EFFECT OF INTRA-UTERINE DEVICES ON
CORPUS LUTEUM FUNCTION

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Experimental evidence has accumulated within recent years indicating that foreign objects placed in the uterine lumen affect the development and maintenance of corpora lutea. Luteal function has generally been measured either by length of the estrous cycle or by luteal weight or size at some stage of the cycle.

The term "intra-uterine device" (IUD) as used in this review will refer to various objects and semisolids which have been inserted or injected into the uterine lumen for a variety of reasons. Only superficial consideration will be given to the nature of any one device. For consistency in timing the days of the estrous cycle, the first day of estrus will be considered as day 1. The "immediate cycle" will refer to that cycle during which the device was inserted. "Subsequent cycles" will be all those after the immediate one.

Most of the published material used in this review has been classified by species or groups of species. Consequently, only partial consideration is given in the text to the chronological order in which the individual papers were published.

The initial part of this review deals with general effects of intra-uterine devices on the lifespan of corpora lutea. Later parts deal with more specific aspects of IUD-induced effects on corpora lutea.

Small Animals. Selye (1933) suppressed estrus in rats after removing the products of conception during the last half of pregnancy by filling the uterus with paraffin. At autopsy 6 wk. after the operation, the ovaries of the treated rats contained many large corpora lutea (CL), which were assumed to be the CL of gestation. Uteri of control animals were not filled with paraffin after removal of the conceptus, and CL regressed within 6 days. It thus appeared that paraffin in the uterus prevented involution of corpora lutea of gestation.

Bradbury (1941) and Greene (1941) injected paraffin into the rat uterus and studied the effect on lactation. Neither investigator examined corpora lutea. However, the paraffin treatment debilitated their rats, an effect which caused them to question some of Selye's conclusions.

Many studies have been made recently on the contraceptive effect of placing foreign materials, usually threads, in rat and rabbit uteri before mating. The thread generally interrupts pregnancy only in the uterine horn in which it is placed. Several investigators (e.g., Marston and Chang, 1964) have autopsied animals of these species during pregnancy, thus having the opportunity to notice effects of IUD on the CL, and Brown and Foote (1966) looked specifically for effects of intra-uterine plastic devices on CL in rabbits. Nobody has yet reported that intra-uterine devices adversely affected the development or maintenance of CL in mated rats or rabbits.

Orsini (1965) placed threads in one or both uterine horns of hamsters and found no effect on the length of subsequent cycles.

Threads have often been tied through the uterine wall of rats on the fourth or fifth day of pseudopregnancy to induce a decidual cell response. The deciduoma prolongs pseudopregnancy for as much as 8 days (Ershoff and Deuel, 1943). The degree of prolongation depends upon the number of threads inserted and thus the amount of decidual tissue formed (Peckham and Greene, 1948; Velardo et al., 1953). This indirect effect of intra-uterine threads on CL life in the pseudopregnant rat is not a unique property of an "IUD", since decidual cell responses induced by other means affect CL life similarly (Velardo et al., 1953).

The induction of deciduoma in pseudopregnant mice and hamsters by inserting threads into the uterus did not delay the recurrence of estrus (Kamell and Atkinson, 1948; Kent and Atkins, 1959).

In studies with guinea pigs, Donovan (1961) and Donovan and Traczyk (1960, 1962) inserted glass beads into both uterine horns on various days of the estrous cycle. Insertion between the 9th and 16th days lengthened the immediate cycle by an average of about 1.5 days; however, sham operations performed during this period of time also lengthened the
cycle slightly. Subsequent cycles in the same guinea pigs were often shortened regardless of the day of insertion (table 1).

Concurrently with the work of Donovan and Traczyk, Moore (1961) also reported the effects of intra-uterine beads on estrous cycle length in guinea pigs. Cycle lengths averaged 16.6 days in six sham-operated controls. A bead inserted into one uterine horn of each of 15 guinea pigs on day 8 increased the immediate cycle length to 22.4 ± 42 days. A bead inserted into one horn of each of nine animals on day 3 shortened the immediate cycles to 11.7 ± 43 days. In later studies, to be discussed in another section of this review, Ginther et al. (1966b) and Bland and Donovan (1966) did not find an effect on cycle length when an IUD similar in size to that used by Moore was placed in one horn only and both ovaries were intact. Bland and Donovan suggested that a thread passing through the endometrium of Moore’s guinea pigs may have accounted for the difference; however, Ginther et al. (1966b) anchored their IUD with a thread through the uterine wall without affecting cycle length.

