PAPERS AND ORIGINALS

Endocrine Changes in Premature Labour

R. L. TAMBY RAJA, ANNE B. M. ANDERSON, A. C. TURNBULL

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Summary

Plasma oestradiol and progesterone levels in peripheral blood have been studied before and during premature labour of unknown aetiology. Hormones were measured by radioimmunoassay using specific antisera. Levels in patients who delivered prematurely were compared with levels measured serially in 33 primigravidae during normal pregnancy and labour.

In 19 out of 25 patients admitted in progressive premature labour the plasma oestradiol level was two standard deviations or more above the mean for the control patients of similar gestational age. The mean ($\pm$ S.E. of mean) plasma oestradiol in premature labour was 19.1 ± 1.1 ng/ml, similar to levels found in labour at term (18.5 ± 1.4 ng/ml). In contrast, in over 50% of cases levels of plasma progesterone during premature labour lay below the mean for gestation though within the normal range. In six patients studied serially oestradiol levels rose dramatically, high values being detected one to 10 days before the onset of premature labour. Serial progesterone levels gave no consistent trend though one patient showed steadily decreasing values.

These studies suggest that the onset of premature labour is preceded by a marked increase in peripheral plasma oestradiol levels, which may be of value not only in the prediction of premature labour but also in its prevention by suppression of the premature oestradiol surge.

Introduction

A major part of perinatal mortality and morbidity occurs in a small minority of infants—namely, those of low birth weight. Less than 7% of all infants weigh less than 2,500 g at birth, and most of the larger “premature” babies make good pro-

gress. The real problem is with the smallest infants. In England and Wales in 1971 only 1% of all babies weighed 1,500 g or less at birth, but in 1971 and 1972 just over 70% of babies of this weight were either stillborn or died within 28 days of delivery (Alberman, 1974). Though there has rightly been great concern about intrauterine fetal growth retardation in recent years it is important to note that in many very small infants the low birth weight was likely to have been the result of a very short gestation.

Premature labour is in many cases associated with causal factors, such as multiple pregnancy, congenital fetal abnormality, maternal infection, or ante-partum haemorrhage, or it may be due to deliberate and appropriate intervention by the obstetrician because pregnancy is complicated by severe pre-eclampsia, retarded intrauterine fetal growth, or diabetes.

Nevertheless, premature birth can and does occur in the absence of any of these causes. In the John Radcliffe Hospital, which had about 5,500 births in 1973, 3% of all admissions to the delivery suite were because of premature labour of unknown aetiology. If the high perinatal mortality and morbidity now occurring in infants of low birth weight is to be reduced one of the most vital needs is to find a means of predicting and preventing premature labour of spontaneous unexplained onset.

The prediction of premature labour was said by Wood *et al.* (1965) to be possible if serial assessments were made of the dilatation and effacement of the cervix combined with external monitoring of uterine activity. Premature labour was said to follow invariably if both premature cervical dilatation and increased uterine contractility occurred before the 34th week of pregnancy. Subsequently, however, Anderson and Turnbull (1969) showed that though the internal cervical os admitted a finger by the 32nd week of pregnancy in 30% of normal primigravidae and that all premature labours occurred in this group they were unable to predict from serial records of uterine contractility which patients would actually deliver prematurely.

No attempts to predict premature labour seem to have been implemented in clinical practice, and in recent years the main emphasis has been on attempting to stop uterine contractions after premature labour is established. This treatment still poses many problems and though beta-adrenergic drugs can be very effective if labour is not too advanced and the mem-

Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford OX3 9DU

R. L. TAMBY RAJA, F.R.C.S., M.R.C.O.G., Research Fellow
ANNE B. M. ANDERSON, M.D., PH.D., Lecturer
A. C. TURNBULL, M.D., F.R.C.O.G., Professor

branes are still intact their usefulness is limited by their troublesome side effects such as tachycardia and hypotension.

If better methods could be developed for predicting premature labour prevention might become a practical possibility. Such an achievement depends on a better understanding of the physiological mechanisms underlying the onset of premature labour as well as labour at term.

That endocrine factors are of importance in the onset of labour seems likely from data that have accumulated on several species, notably sheep, during the past few years and which have recently been reviewed by Liggins *et al.* (1973). In sheep several important endocrine events precede parturition at term. As a result of a rapid increase in the secretion of cortisol by the fetus during the last week of gestation the concentration of progesterone in maternal blood falls, which is followed by an increase in the level of both plasma oestrogens and prostaglandin $F_{2\alpha}$. In association with these events uterine contractions start and lead to delivery of the lamb. We have recently shown that this mechanism may to some extent apply in human pregnancy by showing a fall in plasma progesterone and a rise in plasma oestradiol levels in the mother in the four or five weeks preceding human labour at term (Turnbull *et al.*, 1974).

