamb cortisol 7-10 days and particularly 1-5 days prepartum (Bassett and Thorburn 1969) and shown to be produced by the fetal adrenal (Nathanielsz et al. 1972).

Some investigators have interpreted their results as showing a more rapid rate of increase in fetal cortisol at term in studies based on gestational age (Murphy and Diez d'aux 1972) and at the time of spontaneous labor (Beitins et al. 1973). However Smith and Shearman 1974 demonstrated that total plasma corticosteroid levels in matched human umbilical artery and vein samples rose to a peak at 37-38 weeks and thereafter declined.

Data from this study is best compared to the results of a large number of experiments which were similarly designed to demonstrate some relationship between fetal cortisol and spontaneous labor.

Leong and Murphy 1976 found cord blood cortisol to be significantly higher in spontaneous labor whether the fetus was delivered vaginally or by cesarean section than in comparable situations without spontaneous labor. They argued that cortisol plays some causative role (Murphy 1973).

However an earlier study by Murphy (Murphy and Diez d'aux 1972) and two additional studies (Cawson et al. 1974, Goldkrand et al. 1976) of similar design found a significant difference only between cord cortisols from spontaneous vaginal delivery and cesarean section without labor (vaginal delivery greater than section).

Five other comparable studies failed to demonstrate, as did the present study, any significant difference between the groups (Talbert et al. 1973, Nwosu et al. 1975, Pokoly 1973, Ohrlander et al. 1976, Sylbulski et al. 1976). The trends of the means however in these five studies do follow a pattern of vaginal delivery greater than cesarean section and spontaneous vaginal delivery greater than induced. These trends alone have tempted some authors to suggest a causative role for cortisol.

The trends of cortisol levels in this study are cesarean section without labor less than cesarean section with labor less than vaginal delivery with spontaneous labor less than vaginal delivery with induced labor less than vaginal delivery with spontaneous labor requiring oxytocin assistance, all less than PROM with oxytocin induction in a group dominated by a case of suspected amnionitis. These

findings, which cannot be interpreted to show any relationship of cortisol with spontaneous labor, can be interpreted as giving a clue to fundamental problems in the interpretation of all studies of human fetal cortisol values. The most obvious is stress, both fetal and maternal, as well as the possible contribution of maternal stress to fetal cortisol values.

Stress such as fear, anxiety, pain, physical work, and trauma which all may be involved to varying degrees in the labor and delivery process are known to cause increased adrenocorticoid activity and increase plasma cortisol in humans (Bliss et al. 1956, Mason 1959, Black and Friedman 1968, Bellet et al. 1969, Carter and James 1970). The fetus itself may respond to trauma such as the scalp sample with increased cortisol (Knapstein et al. 1975, Sylbulski et al. 1976). In addition the fetus can respond to hypoxia with the rapid release of ACTH (Boddy et al. 1974).

Knapstein et al. 1975 measured maternal and fetal blood cortisol during labor of all kinds and noted wide swings and overall dramatic increases throughout labor until delivery. Nwosu et al. 1975 noted that initial maternal cortisol values were highest in pre-op section patients than the pre-induction group and lowest in patients at the onset of spontaneous labor. He proposed that elective termination of pregnancy may be more stress-provoking to mothers at least in that population. Although no significant differences were observed between delivery maternal levels in all

groups, a significant rise was noted in the spontaneous labor group. Goldkrand et al. 1976 and Talbert et al. 1973 note significant changes in some groups but no final between group differences.

In addition then to the consideration of fetal stress, the variable and often dramatic changes in maternal cortisol during labor can also affect fetal cortisol levels because unlike sheep, in which there is little transplacental transfer of cortisol (Beitins et al. 1973), human maternal corticosteroids readily cross the placenta (Migeon et al. 1961). Maternal corticosteroids contribute a proportion of cortisol to the fetal cortisol pool (Beitins et al. 1973, Kittinger 1974, Challis and Thorburn 1976).

At least some cortisol is converted to cortisone by ample placental dehydrogenase with transfer to the fetal circulation (Murphy et al. 1974) and this is the probable cause of the quantitative predominance of cortisone in the fetal circulation (Talbert et al. 1973, Dormer and France 1973). Cortisol values in fetal blood are therefore often considered to be solely of fetal adrenal origin although data in anencephalics suggests the transfer is sufficient to give them normal cortisol levels (Nichols et al. 1958) or only slightly lower than normal (Goldkrand et al. 1975). Some contribution of maternal cortisol to fetal cortisol levels especially in the face of maternal stress and acute increases seems difficult to exclude.

If significant between group differences in fetal

cortisol had been found in this study the measurement of maternal cortisol would have been crucial to experimental design. Leong and Murphy 1976 argue that if maternal cortisol values are comparable indifferent groups the fetal values can be compared.

