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PERIPHERAL PLASMA LEVELS OF OESTROGEN
AND PROGESTERONE IN PREGNANT RHESUS MONKEYS
TREATED WITH DEXAMETHASONE

By
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ABSTRACT

The effect of dexamethasone1) on the peripheral plasma levels of the sex
steroids was investigated in four pregnant monkeys during six treatments
at the end of the second and third trimesters. A daily dose of 10 mg
dexamethasone was administered intramuscularly into each pregnant
monkey for three days. All the treated monkeys delivered normal healthy
babies within the expected time of parturition. A decrease in oestrogens and an increase in progesterone in the peri-
pheral blood plasma were observed during the dexamethasone treat-
ment. The increase in the peripheral plasma levels of progesterone ob-
served was greater in the monkeys treated at the end of the second
trimester. The peripheral plasma levels of 17α-hydroxyprogesterone were
very low and showed no change in any of the pregnant monkeys treated
with dexamethasone.

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1) The following abbreviations and trivial names are used:
Progesterone: 4-pregnene-3,20-dione
17α-hydroxyprogesterone (17-OHP): 17α-hydroxy-4-pregnene-3,20-dione
Oestradiol-17β: 1,3,5(10)-oestratriene-3,17β-diol
Oestrone: 3-hydroxy-1,3,5(10)-oestratrien-17-one
Dexamethasone: 9α-fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-
3,20-dione
Clinical and experimental studies in ruminants have revealed the importance of corticosteroids in the termination of pregnancy (Liggins 1969; Fylling 1971; Edqvist et al. 1972). The importance of the adrenals in the maintenance of pregnancy and their contribution to steroidogenesis in the rhesus monkey has not yet been fully evaluated. Limited reports exist on the plasma and urinary levels of corticosteroids or their metabolites during pregnancy in the rhesus monkey. The maternal urinary and plasma hydrocortisone showed no increase (Solomon & Leung 1971) and no changes were found in the plasma 17-hydroxysteroids during the course of gestation in this species (Wolf & Bowman 1966).

The present report deals with the effects of dexamethasone administration on the course of pregnancy and the peripheral plasma levels of oestrogen, progesterone and 17α-hydroxyprogesterone in pregnant rhesus monkeys.

**MATERIAL AND METHODS**

Four pregnant rhesus monkeys with accurate records of mating were used. The breeding, husbandry and blood sampling technique have been previously described (Bosu et al. 1972). The length of the gestation period was determined from the day of onset of the last menstrual flow (L.M.F.). Day 14 of the fertile cycle was considered as Day 1 of pregnancy. Blood samples were collected twice daily (9 a.m. and 3 p.m.) during the experimental period. Dexamethasone 10 mg (dexamethasone sodium phosphate), Decadron®, Merck, Sharp & Dohne, Netherland N. V., Haarlem, Netherlands), was administered intramuscularly daily for 3 days to all animals immediately after the morning blood sampling. Two pregnant rhesus monkeys were treated beginning from Day 113 and 114 after the last menstrual flow (101st and 101st day of gestation) and four animals, including the previous two were treated with dexamethasone starting from Day 163 and 164 after the last menstrual flow (Day 150 and 151 of gestation) (Table 1).

The peripheral plasma levels of immunoreactive oestrogens, hereafter referred to as oestrogens were determined using a rapid radioimmunoassay method (Edqvist & Johansson 1972). The oestradiol-17β and oestrone concentrations in the samples were quantitated by a radioimmunoassay method after separation and purification on Sephadex LH-20 columns. Plasma volumes used ranged between 100 and 200 µl. The values of oestrogens, oestradiol-17β and oestrone reported here have not been corrected for extraction or procedural losses.

Peripheral plasma progesterone and 17α-hydroxyprogesterone were determined by a competitive protein binding method subsequent to column separation and purification on hydrophobic Sephadex (Holmdahl & Johansson 1972). Each determination required 500 µl of plasma and the results reported have been corrected for procedural losses.