We examined the possibility that spontaneous "unexplained" premature labour in human pregnancy might be preceded by changes in circulating levels of the two steroid hormones progesterone and oestradiol-17 β in the hope that changes might be found as dramatic as those which occur before labour at term. Support for the concept that endocrine changes may be of importance in the onset of premature labour is provided by Csapo *et al.* (1974), who showed in a group of women admitted to hospital in premature labour of unknown aetiology that plasma oestradiol levels were slightly higher than in normal controls while progesterone levels were significantly lower.

Patients

We defined premature labour as labour occurring spontaneously without obvious cause more than three weeks before term. Thus we excluded cases in which premature labour was associated with multiple pregnancy, ante-partum

haemorrhage, hydramnios, uterine abnormality, congenital fetal abnormality, pre-eclampsia, diabetes, hypertension, retarded intrauterine fetal growth, or overt maternal infection. Labour was considered to be established when regular uterine contractions, usually monitored with an external tocograph, occurred in every three to five minutes accompanied by progressive dilatation of the cervix. All patients delivered a single live infant weighing less than 3,000 g, and in all infants maturity, as assessed by the paediatrician at delivery, was in keeping with a gestational age of 37 weeks or less.

Two groups of patients were studied. Group 1 consisted of 25 patients admitted in spontaneous premature labour and delivered within 48 hours of admission. These patients were studied only during labour. Group 2 comprised six patients who were studied serially for intervals varying from two to 17 weeks before premature labour. Two of these patients (cases 28 and 31) were attending a research antenatal clinic studying normal pregnancy and unexpectedly went into premature labour. The other four patients were studied serially for a variety of reasons, including spontaneous rupture of the membranes at 31 weeks' gestation and admission on account of uterine irritability.

Methods

Heparinized blood samples were taken from the antecubital vein. Patients in group 1 had blood samples taken once during advanced labour. In group 2 blood samples were taken at intervals as shown in table II. The plasma was separated from the cells by centrifugation and stored at -15°C until assay. All plasma samples were assayed in duplicate for progesterone and unconjugated oestradiol-17 β concentration as described previously (Turnbull *et al.*, 1974).

Each steroid was measured by radioimmunoassay using specific antibodies, the antibody for progesterone being raised against progesterone 11-bovine serum albumin and that for oestradiol against oestradiol-17 β 6-bovine serum albumin.

The percentiles for birthweight of infants delivered at 32 weeks' gestation or more were calculated from data in the second report of the British Perinatal Mortality Survey (Butler and Alberman, 1969) and for infants born before 32

TABLE I—Details of Patients in Progressive Premature Labour

Case No.	Parity		Gestation	Untrimmed Placental Weight (g)	Percentile for Placental Weight	Weight of Fetus (g)	Percentile for Fetal Weight	Plasma Oestradiol (ng/ml)	Plasma Progesterone (ng/ml)	Progesterone: Oestradiol Ratio	Comments
	Births	Abortions									
1	0	0	23	—	—	—	—	16.0	92	5.8:1	Shirodkar Suture N.N.D.
2	1	0	26	215	—	620	—	15.0	55	3.7:1	N.N.D.
3	0	0	27	316	—	1,100	50	13.8	72	5.2:1	N.N.D.
4	1	1	27	500	—	700	10-25	11.6	61	5.3:1	N.N.D.
5	0	0	28	365	—	1,270	50-90	19.0	72	3.8:1	N.N.D.
6	0	0	29	444	—	1,640	75-90	27.5	164	6.0:1	
7	1	0	30	325	—	1,610	50-75	14.3	90	6.3:1	N.N.D.
8	1	3	31	525	—	1,930	50-75	17.8	132	7.4:1	3 previous abortions
9	0	0	32	410	25	1,560	25-50	24.7	138	5.6:1	
10	0	1	33	480	25-50	1,830	25-50	20.0	86	4.3:1	Ruptured membranes at 32 weeks
11	0	0	35	410	10-25	2,500	50-75	20.0	65	3.3:1	
12	0	0	35	420	10-25	2,480	50-75	20.0	125	6.3:1	
13	1	0	35	575	50-75	2,280	25-50	20.8	69	3.3:1	
14	1	1	35	250	<10	2,530	50-75	15.6	105	6.7:1	Previous premature labour at 30 weeks
15	0	0	35	520	25-50	2,870	50-75	19.2	150	7.8:1	
16	0	1	35	530	50-75	2,550	50-75	23.2	100	4.3:1	Previous vaginal termination
17	0	0	36	600	50-75	2,150	10-25	20.8	99	4.8:1	N.N.D. Congenital heart disorder Single umbilical artery
18	0	0	36	500	25-50	2,600	50-75	>30	195	6.5:1	
19	1	0	36	575	50	2,775	50-75	16.9	142	8.4:1	
20	3	0	36	540	25-50	2,785	50-75	9.2	120	13.0:1	
21	0	0	36	626	50-75	2,850	50-75	19.0	132	6.9:1	
22	0	0	36	620	50-75	2,960	50-75	13.7	175	12.8:1	
23	1	0	37	520	25	2,700	25-50	>30	108	3.6:1	
24	2	0	37	600	50	2,900	25-50	15.5	176	11.4:1	
25	2	0	37	600	50	2,780	25-50	23.0	120	5.2:1	

