EFFECTS OF OESTRADIOL AND PROSTAGLANDIN $F_{2\alpha}$ ON THE TIMING OF PARTURITION IN THE RAT

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Summary. Groups of rats were treated with oestradiol or $PGF_{2\alpha}$, or both, at various times between Days 19 and 21 of pregnancy and the times of onset of parturition were recorded.

On Day 20, oestradiol (10 $\mu\text{g}/\text{rat}$) appeared to delay the onset of parturition in those rats which would otherwise have littered in the early part of the normal range, so that all the rats went into labour in the later part of that range. On Day 21, oestradiol (10 $\mu\text{g}/\text{rat}$) advanced the time of littering in about half the rats, but delayed parturition in about 30%.

Prostaglandin $F_{2\alpha}$ ($4 \times 25 \mu\text{g}$) on Day 19 or Day 20 caused all the rats to litter prematurely, but $PGF_{2\alpha}$ ($2 \times 25 \mu\text{g}$) on Day 21 advanced parturition only in rats which normally produced late litters. When oestradiol (10 $\mu\text{g}/\text{rat}$) was given on Day 20 or 21, following treatment with $PGF_{2\alpha}$ ($4 \times 25 \mu\text{g}$) on Day 19 or Day 20, the spread of times of onset of parturition was reduced.

It is postulated that (a) the final changes in preparation for parturition in rats are initiated at different times in different animals between late evening on Day 20 and early evening on Day 21, about 45 hr before parturition; (b) these changes, once started, probably take comparable times in different animals. The spread of times of parturition normally seen is thus attributed to the variation in the time at which the preparations begin and not in the length of time required for their completion; and (c) the first phase of the preparations involves prostaglandin-mediated luteolysis, and that this is followed by a final oestrogen-dependent phase which begins when progesterone concentration falls below a critical level and that of oestrogen attains a critical level.

Oestradiol on Day 20 may have a direct or indirect luteotrophic action in rats close to the onset of luteolysis at the time of dosing, thus causing retardation of luteolysis and delay of littering.

The advance of littering in many rats after oestradiol treatment on Day 21 is attributed to acceleration of the final phase of preparations for parturition in those rats at advanced stages of luteolysis at the time of dosing. Rats in which parturition was delayed by oestradiol treatment on Day 21 are believed to be those in which luteolysis had not begun and in which oestradiol exerted a luteotrophic effect.

The effects of exogenous $PGF_{2\alpha}$ are all attributed to its luteolytic

activity. An anti-inflammatory agent, fenclozic acid (50 mg/kg), given close to the time of parturition, neither delayed nor disturbed normal labour. This suggests that active prostaglandin biosynthesis at the time of parturition is not essential for the parturient activity of the uterus.

INTRODUCTION

There are several reports (Deis, 1971; Chester, Dukes, Slater & Walpole, 1972; Aiken, 1972) implicating prostaglandins (PGs) in the processes leading to parturition in the rat, although it is not yet clear whether PGs are acting primarily as luteolytic factors, as stimulants of uterine smooth muscle or as both in this species.

The administration of oestrogen to rats in late pregnancy has also been shown to influence the timing of parturition (Selye, Collip & Thompson, 1935; Csapo, 1969; Catala & Deis, 1973).

In an attempt to clarify the rôles of prostaglandins and oestrogens in events leading to parturition in the rat, we have examined the effects of $\text{PGF}_{2\alpha}$ and oestradiol, administered at various times between Days 19 and 21 of pregnancy, on the time of onset and course of parturition.

MATERIALS AND METHODS

Pregnant rats (Alderley Park Strain 1) were maintained in conditions of controlled temperature (22°C) and lighting (14 hr light, 10 hr dark) and allowed free access to food and water. They were housed individually during the last 24 to 36 hr before parturition.

Oestradiol, 10 µg/rat, was injected subcutaneously in arachis oil, synthetic (racemic) $\text{PGF}_{2\alpha}$, 25 µg or 50 µg/rat, was injected intraperitoneally in phosphate buffer (pH 7.4), and fenclozic acid (ICI 54,450) was administered by mouth in 0.5% aqueous 'Tween 80'. Some control animals were given the vehicles alone and others were untreated. The times and doses of substances administered are shown in Table 1.

The births of live and dead young were recorded hourly between 08.00 and 18.00 hours and every 2 hr during the night.

