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ON THE INFLUENCE OF ORCIPRENALINE ON UTERINE MOTILITY AND ON PLASMA LEVELS OF ESTRADIOL-17β IN PREGNANT AND PARTURIENT SHEEP

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Orciprenaline infusions in laboring ewes suppressed uterine activity. A complete inhibition of uterine activity could only be obtained in the empty uterine horn of laboring ewes. During late pregnancy a complete inhibition of the pregnant horn could be established with orciprenaline doses much lower than those necessary during parturition. In all treated ewes, aberrant patterns of plasma estradiol-17β levels were observed: very high maternal estradiol-17β levels were detected after treatment with orciprenaline. It is suggested that orciprenaline influences fetal adrenocortical functioning.

tocolysis; myometrial sensitivity; fetus

INTRODUCTION

Suppression of uterine activity by β-sympathomimetic drugs is a common practice, both in human and veterinary obstetrics. One of the hitherto most frequently used compounds is orciprenaline (Alupent). In contrast to other β-receptor stimulators, such as ritodrine, fenoterol and salbutamol, which are more active on uterine β_2-receptors, orciprenaline is a non-specific β-receptor stimulator. Orciprenaline has good tocolytic properties, but this effect is short-lasting (Baillie et al., 1970).

This paper describes the effects of orciprenaline treatment upon uterine motility in pregnant and parturient sheep. The effect of orciprenaline treatment upon the maternal plasma estradiol-17β levels has also been studied.

MATERIAL AND METHODS

Uterine activity was recorded electrophysiologically in Texel sheep, as described by Naaktgeboren (1974). Several pairs of silver electrodes were

sewn onto the myometrial wall and connected to a contact set outside the ewe by silastic-coated cables. Electrical uterine activity was recorded on an Elema–Schönander Mingograph. The duration of the electrical activity was measured per consecutive 12-min periods. In one ewe, a pair of ECG electrodes were implanted subcutaneously, in order to record heart rate and uterine activity simultaneously. All ewes were fitted with a permanent indwelling jugular catheter for blood sampling and for orciprenaline infusions. Five ewes were used (1 single pregnancy and 4 twin pregnancies) for the orciprenaline infusion experiments. Six ewes (4 singletons, 2 twins) served as controls for estradiol-17β values (Bontekoe et al., 1977). The data from 9 other ewes served as control values for uterine activity (Naaktgeboren et al., 1975).

Orciprenaline infusions were started before the onset of expulsion in case of singletons or unilateral twin pregnancy (ewe 9 and ewe 260). In ewes carrying a lamb in both horns (ewes 191 and 237), orciprenaline treatment was started immediately after birth of the first lamb. In ewe 310 orciprenaline was administered immediately postpartum.

Short-lasting infusions (up to 3 h) were given to 4 ewes on 21 occasions, after day 120 of pregnancy.

In the 5 ewes used for the orciprenaline experiments, blood samples were collected every 30 min during the period of infusion, and for some hours after stopping the infusion. Heparinized blood was immediately centrifuged at +4° C and plasma was stored at −25° C until assay was made.

