EFFECT OF INTRAUTERINE DEVICES ON PREOVULATORY LH AND PROGESTERONE LEVELS IN THE CYCLIC HAMSTER

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Intrauterine devices do not affect the cycle length in mice (Bartke, 1970), hamsters (Orsini, 1965; Lau, Saksena & Chang, 1974) and rats (V. D. Castracane, S. K. Saksena & A. A. Shaikh, unpublished data) but cause a delay in post-coital ovulation in rabbits (Janakiraman & Casida, 1968). Ginther, Hawk & Casida (1966) reported an increase in the pituitary LH content of ewes carrying an IUD and IUDs have been reported to block ovulation in the Indian water buffalo (Buch, Shukla & Hawk, 1964). If a similar delay in ovulation or LH discharge could be demonstrated in IUD-bearing hamsters, these animals would provide a convenient model for the study of the mechanism of action of IUDs.

Mature female golden hamsters (Mesocricetus auratus) weighing 130 to 140 g, obtained from a local breeder, were maintained at constant temperature (22 ± 1°C) and artificial lighting (07.00 to 19.00 hours). All females were examined daily for changes in vaginal discharge and were then grouped according to the stage of the oestrous cycle. At least two consecutive 4-day oestrous cycles were recorded for each animal before they were used for experiments. Under pentobarbital sodium anaesthesia, two pieces of ‘Supramid extra’ threads were inserted along the entire length of both uterine horns as described by Saksena & Harper (1974) between 09.00 and 09.30 hours on the day of pro-oestrus. The animals were then rested for two cycles. Peripheral blood samples were collected from the abdominal aorta in heparinized syringes on the day of pro-oestrus under pentobarbital sodium anaesthesia at the times indicated in Table 1. The blood was centrifuged and the plasma obtained was frozen until it was assayed for LH and progesterone.

Peripheral plasma LH concentrations were determined by radioimmunoassay adapted from the method described by Niswender, Midgley, Monroe & Reichert (1968). The LH standard (LER-1213A) as determined by radioimmunoassay was 0.48 times as potent as NIH-LH-S12. Plasma LH concentrations were assayed in 400-µl aliquots.

Ether extracts of the plasma without chromatographic separation were assayed for progesterone by radioimmunoassay (Shaikh, 1972). The antiserum used in the assay exhibited a 90%, 35% and 1.2% cross-reaction with 17α-hydroxyprogesterone, desoxycorticosterone and 20α-hydroxyprogesterone, res-
Table 1. Effect of bilateral IUDs on plasma LH, progesterone and ovulation in the cyclic hamster

<table>
<thead>
<tr>
<th>Time of blood collection at pro-oestrus (hours)</th>
<th>Control (mean ± S.E.)</th>
<th>With bilateral IUDs (mean ± S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of ova shed</td>
<td>LH (ng/ml)</td>
</tr>
<tr>
<td>10.30 to 11.45</td>
<td>—</td>
<td>8.36 ± 0.83(5)</td>
</tr>
<tr>
<td>13.00 to 13.45</td>
<td>—</td>
<td>10.32 ± 1.27(5)</td>
</tr>
<tr>
<td>16.30 to 17.15</td>
<td>—</td>
<td>391.16 ± 92.82* (8)</td>
</tr>
<tr>
<td>19.30 to 20.15</td>
<td>—</td>
<td>70.64 ± 11.20* (9)</td>
</tr>
<tr>
<td>23.15 to 00.00</td>
<td>—</td>
<td>7.84 ± 1.83(5)</td>
</tr>
<tr>
<td>03.15 to 04.00</td>
<td>10.00 ± 1.34(5)</td>
<td>5.06 ± 0.75(5)</td>
</tr>
<tr>
<td>07.30 to 08.15</td>
<td>13.00 ± 1.82(5)</td>
<td>13.38 ± 3.52(5)</td>
</tr>
<tr>
<td>16.30 to 17.15 after injection of 500 µg progesterone at 13.00</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate the number of animals used. Figures with different superscripts, a,b,c, differ significantly (P < 0.05) from each other.

* Indicates values significantly different (P < 0.05) from other groups and from each other.
respectively, but these steroids are found in very small quantities in peripheral plasma. The values reported here may, therefore, be a slight overestimate of the true progesterone values.

The results are shown in Table 1 and Text-fig. 1. The peak levels of LH in the control animals occurred between 16.30 and 17.15 hours. During this period, the LH levels in hamsters with IUDs were also significantly elevated but only reached approximately 7% of the levels observed in the controls. Between 19.30 and 20.15 hours, the LH levels in the hamsters with IUDs showed a peak while those in the control animals dropped significantly. The peak levels of LH in the experimental animals were of the same magnitude as those in the controls. Thus, there was a 2-hr difference in the occurrence of the two peaks. By 23.15 hours, the levels in the two groups of animals had dropped to the same value. The levels of progesterone in the control and experimental animals were not different at 10.30 to 11.45 and 13.00 to 13.45 hours on the day of pro-oestrus, but by 16.30 to 17.15 hours, there was a significant increase in progesterone levels in the controls. No change occurred in the experimental animals. Between 19.30 and 20.15 hours, there was a further rise in progesterone levels in the
control hamsters and also in the experimental animals which did not differ from each other. Later, the progesterone levels dropped gradually in the control and experimental hamsters.