weeks from figures reported from the United States by Babson *et al.* (1970) for white mothers living near sea level who received good obstetric care. Placentas were weighed untrimmed—that is, including the attached cord, membranes, and blood. Percentiles for placental weights at 32 weeks or more were obtained from the data of Thomson *et al.* (1969, and personal communication).

Results

GROUP 1

Levels of oestradiol and progesterone measured in the ante-cubital venous plasma during labour are given in table I. With one exception (case 14) the weights of the fetus and placenta lay between the 10th and 90th percentiles. The placental weight in case 14 was unusually small (250 g) for the weight of the fetus (2,530 g). Six of the 25 babies died, four of the deaths being in infants delivered before the 28th week.

TABLE II—Hormone Levels in Serial Study

Case No. and Clinical Details	Gestation (Weeks)	Plasma Oestradiol (ng/ml)	Plasma Progesterone (ng/ml)
Case 26			
Para 0			
Previous vaginal termination	33	9.2	110
Admitted 33 weeks	34	23.2	100
Delivered 35 weeks	35	16.5	90
Fetus 2,550 g			
Placenta 530 g			
Case 27			
Primigravida	28	12.0	75
Irritable uterus	32	6.2	70
Delivered 36 weeks	34	9.5	80
Fetus 2,870 g	35	9.0	175
Placenta 520 g	36	19.2	150
Case 28			
Para 0			
2 Previous abortions	31 1st day	6.0	135
Delivered 34 weeks	31 5th day	5.7	69
Fetus 2,420 g	32 5th day	19.0	69
Placenta 513 g	33 1st day	18.4	74
	34	19.0	79
Case 29			
Primigravida	31	14	91
Admitted 31 weeks	31 3rd day	11.8	71
Ruptured membranes	32	12.6	69
Delivered 35 weeks	34	25.6	53
Fetus 2,500 g	35	20.0	65
Placenta 410 g	35 1st day	18.0	57
Case 30			
Primigravida			
Admitted 21 weeks	21	12.4	52
contractions	22	16.2	42
Shirodkar suture 22 weeks	23	16.0	92
Abortion 23 weeks			
Case 31			
Primigravida	20	4.4	92
Delivered 37 weeks	25	5.3	78
Fetus 2,870 g	28	7.5	60
Placenta 600 g	32	9.5	166
	34	11.5	116
	36	11.6	172
	37	21.5	144
	37 2nd day	23.0	120

The oestradiol and progesterone levels in these patients are shown in figs. 1 and 2 respectively in relation to the previously published mean (± 2 S.D.) for each steroid measured serially in 33 obstetrically normal young primigravidae from the 20th week of pregnancy up to the spontaneous onset of labour at term (Turnbull *et al.*, 1974).

The striking feature of the results is the high level of plasma oestradiol found in these patients during premature labour. In 19 of the 25 patients the oestradiol level was two standard deviations or more above the mean for gestation in primigravidae with a continuing pregnancy who delivered at term (fig. 1). Only 14 of the 25 patients studied in premature labour were primigravidae, however, and it may be significant that in 13 of these 14 women the oestradiol levels were more

FIG. 1—Oestradiol levels in peripheral plasma of 25 patients admitted in progressive premature labour. Results are shown in relation to mean ± 2 S.D. for oestradiol levels measured serially in obstetrically normal primigravidae with continuing pregnancy (Turnbull *et al.*, 1974).

FIG. 2—Progesterone levels in peripheral plasma of 25 patients admitted in progressive premature labour. Results are shown in relation to mean ± 2 S.D. for progesterone levels measured serially in obstetrically normal primigravidae with continuing pregnancy (Turnbull *et al.*, 1974).

than two standard deviations above the mean of the primigravidae controls whereas almost half of the multiparous patients studied (5 out of 11) had a plasma oestradiol concentration within normal limits for women having their first baby. Possibly the mean plasma oestradiol level in multiparous women is less than in primigravidae or the correlation between high oestradiol levels and premature labour is stronger for primigravidae than for women who have had a previous pregnancy.