**Sheep.** Moore and Nalbandov (1953) made the first deliberate attempts to influence the life of corpora lutea in non-pregnant animals by the use of intra-uterine foreign objects. They inserted beads into the lumen of one uterine horn of ewes 3 days after estrus. Estrous cycles after this treatment were shortened from the normal length of 16.3 days to an average of about 13 days, but those inserted on day 8 lengthened the cycle to an average of 23 days while those inserted on day 13 had no significant effect. The effect of beads on immediate cycles carried over into subsequent cycles; beads inserted on day 3 caused shortened cycles to be lengthened, but inserted on day 8 caused subsequent cycles to be lengthened and beads inserted on day 13 still had no effect. Inskeep et al. (1962) partially confirmed the results of Moore and Nalbandov (1953) and Nalbandov et al. (1955). Beads inserted into the lumen of one uterine horn on day 3 shortened some of the immediate and subsequent cycles to 5 to 8.5 days but had no apparent effect on other cycles. Beads inserted on day 8 had no effect on immediate cycles; they shortened some subsequent cycles, with no effect on others. No lengthening effect was noted either on immediate or subsequent cycles. It was suggested by Inskeep et al. (1962) that the frequent lengthening effect of beads inserted at day 8 by Nalbandov et al. (1955) might have been due to combinations of short and normal inter-ovulatory intervals which were separated by ovulation without overt estrus.

**Cattle.** Cases of short estrous cycles due to the presence of foreign material in the uterus have been reported several times. Yamauchi and Nakahara (1958) noted that estrous cycle lengths were often reduced to 6 to 16 days after the insertion of rubber tubing into the uterus. Hansel and Wagner (1960) inserted inflatable self-retaining rubber catheters into one uterine horn of 27 heifers and cows on the day of estrus or the next day. The catheter was placed in the uterine horn on the side where ovulation had already occurred or would likely occur. Immediate estrous cycle lengths averaged about 13 days, compared with pre-insertion cycle lengths of about 21

<table>
<thead>
<tr>
<th>TABLE 1. EXAMPLES OF IUD EFFECTS ON ESTROUS CYCLE LENGTH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Species</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Sheep*</td>
</tr>
<tr>
<td>Cattleb</td>
</tr>
<tr>
<td>Guinea pigs*</td>
</tr>
</tbody>
</table>

* Data from table 2 of Moore and Nalbandov (1953); the IUD were 8 or 11 mm. plastic beads sutured into the lumen of one uterine horn 3 days after the first signs of heat.

b Data from table 3 of Hansel and Wagner (1960); the IUD were water-inflated balloons inserted into the lumen of one uterine horn during estrus or the first day after estrus.

* Data from tables 2 and 3 of Donovan and Traczyk (1967); the IUD were two beads inserted into each uterine horn at various stages of the estrous cycle. Data does not include immediate post-insertion cycle lengths, and the IUD cycle mean includes three cycles of 25, 25, and 26 days.
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days (table 1); 17 of 23 cycles in heifers were shorter than 18 days.

During the course of studies on the anti-fertility effect of intra-uterine devices in cows, Chatterjee and Lukune (1961) noted shortened and erratic cycling after the insertion of a stainless steel pessary into each uterine horn. Hawk et al. (1964) reported that about half of the observed estrous cycles were shortened to 7 to 17 days in cows with plastic devices in both uterine horns.

Anderson et al. (1965) inserted plastic or vitallium cylinders into one uterine horn of four beef heifers, then recorded estrous cycle lengths for 10 cycles on each heifer. About half of the 40 cycles were shortened (5 to 17 days in length) and half were normal (18 to 25 days in length).

