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

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(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,

1974), followed by involution of the corpus luteum (Koering & Kirton, 1973). Abortion occurs after 35–40 h of PGF2α infusion (Nathanielsz, Abel & Smith, 1972, 1973). Further evidence that PGF2α might be implicated in regression of the corpora lutea in pregnant rabbits was provided by the demonstration that the levels of prostaglandins of the F series in the systemic plasma increase gradually after mid-pregnancy to reach their highest values immediately prior to, or coincident with, the preparturient decline in the concentration of plasma progesterone (Challis, Davies & Ryan, 1973a). In the present experiments we have attempted to block this increase in prostaglandin production by the administration of indomethacin, and report the effects of this treatment on the plasma progesterone levels and the outcome of gestation.

Several investigators have shown that the administration of cortisol or dexamethasone to rabbits during the final third of gestation results in a decline in the concentration of progesterone in the plasma, and in premature delivery of the foetuses (Adams & Wagner, 1969; Kendall & Liggins, 1972; Abel et al. 1973; Nathanielsz & Abel, 1973; Nathanielsz et al. 1973). Because exogenous cortisol depresses the plasma progesterone concentration more slowly than does PGF2α, it has been proposed that the glucocorticoid might act by stimulating the production of PGF2α (Abel et al. 1973), as suggested in other species (Liggins & Grieves, 1971). In order to examine this hypothesis, we have measured the levels of progesterone and prostaglandin F in the plasma during premature delivery induced in rabbits by the administration of dexamethasone.

MATERIALS AND METHODS

Animals

Twenty-four pregnant New Zealand White rabbits (supplied by White Pine Tree Rabbit Co., East Douglas, Mass.) were used in this study. The animals had been mated with a fertile buck for a period of 5–30 min, and the day of mating was designated as day zero of pregnancy.

The animals were randomly assigned to one of five groups. Group I (6 rabbits) received no treatment and served as controls. The concentrations of progesterone and PGF in the plasma in these animals has been reported previously (Challis et al. 1973a). Group II (3 rabbits) received indomethacin (kindly donated by Dr H. R. Behrman, Merck Institute, Rahway, New Jersey), 8 mg/kg, s.c., from days 23–28 of pregnancy. Group III (3 rabbits) received indomethacin, 8 mg/kg, s.c., from days 29–31 of pregnancy. Group IV (4 rabbits) received indomethacin added to the drinking water at a concentration of 80 μg/ml from day 20 until delivery. The daily intake of water was monitored, and the rabbits invariably drank all of the 500 ml of water provided every 24 h. The total daily intake of indomethacin was therefore about 40 mg (i.e. approximately 8–10 mg/kg/day). Group V (8 rabbits) received dexamethasone (Decadron phosphate, Merck, Sharpe and Dohme, West Point, Pa.), 6 mg/day, i.m., from day 21 of pregnancy until delivery.

The animals were bled from a lateral ear vein at 1- to 2-day intervals during pregnancy as previously described (Challis et al. 1973a). Blood samples were taken at 3–4 h intervals from four animals in Group V on the day of the first dexamethasone injection. The blood was collected in chilled heparinized tubes, centrifuged immedi-
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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-silicic 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>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.

![Graph showing concentrations of progesterone and prostaglandin F in plasma](image)

**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.

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**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 prosta-glandin-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.

REFERENCES