Progesterone levels in premature labour fell within the normal range for the controls at the same gestational age (fig. 2), 24 of the 25 patients having plasma progesterone levels within two standard deviations of the mean, though in 11 out of 15 patients delivered between 35 and 37 weeks' gestation the progesterone values were below the mean for control patients. There was no correlation between plasma progesterone levels and the parity of the patient.

The mean levels of both plasma oestradiol and progesterone in the patients in premature labour between 23 and 37 weeks are given in table III, and the similarity to mean levels in labour at term is apparent. The average plasma progesterone: oestradiol ratios were also similar whether labour occurred prematurely or at term (6:1). Of the 25 patients studied in premature labour only three cases, all at 36 or 37 weeks' gestation, had a progesterone: oestradiol ratio greater than 8:1.

TABLE III—Mean Plasma Levels ($\pm$ S.E.M.) of Oestradiol and Progesterone in Labour

	No. of Patients	Oestradiol (ng/ml)	Progesterone (ng/ml)
Premature labour	25	19.1 $\pm$ 1.1	113.0 $\pm$ 2
Term labour	23	18.5 $\pm$ 1.4	112.0 $\pm$ 6

GROUP 2

The data given in table II and in figs. 3 and 4 show that in each of the six patients studied the onset of premature labour occurred at a time when the level of oestradiol in the peripheral circulation was 16 ng/ml or higher. In the five patients who delivered between 35 and 37 weeks of pregnancy the onset of labour was preceded in each case by a marked increase in oestradiol levels, detected in the three patients in hospital 10 days before labour. In the two patients not in

FIG. 3—Serial changes during gestation in peripheral plasma levels of oestradiol measured in six patients before premature labour and delivery.

FIG. 4—Serial changes in peripheral plasma levels of oestradiol in six patients.

hospital the rapid rise in plasma oestradiol was detected only one day before the onset of premature labour. Though the duration of high plasma oestradiol levels varied in these five patients the magnitude of the rise was similar in each case, being a twofold increase on average from the previous values. One patient (case 30) aborted at 23 weeks, having been admitted two weeks earlier with a plasma oestradiol level of 12.4 ng/ml, already more than two standard deviations above the mean for that gestation. On admission the uterus was contracting regularly and the cervix was dilated 4 cm. A Shirodkar suture was inserted and intravenous infusion of a beta-adrenergic drug begun, but uterine contractions continued, the plasma oestradiol level remained high at 16 ng/ml, the suture had to be removed, and abortion followed soon after.

Plasma progesterone levels in these patients showed no consistent trend, only one (case 29) showing steadily decreasing levels from 91 ng/ml on admission at 31 weeks to 57 ng/ml at delivery four weeks later. The weight of the placenta in this case lay between the 5th and 10th percentile for gestation, though the weight of the baby was on the 50th percentile. In cases 26, 27, 28, and 31 the fetal and placental weights were greater than the 25th percentile. The aborted products of conception in case 30 were not weighed.

Discussion

The results show raised levels of oestradiol-17 β in the maternal circulation during premature labour of unknown aetiology. In almost 80% of the cases studied in labour at 23 to 37 weeks' gestation plasma oestradiol levels were greater than two standard deviations above the mean for that length of gestation in a group of primigravidae with a normal continuing pregnancy and were similar to levels in labour at term. That this is likely to be a cause rather than a consequence of labour is suggested by the findings in our serial study where these high oestradiol levels are shown to precede the onset of premature labour by up to 10 days. This surge in maternal plasma oestradiol concentration before premature delivery has not, to our knowledge, been shown previously and offers potential both for the prediction and the prevention of premature delivery of unknown aetiology.

A previous study (Turnbull *et al.*, 1974) showed that a significant rise in plasma oestradiol levels occurred over the five weeks preceding term labour. We found that the surge of plasma oestradiol seems to occur more rapidly in premature labour than at term, being detected only one day before delivery in one patient and, at the most, 10 days before labour. It may be therefore that if at any stage of pregnancy plasma oestradiol levels suddenly rise to term values premature labour will ensue. It is of interest that the two patients in our series who gave least warning of impending premature labour, in that high oestradiol levels were detected only one to two days beforehand, were attending an antenatal clinic for patients with a "normal" pregnancy and unexpectedly delivered three to four weeks before term. The other four patients followed serially were in hospital at the time of their peak plasma oestradiol and in them the pregnancy continued for up to two weeks in the presence of those high values of oestradiol.