Yamauchi and co-workers (1965, 1966) injected 37 to 142 gm. of a viscous gel-like substance into the uterus one or more times during 34 estrous cycles of nine beef or dairy cattle. Injections during the first week of the cycle shortened the immediate cycle length to an average of 13.9 days for 16 cycles; injections after the 11th day either lengthened the immediate cycle by a few days or had no effect, the average length being 23.9 days (Yamauchi et al., 1966).

Yamauchi et al. (1966) injected 60 to 140 gm. of gel into the uterus of each of six beef heifers on the second or sixth day after estrus. Uterine contents were removed 2 days later by flushing the uterus with 800 to 1,500 ml. of sterile saline solution. All six immediate estrous cycles were shortened, suggesting that only a short period of uterine irritation was necessary during the early luteal phase for modification of cycle length. In delimiting the 2-day interval, the possibility should probably be considered that effects of either the gel or the flushing itself might have lingered beyond the time of actual flushing.

Swine. Anderson (1962) placed foreign objects in each uterine horn of 19 gilts on various days during the first half of the estrous cycle. The devices inserted per uterine horn included the following: two metal cylinders, each 24 mm. long and 16 mm. in diameter; two plastic cylinders, each 24 mm. long and either 16 or 20 mm. in diameter, two polyvinyl alcohol sponges, each 20 cm. long and 11 mm. in diameter; three glass beads. Neither immediate nor subsequent cycles were changed in length after insertion into the uterus of any of these devices.

During an investigation on some of the effects of IUD in pigs, one or more plastic spirals 18 cm. in length and 2 cm. outside diameter were inserted by laparotomy into one or both uterine horns of cycling gilts on the first day of estrus (Gerrits and Hawk, 1966). Immediate cycles averaged 19.6 days for 12 sham-operated controls and 20 days for 27 IUD gilts. The gilts were mated at most subsequent estrous periods; all matings to IUD gilts were infertile, with the infertile cycles averaging 20.1 days in length. There was thus no evidence that these IUD affected cycle length, which agreed with the results of Anderson (1962).

CL from 10 of the above gilts with IUD in one horn only and from 10 control gilts were weighed and analyzed for progesterone (Stormshak, unpublished data). Results are given in table 2. Neither progesterone concentration nor total progesterone content per gilt differed between the two groups. However, combined CL weights for days 9 and 14 were significantly lower in IUD than in control gilts, suggesting that devices in the uterus affected CL size even though they did not affect estrous cycle length. All of the gilts used above were mated at the estrus preceding autopsy; seven of 10 IUD gilts and eight of 10 control gilts were pregnant at autopsy, but IUD gilts contained fewer embryos than did controls both at 9 and 14 days (table 2). The possibility must be considered that devices in the uterus affected CL weights in these gilts by causing embryonic mortality or by negating any luteotropic effect of the embryos.

Primates. The placement of IUD in the uterus of the human seems to have little effect on menstrual cycle length, although shortened cycles have been reported during the first 2 or 3 mo. after insertion (Vorys et al., 1964). Whether CL function was affected in such cases is not known.

Kar et al. (1965) found no effect of IUD on the menstrual cycle length of monkeys.

Unilateral Effects of Intra-Uterine Devices

Studies up to about 1965 had shown conclusively that IUD could affect estrous cycle lengths in sheep, cattle, and guinea pigs. These effects sometimes seemed erratic. Some investigators who placed devices only in one uterine horn observed inconsistent effects (e.g., Inskeep et al., 1962, with sheep, and Anderson et al., 1965, with beef heifers). The reason for at least part of these erratic effects became obvious with the discovery that intra-uterine devices affected corpora lutea in the ovary ad-
TABLE 2. EFFECT OF PLASTIC SPIRALS IN ONE UTERINE HORN ON LUTEAL WEIGHT AND PROGESTERONE CONTENT IN GILTS AT TWO STAGES OF THE ESTROUS CYCLE