RESULTS

In this study the day of a sperm-positive vaginal smear is designated Day 1. The variation in times at which individual rats of our strain began to litter was large and considerable variation was also seen in the times at which rats treated with oestradiol, $\text{PGF}_{2\alpha}$ and other agents began to litter. When the times of onset of parturition of the control and treated rats were plotted as histograms, however, striking differences emerged.

Controls

Rats which received control injections of oil or phosphate buffer littered at similar times to those of untreated animals (Text-fig. 1, Group 1). The first rats

TEXT-FIG. 1. Histograms to show the times of onset of parturition in rats treated according to the schedules shown in Table 1.

started to litter early in the afternoon of Day 22 (13.00 hours) and the last rats littered 33 hr later in the evening of Day 23. The times of onset of parturition of the majority of rats were fairly uniformly distributed between 15.00 hours on Day 22 and 14.00 hours on Day 23.

Effects of oestradiol

A much greater proportion of rats treated with 10 μ g oestradiol at 12.00 hours on Day 21 littered earlier than normal, indeed about 55% of them

Table 1. The treatment schedules of rats tested for the effects of oestradiol, PGF₂ and fenclozic acid on the times of onset of littering

Group	No. of rats	Treatment		
		Substance	Day	Time (hours)
1	71	—	—	—
2	42	Oe*	21	12.00
3	15	Oe	21	09.30
4	19	Oe	20	17.00
5	45	Oe	20	12.00
6	15	Oe	20	09.30
7	5	Oe	19	17.00
8	24	PFG _{2α} (2 $\times$ 25 μ g, ■†, or 2 $\times$ 50 μ g, □†)	21	p.m.‡
9	30	Oe	21	12.00
10	9	+ PGF _{2α} (2 $\times$ 25 μ g)	21	a.m.‡□, p.m.■
11	12	PGF _{2α} (4 $\times$ 25 μ g)	20	p.m.
		PGF _{2α} (4 $\times$ 25 μ g)	20	p.m.
		+ Oe	21	09.30
12	10	Oe	20	12.00
		+ PGF _{2α} (2 $\times$ 25 μ g)	20	p.m.
13	9	PGF _{2α} (4 $\times$ 25 μ g)	19	p.m.
14	10	PGF _{2α} (4 $\times$ 25 μ g)	19	p.m.
		+ Oe	20	09.30
15	14	Oe	20	12.00
		+ Fenclozic acid (50 mg/kg)	22 or 23	17.00 □ 09.00 ■

* Oe = oestradiol (10 μ g).

† Solid and open blocks in Text-fig. 1.

‡ p.m. = 14.00 to 17.00 hours; a.m. = 09.00 to 10.00 hours.

started to litter by the time the first 3% of the control rats started (Text-fig. 1, Group 2). About 5% littered later than normal; one rat which delivered six dead pups on Day 25 is not shown. When oestradiol was given at 09.30 hours on Day 21, it caused about a third of the rats to litter earlier and a similar number to litter later than the controls (Text-fig. 1, Group 3).

In marked contrast to rats treated on Day 21, none of the rats given oestradiol

on Day 20 littered during the first half of the normal range (Text-fig. 1, Groups 4, 5 and 6); about 90% started to litter between 08.00 and 16.00 hours on Day 23. All forty-five rats dosed at 12.00 hours (Text-fig. 1, Group 5) started to litter within an interval of 10 hr compared with the 33 hr of the controls. Of the rats which received oestradiol on Day 20, two (10%) were delayed beyond the normal range and two were slightly delayed; all four were treated at 17.00 hours (Text-fig. 1, Group 4).

A small group of rats treated with oestradiol at 17.00 hours on Day 19 showed a more normal distribution of times of onset of littering (Text-fig. 1, Group 7); four of the five rats littered during the first half of the normal range.

These results clearly demonstrate that small doses of oestradiol given late in pregnancy to intact rats can influence the time at which parturition starts. The effect of oestradiol is not so much to advance or delay parturition in all rats, but more to change the distribution of the times of onset. It is also clear that the time at which oestradiol is administered has a crucial bearing on its effect on the timing of parturition.

Effects of $\text{PGF}_{2\alpha}$

The aim of this study was to determine in which circumstances exogenous $\text{PGF}_{2\alpha}$ might affect the time of parturition without adversely affecting the course of labour. The $\text{PGF}_{2\alpha}$ was given intraperitoneally on Days 19, 20 or 21, usually in two or four doses of 25 μg , alone or before or after treatment with oestradiol.