There was no significant difference in the number of ova shed between the two groups of animals or between the two time periods when the ova were examined.

A single injection of 500 µg progesterone at 13.00 hours advanced the LH release in the experimental animals to between 16.30 and 17.15 hours and the levels of LH were four-fold higher than in the controls (Table 1 and Text-fig. 1). Ginther et al. (1966) observed that the pituitaries of ewes with IUDs had a higher content of LH as determined by the ovarian ascorbic acid depletion test. Horie, Ishikura & Matsukawa (1964) likewise reported an increase in the LH and FSH potency of the pituitaries of cattle treated with an intrauterine infusion of gel. Buch et al. (1964) inserted plastic IUDs in Indian water buffaloes and noted failure of CL development which was assumed to be due to a failure of ovulation. In the rabbits bearing IUDs, Janakiraman & Casida (1968) reported on the possibility of a delay in ovulation after mating. This assumption was based on the measurement of pituitary LH content. Makino, Yoshinaga & Greep (1972) showed an IUD-induced delay in the post-coital rise in 20α-hydroxyprogesterone. Hilliard, Penardi & Sawyer (1967) have clearly shown that, in the rabbit, the post-coital pattern of secretion of pituitary LH has a close relationship with that of ovarian 20α-hydroxyprogesterone. This indicated that the suspected delay in ovulation and the increased pituitary LH content in the animals bearing IUDs may be due to decreases or delay in the secretion of steroid hormones, which have a positive feedback effect on LH release. The effect of an IUD on CL function has been reported in guinea-pigs (Ginther, Mahajan & Casida, 1966), pigs (Gerrits & Hawk, 1966), sheep (Ginther, Pope & Casida, 1965) and cows (Ginther, Woody, Janakiraman & Casida, 1966). In pigs (Gerrits & Hawk, 1966), however, a unilaterally placed IUD affects CL development and implantation on both sides. These studies indicate that IUDs may bring about a lowering of blood progesterone levels.

The results obtained in the present study clearly demonstrate a delay in the rise of plasma progesterone levels in hamsters bearing IUDs. It could be argued that the increases of progesterone in control animals between 16.30 and 17.15 hours could be due to the stimulatory effect of LH. The progesterone pattern between 13.00 and 13.45 hours is not known. Earlier studies of Shaikh & Shaikh (1973) had revealed that secretion of progesterone by the rat adrenal reaches a peak between 14.00 and 16.00 hours. At this time, ovarian secretion of progesterone is minimal and the LH values are also at their lowest levels. We believe that progesterone of adrenal origin signals the release of pituitary LH. Indirect evidence from other studies (Lawton, 1972; Feder, Brown-Grant & Corker, 1971; Nequin & Schwartz, 1971) also indicates involvement of adrenal progesterone in the facilitation of ovulation. It has been shown in hamsters that oestrogen is necessary for the ovulatory discharge of LH (Labhssetwar, 1972). The possibility that IUDs may have an effect on the circulating oestrogen levels either by affecting the steroid secretion by the ovary or by stimulating increased oestrogen uptake by the uterus (Labhssetwar & Perser, 1972) cannot be over-
looked. Although the appearance of characteristic pro-oestrous and oestrous vaginal discharge in animals with IUDs may tend to exclude this possibility, it is not known what effect a lowered secretion of oestrogens sufficient to bring about changes in the vaginal smear pattern will have on the preovulatory rise of LH.

The main observation from this study is that the surge of LH is delayed for 2 hr in hamsters with IUDs and that this delay can be prevented by a single injection of progesterone. The rise in LH which appeared at the normal time after exogenous administration of progesterone was four times higher than in the control animals. It is therefore reasonable to assume that the delay of the LH surge in IUD-bearing hamsters could be due to a delay in, or to a lower, secretion of progesterone. It is also clear from Table 1 that this delay in the LH surge does not affect ovulation. It is known, however, that IUDs prevent implantation (Greenwald, 1965), and Henricks (1971) reported a fall in blood progesterone levels after Day 4 post coitum in IUD-bearing animals. The concentration of prostaglandins is increased in the IUD-bearing horns of rats, hamsters (Saksena, Lau & Castracane, 1974) and rabbits (Saksena & Harper, 1974). This causes a drop in progesterone levels (Pharriss & Wyngarden, 1969). In an unpublished study, we observed that administration of progesterone to hamsters with IUDs from Days 2 to 5 post coitum induced decidual cell reactions, suggesting that there was not enough progesterone being secreted by these hamsters.

From the present study, it appears that hamsters may serve as a good model for further studies of the effects of IUDs on gonadotrophin secretion.

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REFERENCES


I. Study the venous for release devices. 