<table>
<thead>
<tr>
<th>Item</th>
<th>Control gilts</th>
<th>IUD gilts</th>
<th>Control gilts</th>
<th>IUD gilts</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. gilts</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Av. No. CL</td>
<td>15.4</td>
<td>13.9</td>
<td>13.8</td>
<td>13.8</td>
</tr>
<tr>
<td>Av. No. embryos</td>
<td>9.4</td>
<td>5.0</td>
<td>9.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Av. CL wt. (mg.) a</td>
<td>476±34</td>
<td>408±32</td>
<td>449±32</td>
<td>346±32</td>
</tr>
<tr>
<td>Progesterone concentration (µg./gm.) a</td>
<td>37±7</td>
<td>44±7</td>
<td>57±7</td>
<td>52±7</td>
</tr>
<tr>
<td>Total progesterone content (µg.) a</td>
<td>246±49</td>
<td>256±47</td>
<td>363±47</td>
<td>268±47</td>
</tr>
</tbody>
</table>

a Values adjusted by covariance to remove effects of variation in numbers of CL. Average CL weights were significantly lower in IUD than in control gilts over both days (P<.05); other treatment, day and interaction sources of variation were not statistically significant.

In guinea pigs, Ginther et al. (1966b) inserted seven mm. lengths of plastic tubing into one or both uterine horns on day 3 of an estrous cycle, at the same time removing one ovary from some of the animals. IUD effects were measured by estrous cycle length. Both immediate and subsequent cycles were shortened when plastic tubing was present in both uterine horns of guinea pigs with two ovaries (table 4). Cycles were also shortened in unilaterally ovariectomized guinea pigs when the tubing and the remaining ovary were on the same side. Cycles were shortened in guinea pigs with two ovaries when tubing was present in one horn only, and cycles were not shortened in unilaterally ovariectomized females when the tubing and the remaining ovary were on opposite sides.

In guinea pigs with both ovaries intact, Bland and Donovan (1966) found a reduction in immediate and subsequent estrous cycle lengths when one or two beads were inserted on day 2, 3, or 4 into each uterine horn. The placement of two beads in one horn only had no apparent effect on cycle length, but four beads in one horn caused some reduction in cycle length. Bland and Donovan attributed this cycle shortening effect of beads in one horn to a probable overflow of luteolytic agent to the opposite ovary.

TABLE 3. INDEX OF CORPUS LUTEUM VOLUME FOLLOWING INSERTION OF TWO GLASS BEADS INTO THE RIGHT UTERINE HORN OF GUINEA PIGS ON DAY 2 OF THE ESTROUS CYCLE

<table>
<thead>
<tr>
<th>Day of autopsy during immediate cycle</th>
<th>No. guinea pigs</th>
<th>Index (D³) for CL of left ovary</th>
<th>Index (D³) for CL of right ovary</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-8</td>
<td>2</td>
<td>2.71</td>
<td>2.96</td>
<td>-0.25</td>
</tr>
<tr>
<td>10-11</td>
<td>4</td>
<td>2.70</td>
<td>1.46</td>
<td>1.24</td>
</tr>
<tr>
<td>12-14</td>
<td>5</td>
<td>2.60</td>
<td>0.91</td>
<td>1.69</td>
</tr>
</tbody>
</table>

a Data from table 1 of Bland and Donovan (1965) and figure 4 of Bland and Donovan (1966).
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Sheep. Ginther et al. (1965, 1966c) placed plastic coils in the anterior part of one uterine horn of 26 animals on day 4 of an estrous cycle. Eighteen of the ewes had one or more CL developing only in one ovary at the time of the operation. The immediate cycle length was shortened to an average of about 12 days in seven ewes in which the device was inserted on the side of the developing CL. Immediate cycle lengths were normal (17.8 days) for 11 ewes in which the device was inserted opposite to the side of developing CL (table 5). The ewes were autopsied on day 6 of a subsequent cycle. In 18 ewes with one or more corpora lutea on one ovary only, CL weighed less if ovulation had occurred adjacent to the device rather than opposite to it (table 6). Eight other ewes had one or two corpora on each ovary. The average weight of a corpus luteum on the side of the device was 151 mg., intact ovaries and in ewes in which the ovary on the IUD side had been removed. This bilateral effect of the IUD may or may not involve only local mechanisms.