When given on Day 21, the principal effect of $\text{PGF}_{2\alpha}$ was to shorten the period during which the rats started to litter (Text-fig. 1, Group 8). This was also the effect on rats given oestradiol on Day 21 either before or after the $\text{PGF}_{2\alpha}$ (Text-fig. 1, Group 9). The more compact period of littering was achieved primarily by advancing parturition in those rats which otherwise, presumably, would have littered during the later part of the normal range. Parturition in the 'earlier' rats was only slightly advanced.

On Day 20, $\text{PGF}_{2\alpha}$ caused premature parturition in almost all the rats (Text-fig. 1, Group 10); littering spanned only 10 hr but nine of the ten rats started to litter between 03.00 and 08.00 hours. Treatment with oestradiol on Day 21 following $\text{PGF}_{2\alpha}$ treatment on Day 20 caused a further advance of parturition in a few animals (Text-fig. 1, Group 11).

When oestradiol and $\text{PGF}_{2\alpha}$ were both given on Day 20, a more normal distribution of times of littering occurred (Text-fig. 1, Group 12). At the dose given ($2 \times 25 \mu\text{g}$), $\text{PGF}_{2\alpha}$ thus appears to nullify the parturition-delaying effect which oestradiol exerts on the normally early littering rats (see Text-fig. 1, Group 5).

These results and the observation that anti-inflammatory agents administered on Days 20 and 21 delay parturition in the rat (Chester *et al.*, 1972) suggested that part of the sequence of events leading to parturition involves the production of PGs about 48 hr before its onset. The function of the PGs is to cause rapid luteal regression, after which an oestrogen-controlled phase of preparatory changes precedes parturition. To test the validity of this hypothesis,

a group of rats was dosed with $\text{PGF}_{2\alpha}$ on Day 19, a day in advance of the time when endogenous PG production probably begins. Oestradiol was then given to some of these rats on Day 20 to see whether parturition with normal labour would follow on Day 21.

The rats given $\text{PGF}_{2\alpha}$ alone littered prematurely, as expected, over a period from 11.00 hours on Day 20 to 21.00 hours on Day 21 (Text-fig. 1, Group 13). The rats which received oestradiol on Day 20 also littered prematurely but the scatter in the times at which premature parturition began was reduced (Text-fig. 1, Group 14).

Effects of oestradiol and $\text{PGF}_{2\alpha}$ on the course of labour

The frequency (every 1 or 2 hr) at which the rats were inspected did not allow us to obtain precise information on the duration of littering, though it would have revealed any significant prolongation in the treated animals. Prolongation of labour was, in fact, seen in only a very few instances. It was our impression that the duration of littering was within the normal range (about 1 to 2 hr) in each of the treated groups and that, in general, the course and outcome of labour was similar to that in the control rats. The only exceptions were the three rats treated with oestradiol on Day 21 in which littering was delayed until late on Day 24 or Day 25 and the rats treated with $\text{PGF}_{2\alpha}$ on Day 19 which littered more than 24 hr prematurely. The rats which went into labour very late bled extensively and delivered mainly still-born young; the rats which were induced to litter early on Day 21 also delivered a high proportion of still-born young, but these were clearly immature.

Effect of fenclozic acid on the course of labour

In order to investigate the possible involvement of endogenous PGs in the process of parturition itself, we examined the effect on the time and course of parturition of an anti-inflammatory agent, fenclozic acid (ICI 54,450; Newbould, 1969), administered shortly before the expected time of delivery.

Anti-inflammatory agents have been shown to inhibit PG synthesis in several experimental preparations (Vane, 1971; Smith & Willis, 1971; Ferreira, Moncada & Vane, 1971), and, when given on Days 20 and 21, they delay parturition in the rat (Chester *et al.*, 1972). In a normal group of rats it is not possible to anticipate the times at which the individual animals will litter and it is therefore difficult to decide when to administer agents that might interfere with the course of parturition. As shown above, however, rats treated with oestradiol on Day 20 are much more predictable in this respect and were therefore used. All the rats treated with fenclozic acid and oestradiol (Text-fig. 1, Group 15) gave birth normally to live young at the same times as the oestradiol-treated controls (Text-fig. 1, Group 5). Fenclozic acid has a serum half-life of 24 hr and its absorption by the oral route is rapid (Platt, 1971); the dose employed was over ten times its effective anti-inflammatory dose level (Newbould, 1969) and the apparent lack of effect on the time and course of parturition is therefore unlikely to be due to inadequate blood levels of the compound.

