THE EFFECTS OF DEXAMETHASONE AND INDOMETHACIN ON THE OUTCOME OF PREGNANCY IN THE RABBIT

J. R. G. CHALLIS,* I. J. DAVIES AND K. J. RYAN

Harvard Medical School, Department of Obstetrics and Gynecology, Laboratory of Human Reproduction and Reproductive Biology, 45 Shattuck Street, Boston, Massachusetts 02115, U.S.A.

(Received 24 June 1974)

SUMMARY

Pregnant rabbits were treated with indomethacin (8–10 mg/kg/day) or dexamethasone (1.2–1.8 mg/kg/day) during late gestation. The effects of these treatments on the concentrations of progesterone and prostaglandin F (PGF) in the peripheral plasma, and the outcome of gestation were studied. Treatment with indomethacin significantly prolonged the length of gestation ($P < 0.01$) compared with control, untreated animals. In these treated animals, the plasma progesterone levels declined at a similar time to that in control rabbits but the increase in systemic PGF normally seen during late pregnancy was reduced. Dexamethasone treatment reliably induced premature delivery within 3–6 days. The plasma progesterone concentration fell rapidly during the first 24 h of dexamethasone administration, but in no animal was this associated with a significant increase in the plasma levels of PGF.

These results are consistent with the suggestion that prostaglandins are involved in the normal initiation of parturition in the rabbit. They do not support the hypothesis that the effect of dexamethasone on the length of gestation is mediated through an increase in the production of prostaglandin F.

INTRODUCTION

Prostaglandin F2α (PGF2α) is luteolytic when administered to pseudopregnant rabbits, and causes a marked decline in luteal weight and in progesterone secretion (Gutknecht, Duncan & Wyngarden, 1970; Scott & Rennie, 1970). In addition, indomethacin, an inhibitor of prostaglandin synthesis, prolongs the functional lifespan of the corpus luteum in pseudopregnant rabbits (O'Grady, Caldwell, Auletta & Speroff, 1972). Similar effects of exogenous prostaglandin have been reported in pregnant rabbits. Following the administration of PGF2α to animals during the final third of pregnancy, there is a rapid decline in the concentration of progesterone in the peripheral plasma (Abel, Taurog & Nathanielsz, 1973; Challis, Porter & Ryan,

injection. Pregnancy

Rabbit

dexamethasone

about

intake

Behrman,

preparturient

Abel,

dexamethasone.

gestation.

to

plasma

PGF2α,

1973).

pregnancy

of

previously

depressed

prostaglandin

in

rabbits

the

in

rabbits.

Abortion

Twelve


Further
evidence

PGF2α

rabbits

demonstrated

prostaglandins

the

series

of

pregnancy,

mid-

reach

highest

values

immediately

prior

coincident

with,

decline

concentration

plasma

progesterone

(Challis,

Davies

Ryan,

1973a).

present

experiments

we

have

attempted

block

increase

progesterone

plasma

administered

indomethacin,

and

effects

treatment

plasma

progesterone

levels

outcome

gestation.

Several

investigators

have

shown

administration

cortisol

dexamethasone

to

rabbits

during

final

third

gestation

results

a

decline

concentration

progesterone

plasma,

pregnancy

delivery

of

foetuses

(Adams

Wagner,

1969;

Kendall

Liggins,

1972;

Abel

et

al.

1973;

Nathanielsz

Abel,

1973;

Nathanielsz

et

al.

1973).

Because

exogenous

cortisol

depresses

progesterone

concentration

lower

than

does

PGF2α,

has

been

proposed

that

glucocorticoid

act

stimulating

PGF2α

(Challis

et

al.

1973),

suggesting

other

species

(Liggins

Grieves,

1971).

In

order

examine

hypothesis,

we

have

measured

levels

progesterone

and

prostaglandin

in

plasma

premature

delivery

induced

rabbits

administration

dexamethasone.

MATERIALS

METHODS

Animals

Twenty-four

pregnant

New

Zealand

White

rabbits

(supplied

White

Tree

Rabbit

Co.,

East

Douglas,

Mass.)

were

used

study.

animals

had

mated

with

a

fertile

buck

for

period

5–30

min,

and

day

mating

designated

day

zero

of

pregnancy.

The

animals

were

randomly

assigned

to

one

of

five

groups.

Group

I

(6

rabbits)

received

no

treatment

served

as

controls.

concentrations

progesterone

PGF

plasma

these

animals

reported

previously

(Challis

et

al.

1973a).

Group

II

(3

rabbits)

received

indomethacin

(kindly

donated

Dr

H. R.

Behrman,

Merck

Institute,

Rahway,

New

Jersey),

8

mg/kg,

s.c.,

days

23–28

pregnancy.

Group

III

(3

rabbits)

received

indomethacin,

8

mg/kg,

s.c.,

days

29–31

pregnancy.

Group

IV

(4

rabbits)

received

indomethacin

added

drinking

water

concentration

80

μg/ml

from

day

20

until

delivery.