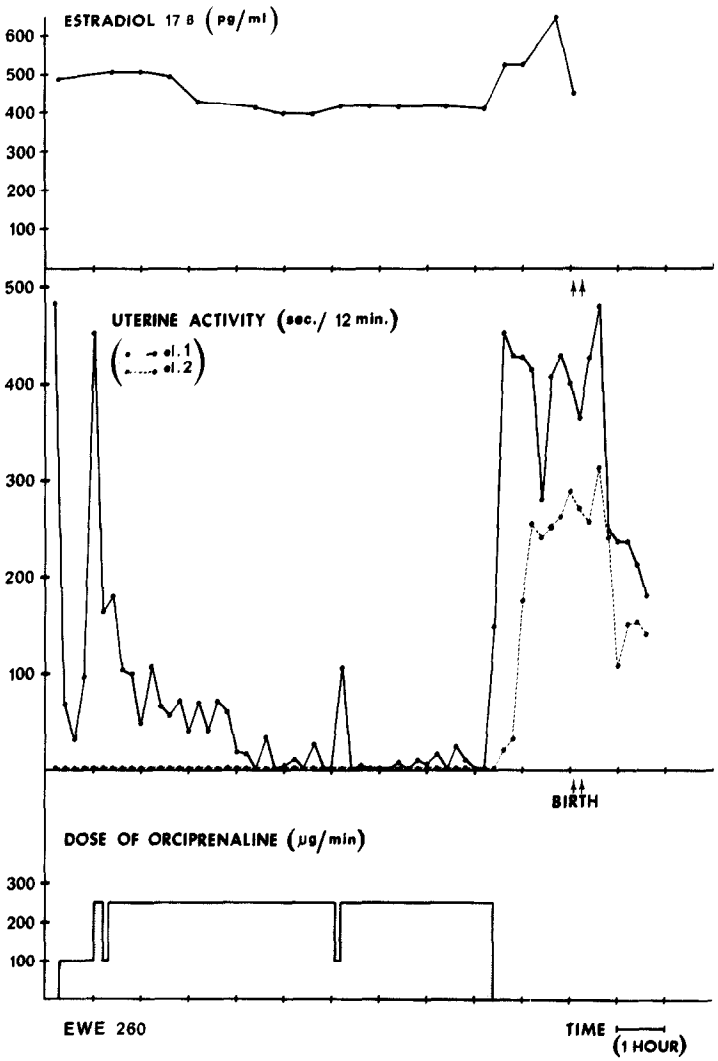
Estradiol-17β levels were determined in triplicate, and in cases of very high estradiol-17β levels up to 12 times, by radioimmunoassay in a way similar to that described by Bontekoe et al. (1977).

RESULTS

Between day 120 and the end of pregnancy, normal uterine motility pattern consists of phases of electrical activity, with a duration of 5—8 min, occurring once to twice per hour. Between the phases of activity single trains and/or spikes may occur. Orciprenaline infusions of 5 μg/min did not influence this spontaneous uterine activity. On almost every occasion doses of 10—25 μg/min caused the longer phases of activity to disappear completely. Sometimes single trains or spikes occurred. Inhibition of uterine motility could as a rule be observed 6 min after the onset of the orciprenaline infusion, whereas it took about 10—15 min for the activity to reappear after stopping the infusion. Occasionally, a dose of 25 μg/min was insufficient to suppress spontaneous activity of the pregnant uterus, but administration of 50 μg/min was in these cases sufficient to establish complete uterine quiescence.

As noted previously, orciprenaline infusion during parturition was started either before complete dilatation was established (10 cm) or after delivery of the first twin. During parturition, however, an infusion rate of 50 μg/min

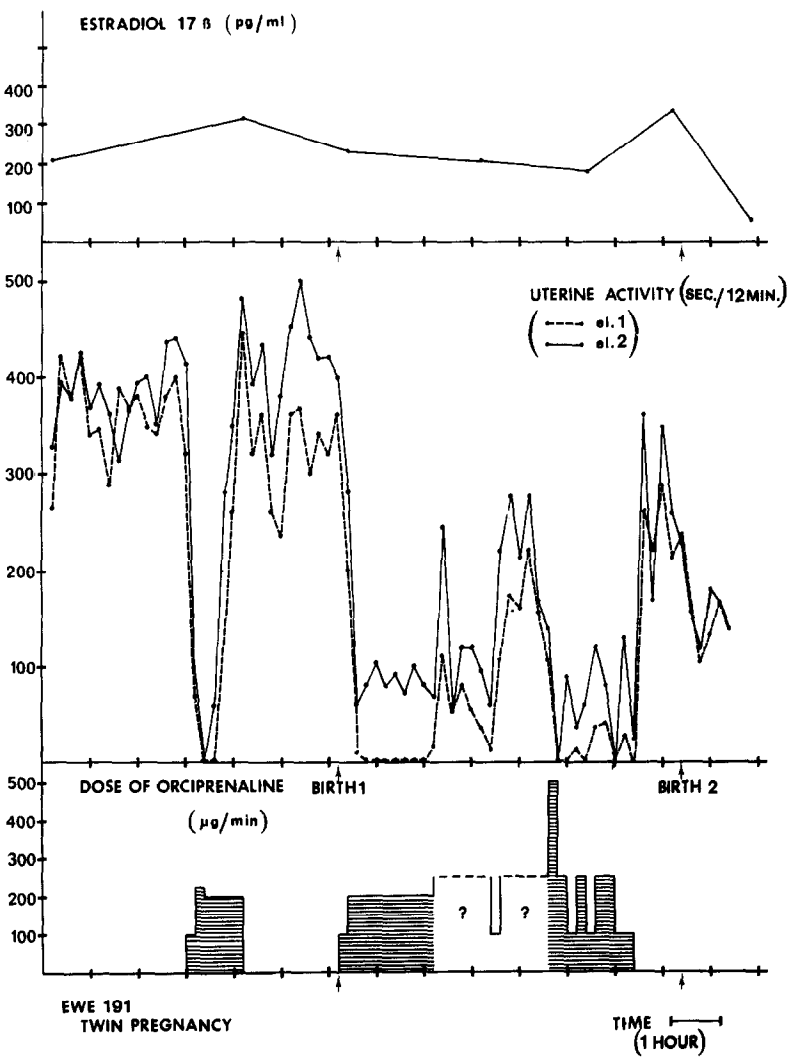
was never sufficient to suppress labor activity. To suppress labor contractions administration of 250—500 μg/min was necessary, although even then a complete inhibition of uterine activity could not always be produced in the pregnant uterine horn. However, in the non-pregnant horn or after expulsion of the fetus a complete inhibition of the contractility could be established with an infusion rate of at least 100—250 μg/min. A decrease in the infusion rate, due to changing of the orciprenaline-containing syringe or leakage in the system, immediately resulted in an increase in uterine activity. After stopping the infusion uterine activity immediately reappeared, but at least 1 h expired between the end of the infusion period and the delivery of the single



