

Increased saliva oestriol to progesterone ratio before idiopathic preterm delivery: a possible predictor for preterm labour?

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Abstract

Saliva oestriol, oestradiol, and progesterone concentrations were measured in 23 women who went into spontaneous preterm labour. The patients fell clinically and biochemically into two groups. The 13 who went into preterm labour with intact membranes had a saliva oestriol to progesterone ratio greater than one in every case and greater than the 95th centile for their length of gestation in 12 cases; by contrast, all those who went into spontaneous preterm labour after prolonged rupture of the membranes had an oestriol to progesterone ratio less than one and below the 50th centile for their period of gestation in the one to four days before delivery. Saliva oestradiol to progesterone ratios were randomly distributed throughout the normal range in both groups.

It appears that preterm labour without prior prolonged rupture of the membranes is, like term labour, preceded by an increase in the saliva oestriol to progesterone ratio. It may therefore be possible to use this ratio to predict preterm labour.

Introduction

Preterm delivery is a main cause of neonatal morbidity and mortality in Britain. The mechanisms underlying the onset of idiopathic preterm labour are poorly understood, and if the incidence of preterm labour is to be reduced we must increase our understanding of the events that lead up to it.

Clinical details of patients going into spontaneous labour. Figures are median values (ranges in parentheses)

	No of patients	Age (years)	Gestation at delivery (weeks)	Birth weight (g)
Preterm labour with intact membranes	13	29 (22-37)	29 (23-34)	1525 (555-1915)
Preterm labour with prolonged rupture of membranes	10	27 (23-37)	32.5 (27-35)	1832 (994-2420)
Term labour	20	31.5 (28-38)	40 (38-41)	3190 (2960-3760)

Most endocrine studies have been directed towards investigating changes in plasma oestradiol and progesterone concentrations before preterm labour.¹⁻³ Measurements of these hormones have not been found to be useful in predicting preterm labour.^{4,5}

We have recently reported finding a consistent rise in the saliva oestriol to progesterone ratio some days before the spontaneous onset of labour at term.^{6,7} Saliva oestrogen and progesterone concentrations reflect the unbound, unconjugated (free, biologically active) plasma steroid concentrations, and saliva estimations have the added advantage that samples can be collected frequently with minimal inconvenience to patients. We have therefore measured

saliva oestriol, oestradiol, and progesterone concentrations in 23 women who went into spontaneous preterm labour.

Patients and methods

Patients at risk for preterm labour were recruited either on the basis of their past obstetric history or after admission to hospital with threatened preterm labour. They fell into two clinical groups. One group (13 patients) had intact membranes and increased uterine activity and the other group (10 patients) had prolonged preterm rupture of the membranes. All went into labour spontaneously and delivered before 37 weeks of gestation. The patients were compared with 20 normal women who went into spontaneous labour at term (see table).

Three of the 13 women in the first group had had intermittent vaginal bleeding during the four weeks before the onset of labour. Seven women in this group received treatment with β sympathomimetics for varying periods. The 10 women with spontaneous preterm rupture of the membranes were treated conservatively, and all eventually went into labour spontaneously before 37 weeks (mean duration of ruptured membranes 25 days, range three to 70). None of the patients were given corticosteroids or antibiotics.

Saliva specimens were collected once a day at about the same time and stored at -40°C until assayed. All samples from a particular patient were assayed in duplicate in the same assay for oestriol, progesterone, and oestradiol by radioimmunoassay, as described.⁷ Briefly, for measurements of oestriol and progesterone duplicate 250 μl saliva samples were mixed with 125 μl of 1.5M sodium carbonate buffer pH 10.5 and extracted with 3 ml freshly distilled diethyl ether. The ether was evaporated and the residue dissolved in 500 μl phosphate buffered saline. Separate 200 μl aliquots were taken and the oestriol and progesterone content measured by radioimmuno-

assay using tritium labelled oestriol and progesterone. For oestradiol measurement duplicate 500 μl saliva samples were mixed with 250 μl sodium carbonate buffer and extracted with 5 ml diethyl ether; after evaporation of the ether the residue was chromatographed on Sephadex LH20 columns using a benzene and methanol (85:15) mixture. The eluate fraction containing oestradiol was collected and evaporated and the oestradiol content measured by radioimmunoassay using tritium labelled oestradiol.