DISCUSSION

Csapo & Wiest (1969) and Wiest (1970) described the changes in levels of progesterone and 20α -hydroxypregn-4-en-3-one (20α -OH-P) during pregnancy in the rat. In rats which littered on Day 23 (our numbering), a significant fall in the plasma and uterine levels of progesterone occurred between Days 20 and 21 and a more rapid fall between Days 21 and 22, whereas the plasma level of 20α -OH-P rose sharply between Days 21 and 22. Wiest (1969), however, showed that 20α -OH-P itself is not a trigger to parturition.

Yoshinaga, Hawkins & Stocker (1969) reported that oestrogen levels in the ovarian venous plasma of pregnant rats rose very gradually from an undetectable level on Day 10 until Day 20 when they rose a little more rapidly until Day 22 and then approximately threefold before parturition on Days 23 to 24. Studies in ovariectomized rats (Jost, 1959; Csapo, 1969; Catala & Deis, 1973) have clearly demonstrated that oestrogen is essential for parturition in the rat; in its absence parturition is delayed and protracted. Our results demonstrate that in intact rats also oestradiol can affect the timing of parturition.

The particular events and factors which regulate these hormonal changes in the rat are not well understood. In ruminants such as the goat (Thorburn, Nicol, Bassett, Shutt & Cox, 1972) and sheep (Liggins, Grieves, Kendall & Knox, 1972; Thorburn *et al.*, 1972), the fetus evidently initiates the events which lead to parturition. In the rat, however, neuroendocrine processes in the female probably determine the time of parturition (see Davies & Ryan, 1972). Our results do not identify the event that ultimately determines the time of parturition in the rat but do, we believe, shed some light on its timing and on the subsequent course of events leading up to delivery. To explain the normal distribution of onset of parturition in our rats and the changes brought about by various treatments, we suggest, firstly, that after the critical initiating event, the preparatory changes leading to parturition take place at about the same rate in most normal rats and so the variation in onset of parturition in such animals is due to a variation in the time at which that critical event occurs. Our results suggest that it occurs in different rats at different times between late evening on Day 20 and early evening on Day 21, about 45 hr in advance of parturition.

The first phase of the preparations for parturition involves, we believe, the production of PGs (probably $\text{F}_{2\alpha}$) which rapidly terminate luteal function causing progesterone levels to fall rapidly and 20α -OH-P levels to rise. The luteal regression caused by exogenous $\text{PGF}_{2\alpha}$ in early pregnancy or pseudo-pregnancy in the rat has been shown to be accompanied by a rise in 20α -OH-P levels (Pharriss & Wyngarden, 1969; Behrman, Yoshinaga, Wyman & Greep, 1971). We believe that a second, oestrogen-dependent, phase of preparations is then initiated when progesterone falls below a critical level and the rising oestrogen levels attain a critical level. Final preparation of the uterus and cervix (Bryant, Greenwell & Weeks, 1968; Datta, Karkun & Kar, 1968) probably takes place during this second phase to permit smooth delivery.

Exogenous oestrogen clearly has one of two effects in the rat in late pregnancy: it can either advance or retard parturition. Oestradiol has been shown to be

luteotrophic in the rat (see Greenwald & Rothchild, 1968, for references) and exogenous luteotrophins have been shown to antagonize the luteolytic effect of exogenous $\text{PGF}_{2\alpha}$ in pregnant hamsters (Johnston & Hunter, 1970) and rats (Behrman, Yoshinaga & Greep, 1971; Chatterjee, 1972). The retarding effect of oestradiol on parturition may be due to this luteotrophic action, though the possibility that it may suppress endogenous PG production or delay the critical initiating signal cannot be discounted. In any event, the extent of the delay in the onset of parturition will depend on how close to luteolysis the rats are when the oestrogen is given. If, at the time of dosing, biosynthesis of PGs is only just starting, the 'luteotrophic' effect of oestradiol will retard luteolysis, and parturition in these rats will be delayed accordingly. If, however, oestradiol is given too far in advance of the onset of biosynthesis of PGs, its effect will have declined before PG production begins and luteolysis will follow its normal course.