However continuous epidural blockade, used in all patients in this study prevents the rise in maternal cortisol seen in women using pethidine alone (Buchan et al. 1973). This may have damped maternal cortisol contribution to the extent that the previously reported significant differences in fetal cortisol labor groups were not observed and reveals that the observed differences were more likely related to maternal (and perhaps fetal) stress than to initiation of labor.

The weight of evidence from all experimental approaches including that of this study suggests that the human fetus does not control parturition through cortisol.

Prolactin

Prolactin has been suggested as a source of tropic stimulation for the sheep and human fetal adrenal and would therefore, through cortisol, be postulated as an important link in the control of parturition. A hormone in addition to ACTH has been considered because the fetal zone is hypertrophic *in utero* but rapidly regresses postnatally with maintenance of cortisol levels.

The concentration of prolactin but not ACTH in human

fetal plasma was found to have good correlation with growth of the fetal adrenal (Winters et al. 1975). The rise in prolactin during pregnancy was shown to parallel the rise in estradiol by the same authors. In the fetal lamb McMillan et al. 1976 found a correlation between mean prolactin concentrations and cortisol during the last 30 days of gestation.

In this study, however, no correlation of fetal prolactin with estradiol or cortisol was found. Cord prolactin levels were significantly greater than maternal levels in all groups which is consistent with a model in which high in utero levels of prolactin maintain the fetal zone.

Maternal prolactin levels were significantly higher in the induced labor group than in the spontaneous labor group with vaginal delivery. These differences in maternal prolactin have no likely relationship to the initiation of labor and indeed the labor and no labor groups with cesarean section are not significantly different from each other or the spontaneous labor with vaginal delivery group. The administration of oxytocin to women with spontaneous labor (Group 5) however led to prolactin levels nearly as high as in the induced group.

This suggests that oxytocin administration may be responsible for the higher maternal prolactin level in Groups 4 and 5. Both hormones play a significant role in lactation and although there is no well described physiologic pathway by which oxytocin can stimulate prolactin it

is possible that such a relationship may exist. Since phenothiazines and related compounds such as the commonly used Vistaril may increase prolactin (Bruce and Ramirez 1970) and this drug was not controlled for in the pre-epidural anesthesia regimen this explanation must be considered. It is doubtful however that consistent differences existed between the regimens of the spontaneous labor groups 3 and 5.

This study did not demonstrate any relationship of fetal prolactin to labor which is consistent with the evidence assembled concerning cortisol.

Estradiol

No significant differences were found between any of the clinical groups in either maternal or cord blood and thus no correlation was demonstrated between estradiol and spontaneous labor. This suggests that there is no acute change associated with labor in humans to parallel that seen most abruptly and dramatically in the sheep over the last 7-10 days and particularly 1-5 days prepartum (Challis 1971, Thorburn et al. 1972).

Indeed no estrogen surge has been demonstrated by the overwhelming majority of authors (Tulchinsky et al. 1972, Shaaban and Klopper 1973, Munson et al. 1970, Loriaux et al. 1972, Sybulski and Maughan 1972, Townsley et al. 1973) who recognize a steady increase without abrupt prepartum changes. However Turnbull et al. 1974 described an abrupt

rise approximately six weeks before delivery which continued until one week before delivery then reached a plateau which was unchanged at the second stage of labor, a curve quite different from that in sheep.

No surge has been demonstrated in non-human primates including the marmoset (Hearn and Lunn 1975), rhesus macaque (Bosu et al. 1973) and chimpanzee (Reyes et al. 1975).

However an unconfirmed prospective study of women at risk of premature labor revealed a rise in plasma estradiol which preceded the onset of labor in those delivering prematurely (Tamby Raja et al. 1974 and 1975).

The acute effects of estrogen on the human myometrium are the subject of controversy. Jarvinen et al. 1965, Pinto et al. 1966, and Larsen et al. 1973 were able to stimulate uterine contractions but not labor by administration of large doses of estrogen to women at term. These studies suggest estrogen may have oxytocic properties.

It has been suggested that this effect may be modulated through effects of estrogen on the $PGF_{2\alpha}$ synthesis as demonstrated in the sheep (Liggins et al. 1976, Liggins et al. 1977). However Larson et al. 1973 failed to demonstrate any increase in PGF. Administration of estrogen to rhesus monkeys in the latter part of gestation did not induce parturition or any increase in PGF (Challis et al. 1974b). No correlation of estradiol and PGFM was demonstrated in maternal or cord blood in this study.