Cattle. Ginther et al. (1966d) inserted a plastic coil by surgery into one uterine horn of heifers on day 3 of the estrous cycle. Immediate cycles averaged 14 days when the coil was inserted on the side of the developing corpus luteum and 21.4 days when the coil was inserted opposite to the corpus luteum (table 8). Subsequent cycle lengths were short (12.6 days) when the coil and the corpus luteum were adjacent and normal (20.2 days) when the coil and corpus luteum were opposite to one another. Rectal palpation every second day indicated that CL on the IUD side developed almost to full size before precocious regression. In accord with the palpation records, luteal weights at day 8 of the autopsy cycle

TABLE 4. EFFECTS OF AN IUD ON ESTROUS CYCLE LENGTHS OF INTACT AND UNILATERALLY OVARIECTOMIZED GUINEA PIGS

<table>
<thead>
<tr>
<th>Item</th>
<th>Both ovaries intact</th>
<th>One ovary removed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No IUD (sham</td>
<td>IUD in one horn</td>
</tr>
<tr>
<td></td>
<td>operated)</td>
<td>only</td>
</tr>
<tr>
<td>No. guinea pigs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Immediate cycle length (days)</td>
<td>16.1</td>
<td>15.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsequent cycle lengths (days)</td>
<td>16.2</td>
<td>16.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined immediate and subsequent cycle lengths (days)</td>
<td>16.2 e</td>
<td>16.1 e</td>
</tr>
</tbody>
</table>

\(^a\) Adapted from Ginther et al. (1966b).
\(^b\) IUD inserted on day 1 of the immediate cycle; immediate vs. subsequent cycle, P<.01.
\(^c\) Means bearing different superscripts are significantly different from each other.

and on the side opposite to the device, 233 mg. (P<.01).

Stormshak and Hawk (1966) and Stormshak et al. (1967) placed a plastic spiral either in the anterior or posterior part of one uterine horn of ewes on day 4 of an estrous cycle. During a subsequent cycle, some of the ewes with a spiral in the anterior part of one horn were injected with HCG from day 3 to 6, and all of the ewes were autopsied on day 8. The spiral exerted unilateral luteolytic effects regardless of its location within the uterine horn (table 7). HCG prevented the luteolytic effect of the spiral. Whether luteal development in the HCG-treated ewes was due to direct stimulation by the injected gonadotropin or to some indirect effect of the gonadotropin is not known.

An IUD in one uterine horn of ewes sometimes exerts luteolytic effects on CL in the opposite ovary. This has been noticed occasionally in this laboratory, both in ewes with did not differ significantly among experimental groups (table 8).

Swine. The 10 IUD gilts represented in table 2 had plastic devices only in one uterine horn. At autopsy the CL taken from ovaries adjacent and opposite to the IUD were handled separately. There was no indication that CL weight or progesterone content in these few gilts was affected unilaterally by the IUD (table 9).

IUD Effects on Pituitary Gland Function.

Pituitary glands were obtained from 11 mated IUD ewes and 17 mated control ewes within a few hours before or after ovulation or on day 4 of the estrous cycle (Ginther et al., 1966a). The devices had been placed in one or both uterine horns 2 to 4 wk. previously. The glands were assayed for LH content by the rat ovarian ascorbic acid depletion test. LH activity tended to be higher in pituitary
TABLE 5. EFFECT OF AN INTRAUTERINE PLASTIC COIL ON IMMEDIATE ESTROUS CYCLE LENGTHS OF EWES WITH CORPORA LUTEA IN ONE OVARY ONLY

<table>
<thead>
<tr>
<th>Corpora lutea per ovary</th>
<th>Coil inserted adjacent to CL&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Coils inserted opposite to CL&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. ewes</td>
<td>Av. cycle length</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>9.2</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>14.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adapted from Ginther et al. (1966c).
<sup>b</sup> IUD inserted on day 4 of the cycle. Adjacent vs. opposite sides, P<.05.

Glands from IUD ewes than from control ewes, both around the time of ovulation and on day 4. These results suggested that intra-uterine devices affect pituitary gland function, perhaps by partially blocking LH release. Also along this line, Horie et al. (1964) stated that infusion of gel into cattle uteri raised the FSH and LH potency of the anterior pituitary gland.