In the three patients in hospital who delivered at 35-36 weeks of gestation plasma levels of oestradiol on admission earlier in gestation were within normal limits for that stage of pregnancy though the patients were admitted with "show," "uterine irritability," and spontaneous rupture of the membranes, but not in true labour. In hospitalized patients, therefore, forewarning of premature labour may be given in adequate time for preventive measures to be instituted if serial measurements of plasma oestradiol are made.

Plasma progesterone levels in the patients studied were

within normal limits, whether the patients were studied serially during pregnancy or were actually in premature labour though in more than half the patients levels in labour lay below the mean for our control group. Csapo *et al.* (1974) recently showed that in patients admitted to hospital for threatened premature labour of unknown aetiology progesterone levels were significantly lower than in normal controls. In the premature labour group, however, the average placental weight was less than that of the normal controls and three of the babies in the series had a birth weight below the 10th percentile. In our series, however, only one of the 25 patients studied in labour had a placental weight below the 10th percentile, and the weight of the baby in all cases lay above the 10th percentile. In the one patient in our serial study where the placenta was small (< 10th percentile) levels of plasma progesterone decreased steadily after admission to reach a level almost two standard deviations below the mean at delivery, showing the trend reported by Csapo *et al.* (1974). In most patients, therefore, there was no evidence of poor placental or fetal growth. The low progesterone:oestradiol ratio in premature labour in our series, similar to the ratio in term labour, was brought about more by raised oestradiol levels than by reduced progesterone values, unlike that in the patients studied by Csapo *et al.* (1974) where progesterone deficiency was the main finding though oestradiol levels were slightly higher than in normal controls. Inclusion of data from patients with retarded intrauterine growth of the fetus or a small placenta by Csapo *et al.* may explain the difference between their results and ours. The absolute levels of plasma progesterone and oestradiol measured by Csapo *et al.* (1974), however, were similar to those measured in our patients and the differing interpretation of the data depends on differences in the control values. In particular, the mean oestradiol levels in the control patients of Csapo *et al.* were very much higher than in our controls.

Support for our finding of a surge in the concentration of plasma oestradiol preceding premature labour is provided by Cohen and Cohen (1974) who measured plasma unconjugated oestradiol in pregnancy. One of their patients, who apparently delivered at 36 weeks' gestation, showed high and sustained levels of oestradiol for several weeks beforehand.

The mechanism of the rapid increase in plasma oestradiol levels before premature labour of unknown cause and the means by which high plasma levels of this potent oestrogen might cause premature uterine activity can be only speculative at present.

Anderson *et al.* (1971) have already provided evidence that the fetal adrenal may play a role in the initiation of premature labour. These authors showed that in babies delivered as a result of unexplained premature labour and who died soon after the weights of the adrenal glands were on average about 1 g more than in infants who died after premature delivery resulting from ante-partum haemorrhage. Though an increase in fetal adrenal weight does not necessarily relate to increased function Lauritzen and Lehmann (1967) found a very much higher excretion of dehydroepiandrosterone during the first few days of life in infants delivered five to eight weeks before term than in full-term neonates. Since dehydro-

epiandrosterone sulphate from the fetal adrenal is likely to be a major precursor for oestradiol synthesis in the placenta (Diczfalusy, 1969) Lauritzen's and Lehmann's results suggest that adrenal steroid production in utero in these premature infants may have been much greater than in infants delivered normally at term. On the other hand, the maternal adrenal may supply the placenta with as much dehydroepiandrosterone sulphate for oestradiol synthesis as does the fetal adrenal (Sitteri and MacDonald, 1966) so that a maternal role in the onset of premature labour cannot be excluded.

The high levels of plasma oestradiol may have a direct effect in stimulating uterine contractility for, at term, maternally administered oestradiol may "hasten" the onset of labour (Pinto *et al.*, 1967) and increase uterine activity (Larsen *et al.*, 1974) or, alternatively, oestradiol may stimulate the synthesis of prostaglandin $F_{2\alpha}$, as in sheep (Liggins *et al.*, 1974). One practical corollary is that it may be possible to prevent premature labour in cases where the oestradiol surge is detected by suppressing maternal and fetal adrenal production of precursors by the administration to the mother of glucocorticoids, thereby reducing maternal plasma oestradiol levels (Tamby Raia *et al.*, 1974).

Our findings provide a new approach to the prediction of premature labour and offer the possibility of preventing this major cause of perinatal morbidity and mortality. Further work is in progress to elucidate the endocrine changes associated with premature labour and to establish therapeutic regimes aimed at preventing its onset.

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