UNILATERAL TWIN PREGNANCY 1

lamb or second twin. In these experiments the postinfusion level of uterine activity was in the lower range of normal (Figs. 1—3 and 6).

In normal pregnancy, one peak in estradiol-17β levels precedes delivery. In single pregnancies this peak reaches values between 100 and 200 pg/ml plasma, and in twin pregnancies values up to 400 pg/ml can be measured (Chamley et al., 1973; Robertson and Smeaton, 1973; Bontekoe et al., 1977). In our orciprenaline-treated ewes, however, aberrant patterns of estradiol-17β levels were found. In a single pregnancy (ewe 9) the onset of the expulsion was postponed by orciprenaline, and the levels of estradiol-17β in this ewe reached higher values than in some of the control twin pregnancies. The peak value was 407 pg/ml (Fig. 5). In a unilateral twin pregnancy (ewe 260)



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the same procedure of delaying expulsion was carried out. Orciprenaline infusion was started after a peak value (550 pg/ml) had been reached. The level remained high (between 400 and 500 pg/ml), and a new peak appeared

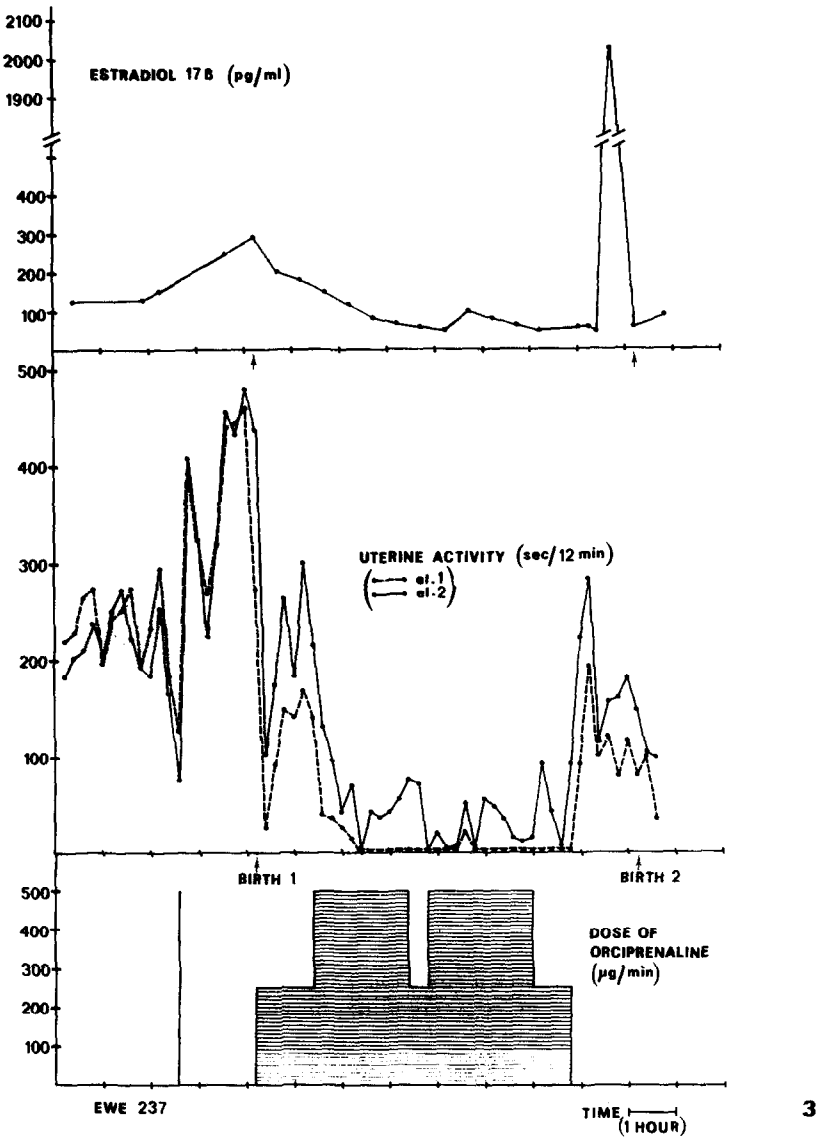


Fig. 1—3. Plasma levels of estradiol-17β (top); uterine activity in sec/12 min (middle); dose of orciprenaline given by infusion (bottom) to a ewe in labor.

Fig. 1. Solid line: pregnant uterine horn; dotted line: non-pregnant horn.

Figs. 2 and 3. Broken line: activity of the uterine horn from which the first lamb is expelled; solid line: activity from the horn which still contains a fetus at the onset of the orciprenaline infusion.

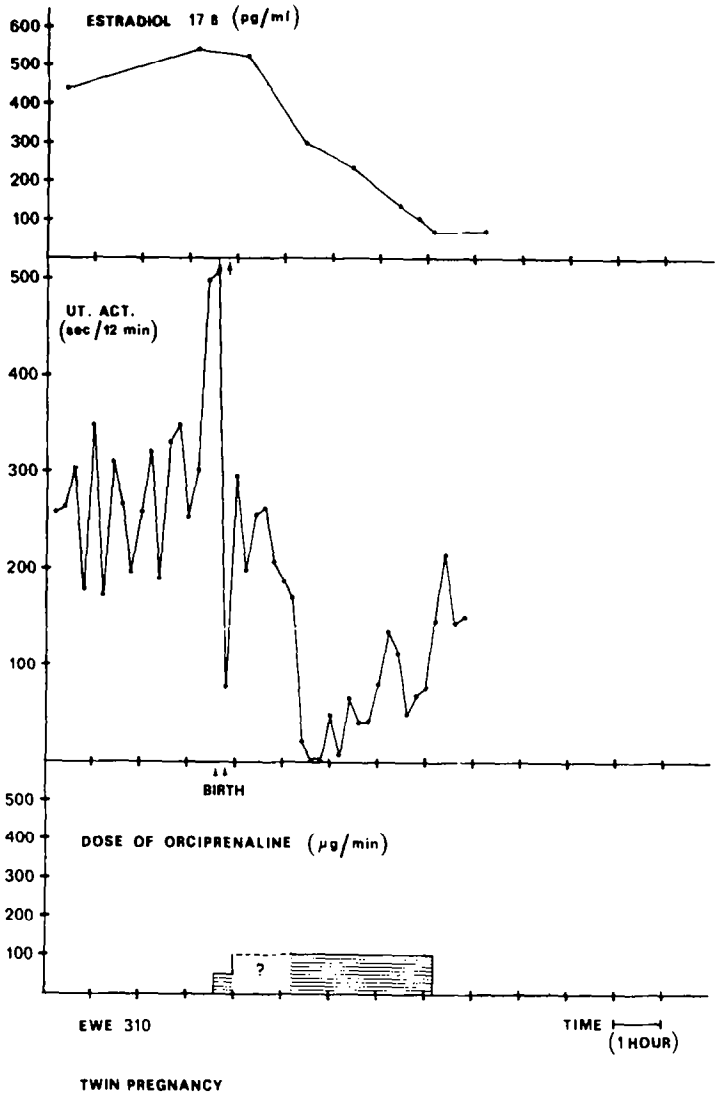
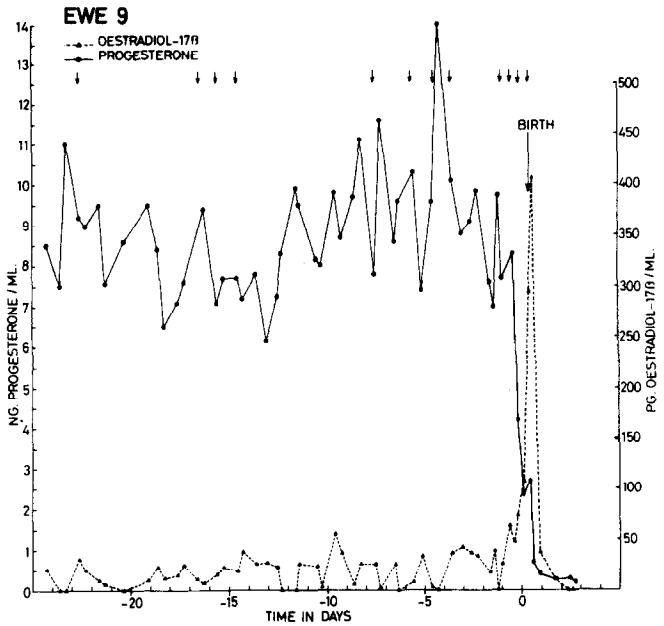