Daily

intake

water

monitored,

rabbits

drank

all

500

ml

water

provided

24

h.

Total

daily

intake

indomethacin

40

mg

(i.e.

approximately

8–10

mg/kg/day).

Group

V

(8

rabbits)

received

dexamethasone

(Decadron

phosphate,

Merck,

Sharpe

Dohme,

West

Point,

Pa.),

6

mg/day,

i.m.,

from

day

21

pregnancy

delivery.

The

animals

bled

lateral

ear

vein

at

1- to

2-day

intervals

during

pregnancy

previously

(Challis

et

al.

1973a).

Blood

samples

were

taken

3–4

h

intervals

four

animals

Group

V

day

first

dexamethasone

injection.

blood

collected

chilled

heparinized

tubes,

centrifuged

immedi-
Pregnancy in rabbits

ately at 4 °C, and the plasma was stored at −15 °C until analysis. Each animal’s haematocrit was checked regularly, and in no instance did the packed cell volume fall below 40%.

Hormone measurements

Progesterone was measured in 0.1 ml volumes of plasma using a radioimmunoassay procedure previously described (Challis, Davies & Ryan, 1973b; Erickson, Challis & Ryan, 1974). Prostaglandin F was measured by radioimmunoassay after its chromatographic separation from prostaglandins of the other series using micro-silic acid columns (Challis et al. 1973a).

RESULTS

Indomethacin treatment

The effect of subcutaneous injections of indomethacin (Groups II and III) on increasing the length of gestation was only marginally significant (Table 1). However, analyses of the plasma samples obtained from animals in these two groups showed that the indomethacin treatment had been ineffective in suppressing the concentration of plasma PGF. The changes in the concentrations of PGF and progesterone in the plasma of these rabbits were similar to those seen in the control group.

Table 1. The effects of indomethacin and dexamethasone on length of gestation in the rabbit (means ± s.d.)

<table>
<thead>
<tr>
<th>Group no. and treatment†</th>
<th>No. of animals</th>
<th>Length of gestation (days)</th>
<th>No. of foetuses:</th>
<th>Average foetal wt (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alive</td>
<td>Dead</td>
</tr>
<tr>
<td>I. No treatment</td>
<td>6</td>
<td>31.5 ± 0.6</td>
<td>7.8 ± 4.1</td>
<td>1.0 ± 2.4</td>
</tr>
<tr>
<td>II. Indomethacin (s.c., day 23–28)</td>
<td>3</td>
<td>32.5 ± 0.5*</td>
<td>6.0 ± 2.6</td>
<td>1.0 ± 1.0</td>
</tr>
<tr>
<td>III. Indomethacin (s.c., day 29–31)</td>
<td>3</td>
<td>32.2 ± 0.6</td>
<td>7.7 ± 0.6</td>
<td>0.7 ± 0.6</td>
</tr>
<tr>
<td>IV. Indomethacin (p.o., day 20 to term)</td>
<td>4</td>
<td>33.4 ± 0.8**</td>
<td>7.0 ± 5.0</td>
<td>4.8 ± 3.8</td>
</tr>
<tr>
<td>V. Dexamethasone (from day 21)</td>
<td>8</td>
<td>25.9 ± 1.1***</td>
<td>0</td>
<td>6.8 ± 0.8***</td>
</tr>
</tbody>
</table>

* P < 0.05 v. Group I; ** P < 0.01 v. Group I; *** P < 0.001 v. Group I. † s.c. = subcutaneous; p.o. = by mouth.

In animals receiving indomethacin in their drinking water (Group IV), the average length of gestation was significantly longer than in the control group (P < 0.01). The mean weight of the individual live foetuses was not significantly different from that of Group I, although the treated animals (Group IV) had, on average, larger litters. One rabbit died on day 33 of the indomethacin treatment. At autopsy she had ten dead foetuses, none of which was macerated. We have taken 33 days as the length of gestation in this animal, but have omitted the hormone data obtained from her.

The mean levels of progesterone and PGF in the rabbits in Group IV and control animals (Group I) are shown in Fig. 1. In the control group, the concentration of plasma PGF increased significantly between days 21 and 30 of pregnancy (P < 0.001; Challis et al. 1973a), whilst in the indomethacin-treated group this increase in PGF
was not seen, and the concentrations of plasma PGF remained at about 300 pg/ml for the remainder of gestation. The plasma progesterone concentration began to decline in both groups of animals on days 28–30 (Fig. 1). In the indomethacin-treated rabbits, the concentration of plasma progesterone remained at 2.5–3.0 ng/ml for an additional 1–2 days, before delivery occurred.

Fig. 1. The concentrations of progesterone (○) and prostaglandin F (●) in the peripheral plasma of (a) untreated pregnant rabbits (Group I, calculated from Challis et al. 1973a), and (b) pregnant rabbits receiving indomethacin during the period indicated by the horizontal bar (Group IV). The values are means ± s.e.m. of 4–7 animals in Group I, and of 3 rabbits in Group IV. The vertical lines labelled P indicate the mean length of gestation in the two groups.