Results

We had previously measured saliva oestriol, progesterone, and oestradiol concentrations twice a week from 18 weeks of gestation and daily for the last 38 days before delivery in 20 normal women with uncomplicated pregnancies who went into spontaneous labour at term and were delivered of a healthy baby of normal birth weight.⁷ The oestriol to progesterone and oestradiol to progesterone ratios were calculated for all the specimens in 20 and 15 of these subjects, respectively, and the medians and 5th, 90th, and 95th centiles computed. The results from that study were used as the normal range of values for comparison with the women going into preterm labour in the current study. As the number of specimens collected from the patients

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going into preterm labour varied from one patient to another (range two to 68) we plotted the mean ratios in the daily samples obtained in the last one to four days before delivery (see figs 1 and 2).

As far as the oestriol to progesterone ratio was concerned the patients fell both clinically and biochemically into two groups (fig 1). In all 13 women

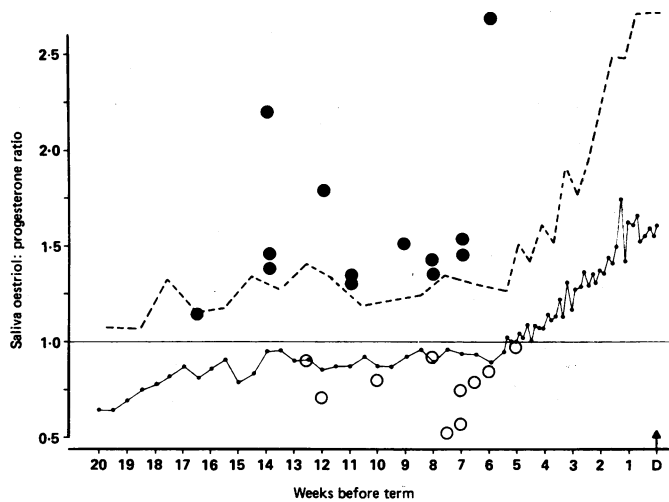


FIG 1—Median (solid line) saliva oestriol to progesterone ratios in 20 normal women till day of term delivery (D). Dotted line represents 95th centile.⁷ Solid circles represent mean oestriol to progesterone ratio in last one to four days before delivery in 13 women going into idiopathic preterm labour with intact membranes. Open circles represent mean ratio in last one to four days before delivery in 10 women going into spontaneous labour after prolonged preterm rupture of membranes. Circles placed at number of weeks before 40 weeks' gestation that delivery occurred.

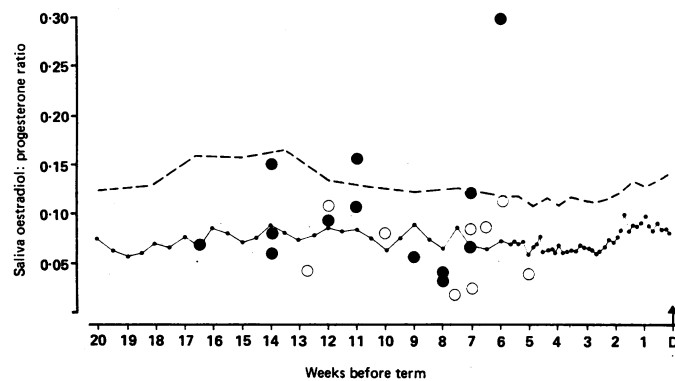


FIG 2—Median (solid line) saliva oestradiol to progesterone ratios in 15 normal women till day of term delivery (D). Dotted line represents 95th centile.⁷ Solid circles represent mean oestradiol to progesterone ratio in last one to four days before delivery in 13 women going into idiopathic preterm labour with intact membranes. Open circles represent mean ratio in last one to four days before delivery in nine women going into spontaneous labour after prolonged preterm rupture of membranes. (There was insufficient saliva to measure oestradiol concentrations in 10th patient.) Circles placed at number of weeks before 40 weeks' gestation that delivery occurred.