Fig. 4. Same as for Figs. 1—3, with dose of orciprenaline given by infusion (bottom) to a postpartum ewe. The activity is only plotted for one of the uterine horns, since both showed equivalent activity.

to be superimposed upon the existing high level, reaching a value of 600 pg/ml just before the birth of the two lambs (Fig. 1).

In two ewes uterine activity was suppressed after the birth of the first lamb. The second peak in estradiol-17β levels occurred almost 1 h after stopping the orciprenaline infusion, and preceded delivery of the second lamb. In ewe 191 the peak values were 317 and 335 pg/ml, and in ewe 237 they were 280 and 2010 pg/ml. In both animals the second peak was short-lived and



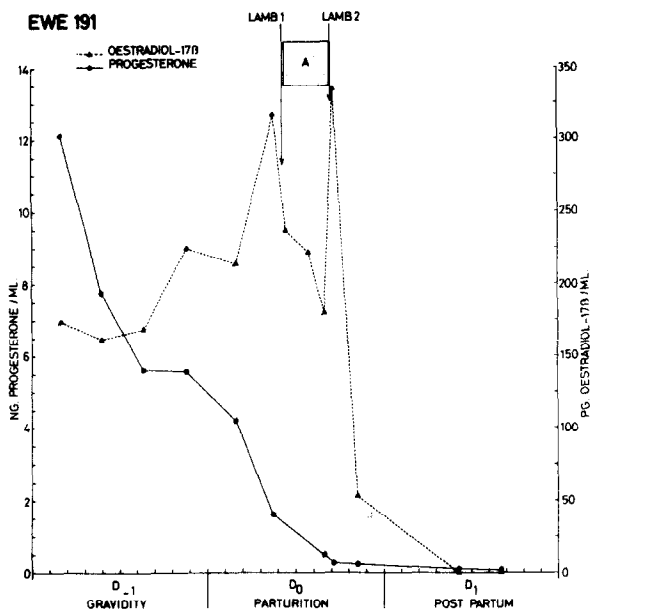


Fig. 5. Plasma levels of estradiol-17β and progesterone in orciprenaline-treated ewes at the end of pregnancy (A = ewe 9) and during parturition (B = ewe 191). A: arrows indicate orciprenaline treatments; B: dotted area (A, Alupent) indicates orciprenaline treatment (cf. Fig. 2).