The effect of dexamethasone in the radioimmunoassay and the competitive protein binding was investigated in the following manner. For the radioimmunoassay duplicate standard curves for oestradiol-17β (0–250 pg), oestrone (0–250 pg) and dexamethasone (0–500 ng) were prepared. In another set of standard curves for oestradiol-17β and oestrone, 100 ng of dexamethasone was added at each point. Radioimmunoassay was
then performed. Similar experiments were performed to test the effect of dexamethasone on the competitive protein binding method. Dexamethasone did not cross-react or interfere in either the radioimmunoassay or the competitive protein binding methods. Known quantities of dexamethasone were added to plasma samples before the extraction step in order to evaluate the influence of dexamethasone on the plasma levels of the steroids in vitro. There were no differences in the steroid concentrations in the samples with or without dexamethasone. The possibility of competition between dexamethasone and the sex steroids for the sex binding globulin in peripheral plasma of pregnant rhesus monkeys was investigated. The ability of dexamethasone to displace \([1,2,6,7-^3\text{H}]\text{testosterone}\) from monkey sex binding globulin was tested in the following manner. A sex binding globulin containing 400 \(\mu\text{l}\) \([1,2,6,7-^3\text{H}]\text{testosterone} + 100 \(\mu\text{l}\) phosphate buffer + 1 ml late pregnancy plasma was prepared. Duplicate standard curves were prepared for testosterone (0-5 ng), oestradiol-17\(\beta\) (0-2.5 ng) and dexamethasone (1-500 ng) and to each point of the standard curves for testosterone and oestradiol-17\(\beta\), 100 ng of dexamethasone was added. Dexamethasone tested in the form in which it was administered to the animals did not displace the sex steroids from the sex binding globulin.

![Graph of steroid concentrations](image)

**Fig. 1.**

Peripheral plasma concentration of oestrogen, oestradiol-17\(\beta\), oestrone and progesterone during dexamethasone treatment at the end of the second trimester in a pregnant rhesus monkey.
The administration of dexamethasone in the schedule described above to pregnant rhesus monkeys at the end of the second and third trimesters did not cause abortion or premature parturition. Normal living babies were delivered uneventfully in all the treated animals (Table 1).

The results of oestrogen, oestradiol-17β, oestrone and progesterone measurements in peripheral maternal plasma during the dexamethasone treatment are shown in Figs. 1–6. The plasma level of oestrogens before dexamethasone treatment in the pregnant monkeys ranged between 500 to 800 pg/ml. The levels decreased after the first day of treatment and remained lower than the pre-treatment values throughout the treatment period. Two days after the end of the treatment the oestrogen levels in all the animals had increased to pre-
Table 1.
Dexamethasone treatment in pregnant rhesus monkeys.

<table>
<thead>
<tr>
<th>Monkey No.</th>
<th>Day* of pregnancy treatment started</th>
<th>Dose of dexamethasone</th>
<th>Duration of treatment</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>100</td>
<td>10 mg im</td>
<td>Daily for 3 d</td>
<td>Part on day 160 + F 413 G</td>
</tr>
<tr>
<td>55</td>
<td>101</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
<td>168 + M 428 G</td>
</tr>
<tr>
<td>67</td>
<td>150</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
<td>159 + F 418 G</td>
</tr>
<tr>
<td>50</td>
<td>150</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
<td>166 + F 445 G</td>
</tr>
<tr>
<td>37</td>
<td>151</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
<td>160 +</td>
</tr>
<tr>
<td>55</td>
<td>150</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
<td>168 +</td>
</tr>
</tbody>
</table>

* Calculated from day 14 of fertile cycle.
+ Gestation length in normal pregnancies 158 to 176 d. Mean 166 d.
M - male baby, F - female baby.

treatment levels. The oestradiol-17β and oestrone concentrations were measured in the plasma samples obtained during five of the six treatments. The pattern of oestradiol-17β and oestrone in these animals was similar to those observed

![Graph](image)

Fig. 3.
Oestrogen and progesterone concentrations in peripheral plasma during dexamethasone treatment at the end of the third trimester in a pregnant rhesus monkey.
for oestrogen. The levels of oestradiol and oestrone were equally depressed during the dexamethasone treatment.

The peripheral plasma levels of progesterone ranged between 1.5 and 4 ng/ml before the dexamethasone treatment in the two monkeys at the end of the second trimester (Figs. 1 and 2). The plasma levels of progesterone in both monkeys increased after the first treatment and remained higher than the pre-treatment levels throughout the treatment period. Discontinuation of treatment was followed by a decrease in the progesterone levels to the pre-treatment level within two days. The plasma progesterone levels in the four monkeys showed individual variations during treatment at the end of the third trimester. The levels of progesterone in plasma were either identical to (Figs. 4 and 5) or slightly higher (Figs. 5 and 6) than the pre-treatment levels.

Peripheral plasma concentrations of oestrogen, oestradiol-17β, oestrone and progesterone during dexamethasone treatment at the end of the third trimester in a pregnant rhesus monkey.