who went into preterm labour with intact membranes the oestriol to progesterone ratio was abnormally high for the period of gestation—that is, greater than the 95th centile in 12 patients and greater than the 90th centile in all cases. By contrast, the oestriol to progesterone ratios in the 10 women with prolonged preterm rupture of the membranes were consistently in the lower part of the normal range for the length of gestation, and these ratios did not change before the spontaneous onset of labour and remained at less than one in every case.

The increase in the oestriol to progesterone ratio in the group with intact membranes was due to a raised oestriol concentration rather than a low progesterone value. All the oestriol concentrations in this group were above the 50th centile for gestation, and in five cases the concentration was above the 95th centile; most of the progesterone concentrations in this group were

also above the 50th centile for gestation but were raised less than the oestriol concentrations in every case.

In the 10 patients with prolonged rupture of the membranes the oestriol and progesterone concentrations were between the 5th and 95th centiles for gestation in all cases and the oestriol to progesterone ratio was less than one in every case.

Oestradiol concentrations and oestradiol to progesterone ratios were randomly distributed throughout the normal range in both groups (fig 2).

Discussion

We have previously shown that the spontaneous onset of labour at term is preceded by a definite increase in the saliva oestriol to progesterone ratio. Saliva steroid concentrations reflect the unbound, unconjugated (free, biologically active) plasma steroid concentrations. That a rise in free oestrogen should precede the onset of labour accords with the known effects of oestrogen and progesterone on myometrial activity.^{6,7} Other studies have focused on measurements of oestradiol, as oestriol had been thought to be a weak oestrogen; but now it is apparent that oestriol may be as active as oestradiol in specific target tissues. For instance, oestriol binds to myometrial oestrogen receptors⁸ and is as effective as oestradiol in stimulating production of prostaglandin F_{2α} by human endometrial cells in culture.⁹ Furthermore, free oestriol concentrations are 10 to 20 times greater than free oestradiol concentrations in late pregnancy.^{6,7}

We found only a minimal increase in the saliva oestradiol to progesterone ratio before the onset of labour at term in our previous study⁷ (fig 2) and did not find any increase in the saliva oestradiol to progesterone ratio in women going into preterm labour in this study. Earlier studies similarly failed to show an increase in the plasma oestradiol to progesterone ratio before preterm labour.^{4,5}

From this study it appears that a rise in the oestriol to progesterone ratio may precede the onset of idiopathic preterm labour and that the normal endocrine changes that precede term labour occur inappropriately early. The normal rise in oestriol in late pregnancy may be due to increased fetal adrenal activity. There is some evidence to support the idea that increased fetal adrenal activity occurs before the onset of preterm labour. Corrected mean adrenal weights in 64 preterm babies who were either stillborn or died within 12 hours of birth were roughly 25% greater in those delivered after idiopathic preterm labour than in those whose delivery occurred after sudden antepartum haemorrhage.¹⁰ It is noteworthy that in five of our 13 cases of preterm labour with intact membranes the saliva oestriol concentrations were above the 95th centile and that they were above the 50th centile in all cases, suggesting increased fetal adrenal activity in this group.