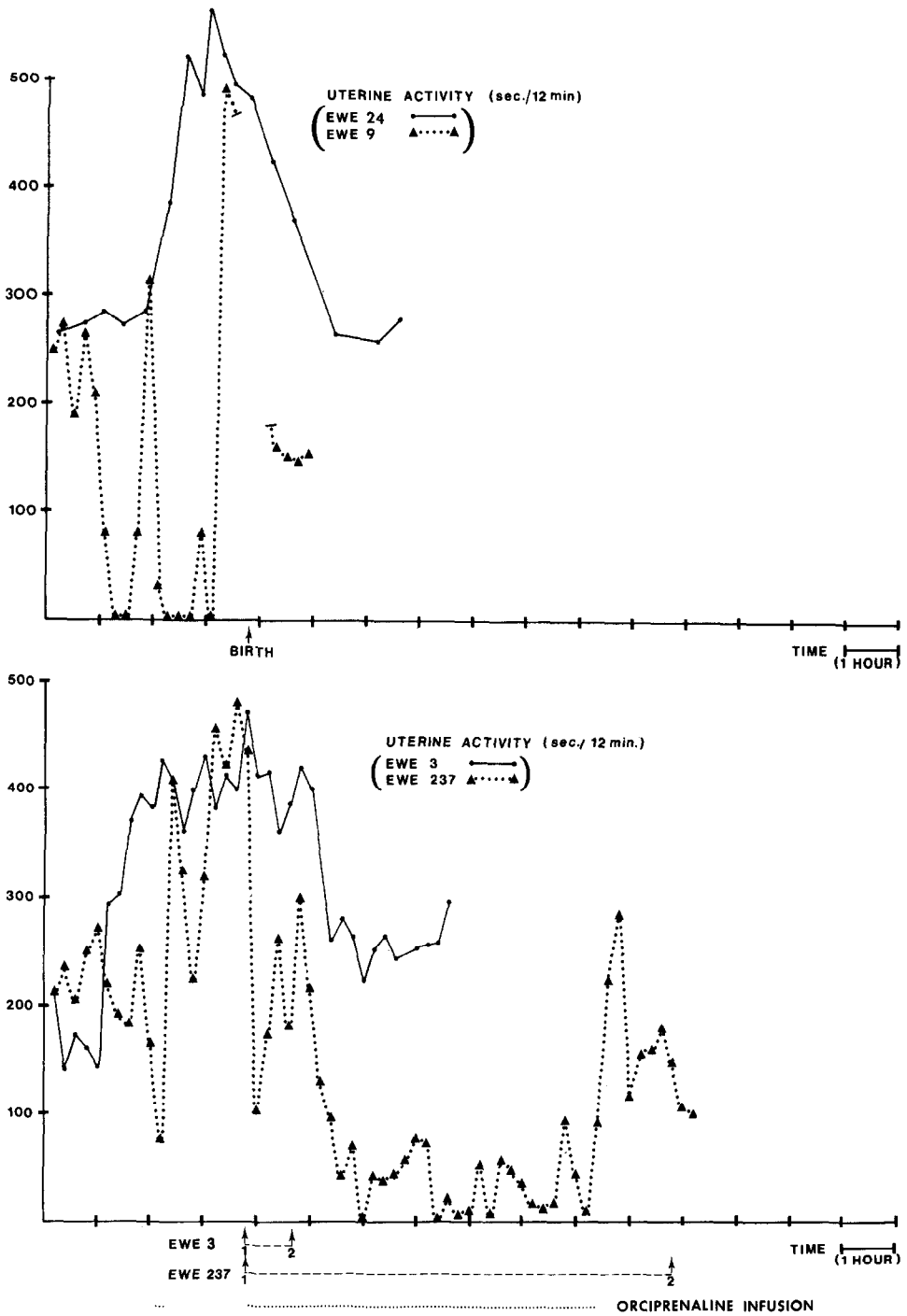


Fig. 6. Comparison of uterine activity during labor between untreated (control) ewes (solid lines) and ewes treated with orciprenaline (dotted lines). Top: single pregnancies. The moment of delivery is plotted on the same spot. Bottom: twin pregnancies. In ewe 237 the interval between the lambs is increased considerably. Birth of the first lambs of both ewes is plotted on the same spot.

TABLE I

SCHEMATIC REPRESENTATION OF THE EXPERIMENTS AND THE OBSERVED PEAK VALUES IN PLASMA LEVELS OF ESTRADIOL-17β

Ewe no.	Kind of pregnancy	Start of orciprenaline infusion	Peak values after treatment	Range (and mean) normal values [1]
9	single pregnancy	before onset of expulsion	407 pg/ml	32—161 (124) pg/ml
260	unilateral twin pregnancy	before onset of expulsion	660 pg/ml	183-317 (270) pg/ml
191	twin pregnancy	after birth of first lamb	335 pg/ml	183—317 (270) pg/ml
237	twin pregnancy	after birth of first lamb	2010 pg/ml	183—317 (270) pg/ml
310	twin pregnancy	after birth of both lambs	—	— —

[1] After Bontekoe et al., 1977.

could be detected in only one sample; the second peak was, moreover, higher than the first one.