Plastic devices inserted into the uterus of Indian water buffaloes prevented formation of corpora lutea (Buch et al., 1964). Based on rectal palpation of the ovaries, the lack of CL development was believed to result from failure of ovulation, an effect of the IUD that might involve the pituitary gland.

Chaudhury and Tarak (1965) found no evidence that sutures in the rat uterus affected pituitary gonadotropin content.

At the present time, the data on pituitary gland LH content in sheep and cattle seem to be the best evidence that foreign objects in the uterus may affect the pituitary gland. The possibility that altered pituitary function may be involved in IUD effects on CL is even less certain. However, the fact that exogenous HCG prevents the inhibitory effect of intra-uterine devices on CL formation in sheep suggests a lack of endogenous gonadotropic hormone stimulation of the developing CL.

Pathways of IUD Effects on the Corpus Lu-teum.

At this stage of investigation, consideration of pathways must remain speculative. The local luteolytic mechanism presumably uses local utero-ovarian pathways, perhaps involving diffusion through intercellular spaces or passage through lymphatic channels or uterine veins that pass near the ovaries or near arteries supplying the ovaries.

In one phase of a study with guinea pigs, Ginther et al. (1966b) inserted plastic tubing into one uterine horn on day 2 of the estrous cycle. In seven guinea pigs the anterior end of the HJD horn was freed by severing its connection to the oviduct, then it was grafted to the anterior end of the opposite horn. In six guinea pigs, the IUD horn was not freed or grafted. On day 10 of the immediate cycle, the average CL weight in guinea pigs without grafted horns was less on the IUD side than on the control side (1.86 and 2.91 mg., respectively, P<.01). In guinea pigs with grafted horns, CL weights were reduced in both ovaries (2.27 mg. on the IUD side and 2.18 mg. on the control side, P<.06 and P<.05, respectively, when compared to 2.91 mg.). The grafting procedure itself was not tested for an effect on CL weight, but if further work shows that the IUD effect is independent of the procedure, the results will provide evidence for passage across the graft of something involved in the luteolytic effect of the IUD.

There is no evidence that the oviduct acts as a pathway in the luteolytic action of intra-uterine devices, even though the possibility has not been definitely ruled out. Stormshak et al. (1967) inserted plastic spirals into both uterine horns of four ewes, salpingectomized several months previously. CL weights at day 8 of a subsequent cycle averaged 50 mg. in the four IUD ewes and 589 mg. in three control salpingectomized ewes (P<.05). This failed to implicate the oviduct as a critical pathway through which the spirals affected CL development, although the insertion of spirals into both horns precluded determination of whether the local luteolytic mechanism was operating in the absence of the oviducts.

In the guinea pigs of Ginther et al. (1966b) mentioned above, in which the two uterine horns were grafted together, the IUD horn was severed from its oviduct at the tubo-

TABLE 6. EFFECT OF AN INTRAUTERINE PLASTIC COIL ON CORPUS LUTEUM WEIGHTS AT DAY 6 OF THE ESTROUS CYCLE OF EWES WITH CL IN ONE OVARY ONLY

<table>
<thead>
<tr>
<th>No. corpora lutea per ovary</th>
<th>CL adjacent to coil&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CL opposite to coil&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. ewes</td>
<td>CL weight</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>207</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>147</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adapted from Ginther et al. (1966c).
<sup>b</sup> Coils were inserted on day 4 of the previous cycle. Adjacent vs. opposite side, P<.01.
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...uterine junction; the IUD still affected CL on the IUD side. Whether the grafting procedure might have disturbed the usual pathways used by the local luteolytic mechanism is not known. In relevant work, Barley et al. (1966) found that severing the oviduct did not increase the length of pseudopregnancy in the rat, but cutting the oviduct and mesosalpinx and retracting the uterine horn from the ovary did lengthen pseudopregnancy.