Extremely low rates of estrogen production associated

with placental sulfatase deficiency is associated with prolonged pregnancy and failure to respond to induction of labor in primips although multips may begin labor spontaneously at or before term (France et al. 1973). The problem in the primips appears to be associated with the state of the cervix which is hard, small, and closed resembling a non-pregnant cervix. Changes in the cervix are some of the earliest events in parturition. These patients suggest that estrogen plays at least a permissive role in these changes. Nevertheless spontaneous labor and delivery occurs in the face of markedly reduced plasma estrogens in women who begin labor after corticosteroid treatment (Gamissans et al. 1975, Nwosu et al. 1976).

The present study also showed that maternal estradiol is significantly higher than cord estradiol in all groups and there was a high correlation between the two values in all groups. This probably reflects the placenta as the predominant common site of estrogen synthesis from precursors provided by the maternal and fetal adrenal.

Duration of labor was shown to be significantly negatively correlated with cord estradiol levels. In a previous study ACTH and cortisol were correlated with duration of labor (Burns 1976) but no data exists to support a relationship with estradiol. This may be a spurious nominal significance secondary to the calculation of all correlation coefficients without physiologic relevance.

Progesterone

The data shows no significant differences in maternal or cord progesterone levels between any of the clinical groups and thus no correlation was demonstrated with spontaneous labor. This suggests that there is no acute change in progesterone levels comparable to that seen in sheep.

These findings are consistent with the overwhelming majority of studies which have failed to demonstrate any significant fall in peripheral plasma progesterone levels before the onset of human labor (Eton and Short 1960, Greig et al. 1962, Kumar et al. 1964, Llauro et al. 1968, Yannone et al. 1968, Craft et al. 1969, Johansson and Jonasson 1971, Tulchinsky et al. 1972, Shaaban and Klopper 1973).

However Csapo et al. 1971 and Turnbull et al. 1974 found a significant decrease in plasma progesterone during the last few weeks of pregnancy. Turnbull's study described a sharp decrease approximately five weeks before delivery which continued until one week before delivery then remained constant when measured at the second stage of labor, a curve quite different from that of the sheep.

No significant decrease in peripheral progesterone levels over any time course has been demonstrated in non-human primates including the marmoset (Hearst and Lunn 1975), rhesus macaque (Hodgen et al. 1972, Bosu et al. 1973, Weil et al. 1969, Challis et al. 1974a) and the chimp (Reyes et al. 1975).

There is some question whether stable peripheral levels reflect the uterine circulation since a study in the macaque demonstrated a uterine circulation fall of progesterone with stable peripheral progesterone levels (Thau et al. 1976, Lanman 1977). Any documentation of peripheral progesterone, or indeed any peripheral hormone alone, must consider the possibility that the hormone acts through local changes in target organ concentration not reflected in peripheral plasma levels or changes in target organ sensitivity.

However the significance of any demonstrated change in progesterone is difficult to ascribe to the "withdrawal of inhibitory influence" model of initiation in the absence of evidence for a direct inhibitory influence of progesterone on human myometrium in vivo. Attempts to inhibit uterine activity with huge doses of progesterone and medroxy-progesterone via intramuscular, intravenous, intramyometrial, and intramniotic routes have met with consistent failure (Hendricks et al. 1961, Wood et al. 1963).

Additional findings of this study are that cord progesterone is significantly higher than maternal progesterone in all groups and there is no correlation between maternal and cord levels. Therefore both circulations must be sampled independently and data concerning changes in peripheral maternal changes is not necessarily applicable to the fetal environment where some regulatory role for progesterone may be found (see review by Liggins et al. 1977).

13,14-Dihydro-15-Keto $PGF_{2\alpha}$ PGFM

The data provides further evidence for involvement of $PGF_{2\alpha}$ in the labor process and suggests its primary role in control of human labor.

The spontaneous labor group with vaginal delivery had the highest concentrations of PGFM in both maternal and cord circulation. The maternal PGFM concentrations in patients with spontaneous labor interrupted by cesarean section were significantly higher than those patients without labor delivered by cesarean section. This group without labor was the only one with low PGFM. Maternal and cord values were highly correlated reflecting the internal consistency of the assay and suggesting a common source.

Crucial to interpretation, however, is the finding that successful oxytocin induction of labor in women without spontaneous onset of labor produced higher concentrations of PGFM than those observed in spontaneous labor interrupted by cesarean section. Indeed although induced patients delivered vaginally had maternal and cord PGFM lower than spontaneous vaginal delivery this difference was not significant.

Green et al. 1974 also found that patients with oxytocin induction as well as those with spontaneous labor show increased levels of PGFM during labor. That study demonstrated a progressive rise in PGFM in all clinical groups although the increase was more regular in spontaneous labor than in induced labor with correlation to increasing cervical

dilatation. Interruption of this progressive rise by cesarean section would be likely to produce lower maternal values as observed in this study.