In ewe 310 orciprenaline treatment after birth of the first of twin lambs did not prevent the birth of the second lamb, which took place almost immediately after expulsion of the first lamb. In this ewe a second estradiol-17β peak was not observed at the end of orciprenaline treatment during the postpartum period. The observations are schematically represented in Table I.

On the days before delivery the estradiol-17β levels in all ewes were below 100 pg/ml, and hence did not differ from control values. Progesterone levels in all ewes did not differ from controls (Fig. 5a and b).

Although good inhibition of labor contractions was produced in ewe 9, the dilatation of the cervix progressed in the subsequent $4\frac{1}{2}$ h from 2 to 10 cm. In ewe 1, included in other experiments, no progress in dilatation occurred during 8 h of normal labor activity.

Figures 1—4 represent all data concerning the dose of orciprenaline, the uterine activity and the estradiol-17β plasma levels in 4 parturient ewes. For ewe 9 only the levels of estradiol-17β and of progesterone are plotted (Fig. 5). In Figure 6 experimental and control ewes are compared.

In the pregnant ewe the heart rate was about 70 beats/min. In the laboring ewe orciprenaline infusions (250 μg/min) increased the ewe's heart rate from 70—80 beats/min to 130—140 beats/min, with occasional fluctuations up to 150 beats/min.

DISCUSSION

During parturition much higher doses of orciprenaline are necessary to suppress myometrial activity than during pregnancy. A complete inhibition

of labor activity in the pregnant horn could only be established by doses which severely influenced the ewe's heart rate. This is in accordance with observations in human obstetrical practice, where β-receptor stimulators have a similar cardiac influence: this cardiac-stimulating effect limits the therapeutic value of β-mimetic drugs (Baillie et al., 1970; Liggins and Vaughan, 1973).

Factors influencing the sensitivity of the myometrium to orciprenaline

Baillie et al. (1970) observed that orciprenaline seldom arrested labor when the cervix was dilated or the membranes were ruptured. Similarly, Liggins and Vaughan (1973) observed that salbutamol treatment tended to fail when the cervix was more than 3 cm dilated. In our experiments orciprenaline treatment was, in all but one case, started when dilatation of the cervix was complete. However, the decreasing sensitivity to orciprenaline during labor cannot only be ascribed to the fact that labor was already advanced, since, during parturition, the horn which does not contain a fetus (the non-pregnant horn in cases of unilateral pregnancy or single pregnancy), or the just-emptied horn (in cases of bilateral twin pregnancy), is much more sensitive to orciprenaline than the pregnant horn. One explanation for this phenomenon might be that stretching of the uterine wall decreases the sensitivity to orciprenaline. But, on the other hand, we observed that during pregnancy the uterus is much more sensitive to orciprenaline than during parturition. This is in accordance with observations of Taverne et al. (1976), who studied the influence of the non-selective β-mimetic compound isoxsuprine (Duphaspasmin) in domestic cattle. However, during late pregnancy the uterus is also very stretched; nevertheless, the effectiveness of orciprenaline in inhibiting uterine contractile activity is greater than during parturition. During parturition the estrogen/progesterone ratio is changed considerably, as compared to that during late pregnancy (Bontekoe et al., 1977). The decreased sensitivity to orciprenaline during labor could also be attributed to the change from progesterone domination to estrogen domination; the combination of at least these 3 factors influences the sensitivity to and hence the effectiveness of orciprenaline: the lowest sensitivity is seen when labor is advanced, and the myometrium highly stretched and estrogen-dominated.

In one ewe (ewe 9) orciprenaline treatment was started when the cervix was 2 cm dilated. Cervical dilatation progressed in spite of the fact that contractions were suppressed. In another ewe we observed that cervical dilatation did not progress, although labor activity was normal. Sümes and Creasy (1976) treated laboring sheep with the β_2-receptor stimulator, ritodrine, and observed that cervical dilatation proceeded in 3 out of 13 experiments (lasting 6—9 h), while they were able to suppress uterine activity in every case. It might therefore be concluded that cervical dilatation is not totally dependent upon uterine contractions; suppression of uterine contractions does not always imply that labor is effectively arrested.