The ability of oestradiol to advance parturition probably results simply from accelerating the attainment of the level needed to initiate the second phase of preparations. This action of oestradiol will therefore only be expressed in rats in which luteolysis is in progress. Again, the degree of effect will depend upon the extent of luteolysis in the rats at the time of dosing. In rats in which progesterone levels have been depressed close to or below the critical level, exogenous oestradiol will advance the second phase of preparations and littering will be brought forward. In rats in which luteolysis is less far advanced, the higher progesterone levels will block the effect of the oestradiol and the time of littering will be unaffected.

If, as we suggest, the initiating event leading to parturition does not occur simultaneously in all the rats in a group, the group cannot be regarded as a uniform population from Day 20 until parturition. At 17.00 hours on Day 20, luteolysis is probably in progress in only a few animals but imminent in many. In these animals—which, if untreated, would litter early in the normal range—exogenous oestradiol on Day 20 would be expected to retard luteolysis, causing them to litter at a later time in the normal range. Up to about 12.00 hours on Day 21, a group of rats will comprise some rats in which luteolysis is advanced (those which normally litter early), others in which luteolysis has been in progress for a shorter time and some in which luteolysis has yet to start (those which litter late in the normal range). After oestradiol treatment on Day 21, parturition in the first sub-group of rats will be advanced (since progesterone levels are already low), largely unaffected in the second sub-group, and delayed beyond the normal range in the third sub-group in which oestradiol will delay luteolysis. At 09.30 hours on Day 21, our rats appeared to be about evenly distributed between the three sub-groups while by 12.00 hours over half the rats responded to oestradiol with advanced parturition and fewer than 10% were delayed.

The effects of exogenous $\text{PGF}_{2\alpha}$ also broadly support our hypotheses. Given on Day 19 or 20, $\text{PGF}_{2\alpha}$ evidently initiated luteolysis in all the rats, causing them to litter prematurely about 36 to 40 hr later. The greater spread of times of littering of the rats treated on Day 19 was reduced by additional oestrogen treatment on Day 20 and probably reflects the normally lower endogenous

oestrogen levels on Days 20 to 21. When given to normal or to oestradiol-treated rats on Day 21, PGF_{2α} appeared to expedite luteolysis in those rats in which endogenous luteolysis started late (the only rats affected were those which would otherwise have littered late); it did not significantly advance parturition in the majority. All the effects of PGF_{2α} can be explained in terms of luteolytic action.

The failure of a large dose of fenclozic acid, a potent anti-inflammatory agent, given close to the expected time of parturition, to interfere in any way with the normal progress of littering or with the viability of the young argues strongly that active biosynthesis of PGs is not essential for the parturient activity of the uterus.

From observations on the duration of littering and mortality of the young in rats treated with various anti-inflammatory agents, Aiken (1972) concluded that PGs were probably not involved in the timing of parturition but were necessary for its smooth progress. However, in Aiken's experiments the day of pregnancy when treatment was started was uncertain, as also was the day of parturition. Also, dosing was continued daily until delivery. In a similar study, Chester *et al.* (1972) showed that anti-inflammatory agents given on Days 20 and 21 can delay the mean time of onset of parturition of a group of rats by more than 24 hr compared with untreated rats. In our experience, when parturition is delayed by 24 hr or more beyond the normal range, the rats suffer prolonged and difficult labour whatever the treatment responsible for the delay.

Our results lead us to believe that the rôle of PGs in late pregnancy in the rat is to reorganize the prevailing steroid hormone levels in preparation for parturition and not to stimulate the uterus during parturition. This view accords with the observations of Fuchs (1972) that, although intravenous infusions of PGF_{2α}, PGE₁ or PGE₂ on Days 21 and 22 demonstrably provoke uterine contractions, they do not induce littering but cause a high incidence of fetal death. Only oxytocin, infused during the afternoon on Day 22, successfully induced littering.

In summary, we suggest that a sequence of changes occurs during the last 48 hr of pregnancy in the rat before it is in a condition to allow smooth delivery of the young. Endogenous PGs are probably instrumental during the first part of this sequence in reorganizing the steroid hormone levels to permit oestrogens to initiate the final preparations for parturition. The action elicited by exogenous oestradiol on Day 20 of pregnancy is probably a pharmacological effect since endogenous oestrogen levels are low at this time. On Day 21, however, exogenous oestradiol most probably augments the physiological action of oestradiol, endogenous levels of which are rising by this time.

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