In the pioneering work of Nalbandov and co-workers (Moore and Nalbandov, 1953; Nalbandov et al., 1955) on the effects of intrauterine beads on the estrous cycle of sheep, the segment of uterine horn containing the bead was resected in some sheep and sutured back in place. Moore (1961) did the same thing with guinea pigs. Cycle lengths were normal in such animals, the operation preventing the usual effects of the beads on cycle length and thus presumably on the corpus luteum. These results suggested to the investigators, and to other writers since that time, that the effect of the bead on the CL involved neural or neurohumoral pathways to the pituitary gland. In addition to disrupting neural connections to the resected segment, the experimental procedure might also have suppressed the function of the local luteolytic mechanism, which was not known at that time to exist. Consequently, it is difficult at present to interpret the results. If it turns out that participation of systemic mechanisms is required for manifestation of IUD-induced luteolysis, and particularly if the systemic mechanisms operate through neural pathways, then the interpretation given by Nalbandov et al. (1955) to the results of uterine resection will have been at least partially correct.

## Table 7. Effect of IUD Location and HCG Injection on Corpus Luteum Weights of Ewes at Day 8 of the Estrous Cycle

<table>
<thead>
<tr>
<th>Spiral location</th>
<th>CL adjacent to spiral</th>
<th>CL opposite to spiral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. observations</td>
<td>Av. CL weight</td>
</tr>
<tr>
<td>None</td>
<td>6</td>
<td>458</td>
</tr>
<tr>
<td>Posterior</td>
<td>6</td>
<td>252</td>
</tr>
<tr>
<td>Anterior</td>
<td>6</td>
<td>182</td>
</tr>
<tr>
<td>Anterior + HCG</td>
<td>6</td>
<td>525</td>
</tr>
</tbody>
</table>

* Adapted from Stormshak et al. (1967). HCG injected day 3 to day 6 inclusive.

**Discussion**

Little is known of the mediating factors involved in the IUD-activated luteolytic mechanism. It is not known whether this mechanism is similar in kind or degree to that which causes regression of fully developed CL at the end of an infertile estrous cycle. Neither is it known whether the mechanism is similar to any of the various experimentally-induced luteolytic mechanisms, such as those activated by oxytocin in cattle (Armstrong and Hansel, 1959), by induced uterine inflammation in cattle and sheep (Hansel and Wagner, 1960; Brinsfield and Hawk, 1967), or by steroid hormones in several species, e.g., by progesterone in sheep, cattle and guinea pigs (Woody et al., 1967).

The term “uterine distention” has been used often in the literature on the subject of IUD effects on CL. The term has apparently been used both to describe the physical effects of inserting something into the uterus and to imply neural or perhaps myometrial involvement in the IUD effect. At the present time, the degree to which either neural pathways or the myometrium participate in IUD effects on the CL is not known. Neither is it known to what extent uterine distention per se is necessary in order to evoke IUD effects on the CL. However, there is little doubt of some relationship between the size or number of objects placed in the uterus and their effect on corpora lutea (Nalbandov et al., 1955; Bland and Donovan, 1966).

Estrous cycle lengths vary considerably in IUD animals. Moore and Nalbandov (1953) and Nalbandov et al. (1955) found much greater variability in cycle length in sheep with beads in the uterus than in control sheep. Ginther et al. (1966c) reported that some ewes returned to estrus as soon as 1.5 to 4.5 days after insertion of coils into the uterus on day 4, and estrous cycles of 5 or 6 days length have been seen frequently in IUD sheep at Beltsville. In cattle, Hansel and Wagner (1960), Hawk et al. (1964), and Anderson et al. (1965) reported a number of cycles of 7 to 10 days with devices of one type or another in the uterus, but Ginther et al. (1966d) found that CL weights in heifers at day 8 were not yet significantly smaller in IUD animals than in controls. Bland and Donovan (1966) found that CL...
weights apparently increased at similar rates in IUD and control guinea pigs until about day 9, then weights in IUD animals began to decline prematurely. The results of these several studies indicate that IUD can block CL development during the first few days post-ovulation and also cause precocious regression of nearly full sized CL. This IUD-induced variation in estrous cycle length does not necessarily mean that similar variability exists in the time at which intra-uterine devices trigger a luteolytic mechanism; temporal relationships between triggering of the mechanism and actual regression of corpora lutea are not known.