The influence of orciprenaline on plasma levels of estradiol-17β

In the last week of pregnancy cortisol levels in the fetal lamb start to rise, while ACTH levels are not elevated at that time. Cortisol enhances the fetal adrenocortical response to ACTH, leading to increased production of dehydroepiandrosterone sulfate by the fetal adrenal cortex. Moreover, cortisol activates the entire enzyme system of the ovine placenta, resulting in high activity of the 3-sulfatase and aromatizing enzymes, resulting in excretion of large amounts of unconjugated estrogens, the major stimulus for the release of prostaglandin $F_{2\alpha}$ and consequently of parturition (Liggins, 1976).

The rise in circulating estrogens preceding parturition is of fetal origin. We presume that the second rise in plasma levels of estradiol-17β observed in the orciprenaline-treated ewes and the elevated estradiol-17β levels after treatment during pregnancy are also indicative for fetal adrenocortical activity. Indeed, in ewe 310, treated with orciprenaline after birth of the two lambs, no second peak in estradiol-17β levels was detected: changes in estradiol-17β levels due to orciprenaline treatment obviously involve fetoplacental functioning.

β-Mimetic drugs induce dilatation of the myoendometrial vasculature, but the placental vasculature is maximally dilated, and does not respond with further dilatation after β-adrenergic stimulation (Greiss, 1972). Klöck et al. (1972) observed an increase in uterine blood flow due to treatment with fenoterol (an orciprenaline derivative) in sheep. Lippert et al. (1976) found that, in the human, fenoterol increases both placental and myometrial blood pools. However, Ehrenkranz et al. (1976) observed that ritodrine infusions to pregnant sheep initially decreased uterine flow, but that flow normalized when the infusions lasted more than 2 h. In our experiments the elevated estrogen levels were observed 1 h after stopping orciprenaline infusion, and were therefore probably not a primary effect of enhanced uteroplacental flow due to adrenergic stimulation. The estrogen peak preceding parturition might be the reaction of the fetus to the relative decrease in placental functioning near term. β-Mimetic drugs inhibit uterine contractions, which might lead to increase in myometrial blood flow, therefore to temporary improvement of placental functioning and, hence, of fetal condition. Sybulski and Maughan (1972) observed a rise in maternal plasma estradiol levels near term in 4 isoxsuprine-treated women, with pre-existing low levels of plasma estradiol, although levels remained in the lower range of normal. Also in the human the fetoplacental unit plays an important role in the production of estrogens (Ohrlander et al., 1975; Lefebre et al., 1976). Ehrenkranz et al. (1976) observed that, during 2 h of infusions with ritodrine to pregnant sheep, fetal arterial pH, pCO_2 and pO_2 remained within normal physiological limits. In our experiments, the condition of the lambs delivered after orciprenaline treatment was, after a small recovery phase, very good.

Flint et al. (1974) observed that orciprenaline administration to pregnant sheep on day 123—134 of pregnancy raised utero-ovarian progesterone levels, which may also be indicative for improved placental functioning. The

occurrence of the second estrogen peak could be the reflection of the adrenocortical response of the fetus to cessation of the orciprenaline infusion, hence a reaction to a sudden decrease in blood flow due to the increase in uterine activity. In this respect it is interesting to note that estrogens produce a marked decrease in vascular resistance and an increase in uterine blood flow and oxygen transfer, reaching a peak in approximately 2 h (Nuwayhid et al., 1975; Resnik et al., 1976). Exogenous administration of dehydroepiandrosterone to the fetus results in increased concentrations of estrogens, followed by an increase in uterine blood flow (Pupkin et al., 1975). The enhanced production of estrogens near term and after cessation of the orciprenaline treatment may lead to a beneficial increase in blood flow.

Treatment of premature labor is a common practice, and some authors presume that β-mimetic drugs may be favorable in cases of chronic placental insufficiency. It is, however, also possible that, due to these temporarily favorable effects, a poor fetal condition may be masked. In that case, premature labor is always better than prolongation of pregnancy (Unbehaun, 1974). Moreover, treatment with β-mimetic drugs often tends to fail, particularly when labor is already advanced. In that case, also the maternal intolerance to the necessary high doses limits the therapeutic value of this treatment.

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