Fig. 4.
DISCUSSION

The failure of dexamethasone administration in pregnant rhesus monkeys to influence the course of pregnancy observed in this study is similar to the observations in pregnant women on dexamethasone treatment (Warren & Cheatum 1967; Fylling 1972). In ruminants corticosteroid treatment at comparable stages of gestation results in abortion, foetal death or premature parturition (Fylling 1971; Edqvist et al. 1972). These observations and the present findings indicate the comparative difference of corticosteroids in the termination of pregnancy in primates and ruminants. The decreases in the plasma levels of oestrogens during dexamethasone treatment observed in this study are similar to the decrease in urinary oestrogen excretion in pregnant women during corticosteroid treatment (Warren & Cheatum 1967). In cows treated with dexamethasone in late gestation, increases in the oestrone levels in the plasma were observed (Edqvist et al. 1972).

During corticosteroid treatment in pregnant women the plasma levels of
progesterone have been reported to remain within the normal range (Fylling 1972). In ruminants dexamethasone administration caused decreases in the plasma levels of progesterone prior to the induced premature parturition (Edqvist et al. 1972; Fylling 1971). In the pregnant monkeys treated at the end of the second trimester the progesterone levels increased to levels far above the concentrations observed in normal pregnant animals (Bosu et al. 1973). On the other hand, there were no significant changes in the plasma levels of progesterone in the animals treated at the end of the third trimester, similar to the finding in pregnant women (Fylling 1972). It is possible that in the present study the progesterone pattern during treatment at the end of the third trimester in comparison to treatment at the end of the second trimester in the pregnant rhesus monkeys, may have been due to increased progesterone metabolism in late pregnancy. This assumption is supported by the high urinary concentrations of progesterone metabolites in late pregnancy, i.e. concentrations higher than at any other stage of pregnancy in the rhesus monkey (Linkowski & Wolf 1972). The low levels of 17α-hydroxyprogesterone in
plasma observed in this study are similar to our earlier findings in pregnant rhesus monkeys during normal pregnancy (Bosu et al. 1973). Since the levels were around the detection limits of the method used, it was impossible to determine any effect of the dexamethasone treatment on the plasma levels of 17α-hydroxyprogesterone in pregnant rhesus monkeys.

Corticosteroids are believed to act centrally when administered to pregnant women through inhibition of ACTH production by both foetal and maternal adrenals (Oakey 1970). The present data seem to indicate that the effect of dexamethasone in pregnant rhesus monkeys might be similar. Bashore et al. (1970) have shown in the rhesus monkey that labelled cortisol injected into the maternal circulation is transported to the foetus.

In the light of the present findings the probable site and effect of dexamethasone treatment in pregnant rhesus monkeys would appear to involve inhibition of the 17α-hydroxylase enzyme system in the adrenal steroidogenic pathway, resulting in the depression of oestrogen production and increase in the progesterone levels. Blockade or inhibition of the 17α-hydroxylase system would also result in decreased utilization of progesterone for corticosteroidogenesis. In this regard progesterone has been shown to be a more efficient substrate for α-ketonic steroidogenesis in both the foetal (Kittinger & Beamer 1971) and adult rhesus female adrenals (Lantos et al. 1968). This explanation is supported by the observations in pregnant women that dexamethasone administration results in a depressed adrenal function as indicated by the diminished excretion of 17-ketosteroids and reduced levels of androgenic oestrogenic precursors. The efficiency of utilization of the precursors for oestrogen production during dexamethasone treatment, however, remains essentially unaltered (MacDonald & Siiteri 1965; Hausknecht 1965). Thus the decreased levels of total oestrogens, oestradiol and oestrone in this study may be due to a decrease in precursor supply, rather than to a decrease in the utilization of the precursors for oestrogen formation, as is clearly indicated by the identical depression of both the oestradiol and oestrone levels in the plasma during treatment.

The results of the measurements of the hormone levels during dexamethasone treatment in pregnant rhesus monkeys suggest that the adrenals play a role in steroidogenesis, though, their steroidogenic function does not appear to be essential for the maintenance of pregnancy.

In the rhesus monkey neither foetal adrenalectomy (Mueller-Heubach et al. 1972) nor total foetal removal (Dorfman & Van Wagenen 1941) seem to affect the course of pregnancy. One might conclude from the foregoing and the present results of adrenal suppression with dexamethasone in pregnant rhesus monkeys that neither the foetal nor maternal adrenals appear to play important roles in the termination of pregnancy in the rhesus monkey as appears to be the case in ruminants.
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REFERENCES


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