There is an increase in uterine gap junction formation and in the number of myometrial oxytocin receptors in women in preterm labour as well as those in labour at term,^{11,12} and peripheral concentrations of prostaglandin metabolites are raised in both term and preterm labour.¹³ It is known that oestrogen enhances and progesterone suppresses these developments. An increase in spontaneous uterine activity and in uterine sensitivity to oxytocin have also been found in some women subsequently going into idiopathic preterm labour.^{14,15}

The underlying cause of preterm labour after prolonged preterm rupture of the membranes is clearly different from that of preterm labour with intact membranes. Possibly local infection may weaken the membranes and lead to their spontaneous rupture.^{16,17} Several organisms have been found to possess greater phospholipase A₂ activity than that of the membranes and it has been suggested that this may cause increased prostaglandin production by the membranes.^{18,19} Thus bacterial infection might lead to the onset of labour by a method which bypasses the increase in the oestrogen to progesterone ratio that normally occurs before labour.

Clinical scoring systems^{20,21} and biochemical²² and biophysical²³ markers that have been tried for predicting preterm labour have not been very helpful in practice. From our study it appears that preterm labour without prior prolonged rupture of the membranes is preceded by an increase in the saliva oestriol to progesterone ratio.

If this occurs as long before the onset of preterm labour as does the increase in the saliva oestriol to progesterone ratio before the spontaneous onset of labour at term it might be possible to use measurements of this ratio to predict preterm labour—and so initiate treatment in time to prevent its occurrence in some cases. Studies are currently underway to address this issue.

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Impact of gestrinone on the course of asymptomatic endometriosis

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Abstract

A new drug, gestrinone, was subjected to the first double blind, randomised placebo controlled trial of any treatment of endometriosis. The disease deteriorated in eight (47%) of the 17 patients prescribed placebo (95% confidence limits 23% and 71%) compared with none of the 18 patients prescribed gestrinone ($p=0.002$). There was a difference in elimination of the endometriosis in the gestrinone group compared with placebo but this was not statistically significant ($p=0.057$). There was a significant difference in improvement of the disease in the gestrinone group compared with placebo ($p=0.004$), confirming that gestrinone is an effective treatment of endometriosis.

Endometriosis deteriorates in at least 23% of patients; as it is impossible to predict in whom this will happen, treatment appears to be warranted in all cases.

Introduction

Androgens,¹ progestogens,² danazol,^{3,4} and luteinising hormone releasing hormone agonists^{7,8} have all been shown to improve endometriosis either clinically or visually in uncontrolled trials.

Before the advent of laparoscopy only symptomatic disease was treated, but now it is becoming increasingly common to diagnose asymptomatic disease, especially in infertile women. The relevance of the finding is unknown and it may be solely a reflection of an increased prevalence of the disease in nulliparous patients, who are overrepresented in infertile women.⁹ The problem is compounded by the fact that there is no placebo controlled trial of any treatment of endometriosis and therefore no information about the course of the disease. Possibly asymptomatic endometriosis resolves spontaneously in most women. These uncertainties have resulted in some clinicians treating and others not treating asymptomatic endometriosis. The introduction of gestrinone (Roussel-UCLAF, Paris) for phase III clinical trials provided a unique opportunity to perform a placebo controlled trial of a treatment of endometriosis and thus define the course of the disease and assess objectively the impact of treatment.

Patients and methods

All the patients were infertile and had been comprehensively investigated with no diagnosis being reached before laparoscopy. Their median age was 28 years (range 21-35) and median duration of infertility 36 months (range 18-72). Each patient was made fully aware of the purpose of the study and of the possibility of allocation to a placebo before giving written consent. The protocol was approved by the local ethical committee.

Study design—The study was a randomised, double blind placebo controlled trial of gestrinone in the treatment of asymptomatic endometriosis. Forty patients were recruited after a laparoscopy at which mild or moderate asymptomatic endometriosis had been diagnosed. The disease was staged using the American Fertility Society scoring system.¹⁰ In this system a score of 1 to 5 signifies mild endometriosis, 6 to 15 moderate endometriosis, and greater than 15 severe disease. Only those patients with asymptomatic

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