Presumably the triggering of the IUD-activated luteolytic mechanism occurs in the uterus. The triggering action may be embodied in some of the known responses of uterine tissue to the presence of foreign objects. In cows with a plastic spiral in one uterine horn, the mucopolysaccharide content of the endometrium was nearly doubled in the spiral area as compared to non-spiral areas on days 4 and 8 of the cycle (Cooper and Hawk, 1967a), endometrial vascular permeability to circulating vital dye was decreased in endometrial tissue compressed by the spiral and increased in other areas around the spiral (Cooper, unpublished data) and motility patterns were changed in strips of myometrium incubated in vitro (Brinsfield, unpublished data).

Intra-uterine devices have caused histopathological changes in the endometrium in many species (e.g., Moyer and Mishell, 1964; Bonney et al., 1966; Hawk et al., 1964; Hawk, 1967; Yamauchi et al., 1966). The mild leukocytic infiltration of the endometrium often seen around intra-uterine devices indicates that these foreign objects act as weak but chronic irritants. Whether some phase of the inflammatory response is directly connected with the luteolytic effect of the IUD is not known, although the possibility must be considered. Hansel and Wagner (1960) inhibited CL development or maintenance in cattle by infusing the uterus with bacterially contaminated semen at estrus. Subsequent purulent discharges indicated the existence of uterine infection or inflammation, Brinsfield and Hawk (1967) inhibited CL development in sheep by

<table>
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<th>Adjacent side</th>
<th>Opposite side</th>
<th>Adjacent side</th>
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<td>No. gilts</td>
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<td>Av. no. CL</td>
<td>7.5</td>
<td>6.4</td>
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<tr>
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<td>Av. CL wt. (mg.)</td>
<td>416±19</td>
<td>409±19</td>
<td>340±22</td>
<td>358±23</td>
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<tr>
<td>Progesterone concentration (µg./g.m.)</td>
<td>42±11</td>
<td>41±11</td>
<td>44±13</td>
<td>50±14</td>
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<tr>
<td>Total progesterone content (µg.)</td>
<td>124±36</td>
<td>123±36</td>
<td>105±43</td>
<td>156±44</td>
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</table>

* Values adjusted by covariance to remove effects of variation in numbers of CL.
Average CL wt. differed significantly between days (P<.05). Other sources of variation were not statistically significant.
inducing infection in the uterine lumen with *Escherichia coli* on the day after estrus. In the latter study, CL weights at day 8 averaged 513 mg. in seven control ewes and 94 mg. in seven infected ewes (P<.01). Under other circumstances, uterine infection can prolong the life span of corpora lutea (Ginther, 1966; Coudert and Short, 1966).

Intra-uterine devices also change uterine function in species in which the IUD is not known to shorten the life span of corpora lutea. In rats, a thread placed in the uterine lumen before estrus inhibited the deciduol cell response to traumatization or to histamine injection on the fourth or fifth day of pregnancy (e.g., Margolis and Doyle, 1964). The inhibition was localized to the uterine horn containing the thread. In monkeys, intra-uterine devices caused an increased rate of oxygen consumption by uterine tissue, although the concentration of a number of chemical constituents of the tissue were not changed (Kar et al., 1965). Intra-uterine threads or plastic devices have caused uterine growth in rats (Kar et al., 1964), rabbits (Ledger and Bickley, 1966) and goats (Janakiraman et al., 1966).

Whether intra-uterine devices affect the pituitary and whether altered pituitary function is involved in IUD effects on CL certainly require further study over a number of species. Nevertheless, at this point, it is possible to envision an IUD-activated luteolytic mechanism composed of two parts: a uterine component, perhaps a luteolytic substance, that inhibits CL development or causes CL regression through local pathways, and a systemic component that decreases the production or release of the pituitary luteotropic hormone. The fact that injected HCG prevents the luteolytic action of an IUD in the ewe raises the possibility that the local component can inhibit CL development or cause CL regression only when the level of gonadotropic hormone stimulation is lower than normal due to the action of the systemic component.

**Literature Cited**


