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UTERINE EFFECTS OF INHIBITION
of
PROGESTERONE SYNTHESIS
by a specific
3β HYDROXYSTEROID DEHYDROGENASE INHIBITOR

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1. A reduction in the circulating level of progesterone in the luteal phase of the menstrual cycle will lead to menstruation.

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REFERENCES

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1. Inhibition of 3β-hydroxysteroid dehydrogenase activity in first-and second-trimester human pregnancy and the luteal phase using Epostane.

2. Prolonged inhibition of placental and ovarian 3β-hydroxysteroid dehydrogenase during pregnancy and the luteal phase of the menstrual cycle.

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SUMMARY

The steroid hormone progesterone is considered indispensable for pregnancy - it is the 'hormone of pregnancy' as described by Corner (1928). It is generally agreed that the role of progesterone in all species is to prepare the endometrium for pregnancy and to contribute to the maintenance of myometrial quiescence from implantation to the end of pregnancy. There is however, a conflict of opinion concerning its role in pregnancy termination. In some species, for example the sheep, there is considerable evidence that progesterone provides an important link between fetal cortisol and the control of uterine activity. But in human pregnancy the evidence is conflicting.

The present study investigates the role of progesterone in the initiation of uterine activity in:
- late pregnant ewes,
- early human pregnancy and
- the luteal phase of the human menstrual cycle.

The study was designed following the development of a 3 β-hydroxysteroid dehydrogenase (3 β-HSD) inhibitor (Epostane) by Sterling Winthrop Research. In vitro, Epostane acts competitively to inhibit the conversion of pregnenolone to progesterone. This provides a method of investigating the role of progesterone in the classical manner - depressing the rate of secretion.

METHOD

1. Late pregnant ewes
Six animals were studied at 131 ± 2 days of pregnancy.

(i) Progesterone production was inhibited by administration of Epostane.

(ii) Hormone levels in the ewe were monitored to detect changes early in parturition.

(a) Maternal catheters were placed into a carotid artery and a jugular vein.

(b) The concentrations of progesterone, oestradiol-17β cortisol and 13, 14-dihydro-15-keto-prostaglandin F₂ (PGFM) were measured by radioimmunoassay.

(iii) Hormone levels in the fetus were monitored to measure fetal responses to falling concentrations of progesterone.

(a) Fetal catheters were placed in a carotid artery or a jugular vein.

(b) The concentrations of progesterone and cortisol were measured by radioimmunoassay.

(iv) Uterine activity was monitored by an intra-amniotic pressure transducer.

(v) The fetus and the fetal adrenals were weighed after delivery.

2. **Early Human Pregnancy**

Sixty-five pregnant women between five and 18 weeks of pregnancy were studied.

(i) Progesterone production was inhibited by oral administration of Epostane.

(ii) Hormone levels were monitored to assess the effect
of inhibition of 3β-HSD on ovarian and placental steroidogenesis.

(a) Serial venous blood sampling was performed via an indwelling forearm catheter.

(b) The concentrations of progesterone, cortisol, oestradiol-17β and PGFM were measured by radioimmunoassay.

(iii) A detailed history, physical examination, haematological and biochemical assays were performed prior to and on completion of the study to exclude adverse effects.

(iv) The effect of inhibition of progesterone secretion on uterine activity was determined by pressure monitoring and/or direct questioning.

3. Human Menstrual Cycle (Luteal Phase)

Thirty-three women in the luteal phase of a menstrual cycle were studied.

(i) Progesterone production was inhibited by oral administration of Epostane.

(ii) Hormone levels were monitored to assess the effect of inhibition of progesterone secretion on ovarian steroidogenesis.

(a) Serial venous blood sampling was performed, usually via an indwelling forearm catheter.

(b) The concentrations of progesterone, oestradiol-17β and cortisol were measured by radioimmunoassay.

(iii) Detailed history, physical examination, haematological tests and biochemical assays were
performed prior to and on completion of the study to exclude adverse effects.

(iv) The effect of inhibition of progesterone secretion on the timing of the subsequent menstruation was recorded.

RESULTS

1. Late Pregnant Ewes

(i) In all animals, detectable uterine contractions were recorded via the intra-amniotic catheter four to six hours after treatment.

(ii) Three of the six animals delivered within 36 hours and the remaining three were in established labour when the experiment was terminated.

(iii) The fetal condition as determined by arterial pO₂ and pH were normal throughout labour.

(iv) Maternal progesterone in both the uterine vein and peripheral plasma fell precipitously to levels of less than 1.0 ng/ml and remained at this level until immediately prior to delivery.

(v) Plasma concentrations of oestradiol-17β were not significantly altered in either the uterine vein or peripheral plasma.

(vi) Maternal cortisol concentrations followed the expected diurnal variation.

(vii) There was a dramatic and progressive rise in PGFM concentrations which were significantly different from the pretreatment values at four hours.

(viii) Fetal plasma progesterone concentrations fell
below measurable levels by the time of the first post-treatment sample.

(ix) Cortisol concentrations in the fetal plasma rose significantly throughout the study in parallel to the rise in PGFM levels in the maternal plasma.

2. **Early Human Pregnancy**

(i) Epostane suppressed progesterone production without significant side effects. The fall in the serum progesterone levels was both dose- and gestation-related.

(ii) Serum oestradiol-17β levels fell in parallel to serum progesterone. The fall was both gestation- and dose-related.

(iii) Serum cortisol levels were not significantly affected by Epostane (300 mg daily for five days).

(iv) Despite a decline in serum progesterone to levels below the minimal value (10 ng/ml) said to be necessary for the maintenance of human pregnancy (Csapo and Pulkkinen, 1978), there was no clinical effect in four of the five treated women.

3. **Human Menstrual Cycle (Luteal Phase)**

(i) Epostane suppressed progesterone production without side effects. The fall in the serum progesterone concentration was dose-dependent.

(ii) Serum oestradiol-17β levels were not affected.
(iii) Serum cortisol levels were not significantly affected.

(iv) The fall in serum progesterone levels was accompanied by early menstruation in five out of eight treated women.

CONCLUSIONS

1. Late Pregnant Ewes

(i) Epostane inhibits the synthesis of progesterone, probably by inhibiting the activity of 3 ß-HSD (hydroxysteriod dehydrogenase).

(ii) A fall in the concentration of progesterone alone is sufficient to initiate the chain of events leading to parturition.

(iii) A decline in the concentration of progesterone stimulates the synthesis of PGF$_{2a}$.

(iv) A substantial and prolonged decline in the level of progesterone is required to initiate parturition in the ewe.

(v) Although the decline in the concentration of progesterone achieved in this study did initiate parturition it is unlikely that progesterone acts in isolation to initiate parturition in the ewe.
2. EARLY HUMAN PREGNANCY

(i) Epostane inhibits the synthesis of progesterone, probably by inhibiting the activity of 3 β-hydroxysteriod dehydrogenase.

(ii) A rapid decline in the concentration of progesterone is not the trigger to the initiation of uterine activity in human pregnancy.

(iii) It is unlikely that a physiological change in the concentration of progesterone leads to parturition in women.

(iv) A substantial and prolonged decline in the level of progesterone achieved by pharmacological means may initiate uterine activity in early human pregnancy.

3. HUMAN MENSTRUAL CYCLE (Luteal Phase)

(i) Epostane inhibits the synthesis of progesterone, probably by inhibiting the activity of 3 β-hydroxysteriod dehydrogenase.

(ii) A rapid decline in the level of progesterone is not the trigger to menstruation women.

(iii) A sustained and prolonged decline in the level of progesterone is required to initiate menstruation.