Dexamethasone treatment

High doses of dexamethasone injected daily into pregnant rabbits beginning on day 21 after mating always resulted in premature delivery of the foetuses within 4–6 days (Table 1). In these animals (Group V) there was a dramatic drop in the concentrations of plasma progesterone during the first 24 h of dexamethasone treatment. Because a daily sampling regimen revealed no increase in the levels of PGF in the plasma in four animals treated with dexamethasone, a further four animals were bled more frequently during the first 24 h of treatment. As shown in Fig. 2, the levels of plasma PGF were remarkably constant in individual rabbits during this period, and in no animal was there any indication that the decline in progesterone resulting from the dexamethasone treatment was associated with elevated levels of plasma PGF.
Fig. 2. The effect of daily i.m. dexamethasone on the concentrations of progesterone (○) and prostaglandin F (●) in the peripheral plasma of four rabbits during late pregnancy. P indicates the day on which delivery occurred.

DISCUSSION

These experiments have shown that indomethacin, an inhibitor of prostaglandin synthesis (Vane, 1971), is able to prolong significantly the length of pregnancy in the rabbit. This finding substantiates information available from studies on primates. In the rhesus monkey, indomethacin prolonged the length of gestation by about
20 days (Novy, Cook & Manaugh, 1974), and in human subjects undergoing mid-trimester abortion with intra-amniotic saline, the induction-abortion interval was significantly prolonged in patients treated with indomethacin (Waltman, Tricomi & Palau, 1973). These results suggest a common involvement of prostaglandins in parturition in different species. It seems significant that these species include the rabbit, in which progesterone is synthesized mainly by the corpus luteum, and primates in which progesterone is primarily of placental origin (Davies & Ryan, 1972).

It might be considered that indomethacin prolonged gestation by blocking prostaglandin-induced luteal regression. Prostaglandins cause luteolysis in pseudopregnant rabbits (Gutknecht et al. 1970; Scott & Rennie, 1970; Pharriss, Tillson & Erickson, 1972) and indomethacin will prolong pseudopregnancy (Caldwell, Speroff, Brock, Auletta, Gordon, Anderson & Hobbins, 1972; O'Grady et al. 1972). While indomethacin treatment did not completely eliminate circulating PGF, and this low level of PGF might induce luteal regression (Nathanielsz et al. 1973), the present results give no indication that the decline in luteal function in the indomethacin-treated animals was delayed as compared with the controls.

An alternative explanation for the prolongation of pregnancy by indomethacin might be related to the inhibition of synthesis of intramyometrial prostaglandin. In the rat, indomethacin inhibited both release of prostaglandin and spontaneous contractions of the uterus (Vane & Williams, 1973). In addition, in both the rat (Vane & Williams, 1973) and the rabbit at term (Hertelendy, 1973), the myometrial contractile response to oxytocin was abolished by the administration of indomethacin. Furthermore, in the rabbit, it has been shown that progesterone inhibits the myometrial response to PGF2α (Porter & Behrman, 1971). These studies are consistent with the concept that PGF2α synthesized in the myometrium is an important component in the control of uterine contractility. The present results indicate that a fall in the level of plasma progesterone, which reflects changes in the concentration of myometrial progesterone (Challis, Davies & Ryan, 1974), is inadequate per se to induce parturition. In both the indomethacin-treated animals and the dexamethasone-treated animals, pregnancy continued for a period of days after progesterone concentrations had declined to levels normally associated with parturition.

The present results provide no support for the hypothesis that the abortifacient action of dexamethasone or cortisol is mediated through an increase in the levels of PGF in the plasma which, in turn, cause luteolysis. In none of the eight rabbits treated with dexamethasone was an increase in PGF noted. Even allowing for the probably intermittent nature of prostaglandin release (Thorburn, Cox, Currie, Restall & Schneider, 1972), the number of samples studied makes an increase in plasma PGF unlikely. An alternative explanation might be that dexamethasone acts directly on production of ovarian progesterone, resulting in the very rapid decline in levels of plasma progesterone seen during the first 24 h of treatment. In the sheep placenta, it has been suggested that dexamethasone treatment increases the catabolism of pregnenolone and progesterone (Anderson, Flint & Turnbull, 1974), and a similar effect on corpus luteum function in the pregnant rabbit might be considered.

We are indebted to Dr H. R. Behrman (Merck Institute) for the indomethacin, to Dr J. E. Pike (Upjohn Co.) for authentic prostaglandins and to Drs B. V. Caldwell
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(Yale University) and D. Tulchinsky (Boston Hospital for Women) for antisera. We thank Ms Jodie Schabort, Ms Trudy Lanman and Ms Julie Siu for their fine technical assistance and Mr J. Senier and Ms J. Borden for help with the animals.

This work was supported by United Cerebral Palsy Grant No. R-226-72, and a postdoctoral fellowship from United Cerebral Palsy to J.R.G.C.

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