Although the high level of PGFM observed in induced labor and the low level observed in spontaneous labor slowed after epidural anesthesia (Group 5) may appear to suggest $PGF_{2\alpha}$ is only a byproduct of myometrial contractions, Green et al. 1974 demonstrated no specific increase in PGFM with each myometrial contraction and showed that previous data suggesting such an increase was unreliable.

Another interpretation of the data is that oxytocin induction which can clinically mimic spontaneous labor at term does so by facilitating comparable $PGF_{2\alpha}$ increases. Oxytocin does not play a significant role in the initiation of labor in normal subjects (Cobo 1968, Chard 1973) and is well known to be ineffective before term. However prolonged intravenous infusion of subthreshold amounts of $PGF_{2\alpha}$ have demonstrated a progressive enhancement of oxytocin response (Hutton and Liggins unpublished data cited in Liggins et al. 1977). This suggests such subthreshold amounts of $PGF_{2\alpha}$ at term permit successful induction perhaps via some positive feedback loop which produces $PGF_{2\alpha}$ increases almost but not completely comparable (Green et al. 1974) to those in spontaneous labor and with similar results.

There is other evidence which strongly suggests that $PGF_{2\alpha}$ in humans plays a dominant role in the initiation of labor rather than being a mere byproduct or mechanism to

support and enhance labor alone.

Administration of $PGF_{2\alpha}$ can closely simulate spontaneous labor well before term.

Green et al. 1974 showed a modest increase in PGFM close to term which preceded the sharp increase during active labor. The concentration of $PGF_{2\alpha}$ in amniotic fluid shows a similar pattern of increase (Salmon and Amy 1973, Keirse et al. 1974). Evidence that supports prepartum release of $PGF_{2\alpha}$ was also reported by Hillier et al. 1974 who found significantly higher concentrations of $PGF_{2\alpha}$ in amniotic fluid obtained early in spontaneous labor than early in induced labor although uterine activity in the latter was greater.

$PGF_{2\alpha}$ inhibitors such as aspirin and indomethacin can delay the onset of labor at term (Lewis and Schulman 1973, Gyory et al. 1974, Zuckerman 1974). Aspirin significantly extends the injection abortion interval in patients treated with intramniotic urea (Niebyl et al. 1976) and indomethacin has a comparable effect in saline induced abortion (Waltman et al. 1973).

Indeed midtrimester abortion, although not an experimental model for spontaneous labor at term, demonstrates the importance of local intrauterine mechanisms that can initiate and accomplish parturition in 24 hours without significant fetal, placental, or maternal participation at a time when the pregnancy is most stable (Liggins et al. 1977). Mechanical, physical (urea, NaCl, glucose) and chemical

(dilute formaldehyde) methods as well as infection (amnionitis) can all induce midtrimester abortion (see review by Gustavii 1973).

Gustavii 1973 proposed that the various methods have in common a mechanism for release of prostaglandins as the data from prostaglandin inhibitors suggests. Detailed biochemical data is accumulating to demonstrate that the decidua and fetal membranes are uniquely suited for prostaglandin production and may be the major site of $PGF_{2\alpha}$ in parturition (Liggins et al. 1977). Marked degenerative changes in the decidua have been demonstrated after saline treatment (Gustavii 1973, Vassilakos et al. 1974). Degenerative changes in the placenta as well were shown by Wynn 1965 and Jakobovits 1970. Expulsion of the dead fetus may well involve comparable degenerative changes.

These data suggest how a minor local mechanical stimuli such as shipping the membranes may be so effective in promoting labor yet so unlikely to disturb placental, fetal, or maternal function (Liggins et al. 1977).

Prostaglandins in subthreshold amounts and also by direct application have been shown to effect cervical changes with some reports of marked ripening in sheep and humans (Calder and Embry 1973, Weiss et al. 1975, Liggins et al. 1976). These changes are some of the earliest in labor and preceed regular myometrial activity.

All this evidence weighs heavily in favor of a primary role for $PGF_{2\alpha}$ in human parturition as suggested by this

study.

Conclusion

The data in this study supports the mounting evidence of other investigators that 1) the human fetal pituitary-adrenal axis does not play a dominant role in parturition, 2) human labor takes place in the absence of any abrupt changes in the placental production of progesterone or estrogen, and 3) $PGF_{2\alpha}$ is involved in the labor process and probably plays a dominant role in the initiation of labor in humans without endocrine regulatory mechanisms grossly comparable to sheep.

The presence of such extensive differences between the sheep model and the human mechanisms for control of parturition demands that an alternative hypothesis be formulated in the human subject such as the "genetic membrane model" of Liggins et al. 1977 or the "lysosome theory" of Gustavii (Gustavii 1972, Brunk and Gustavii 1973, Gustavii 1975, Schwartz et al. 1974). Likewise these differences, in the absence of a suitable animal model, dictate that final determinations must come from human data.

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