EFFECTS OF SMALL DIAMETER IUDs ON FERTILITY AND LENGTHS OF
ESTROUS CYCLES IN EWES

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SUMMARY

Two experiments were conducted utilizing ewes to determine the effects of small diameter IUDs on fertility, lengths of estrous cycles and uterine histology. In both experiments, IUDs were inserted bilaterally at day 3 of the estrous cycle (estrus = day 0). The IUDs were single strands of nylon suture (.3 mm diameter) lying free in the uterine lumen except at a point of attachment near the uterotubal junction. In both experiments, the lengths of the first estrous cycle (cycle in which surgery was performed) and second estrous cycle were determined. All ewes were mated to fertile rams at the estrus beginning the third cycle. In experiment I, ewes which failed to conceive at the first mating were bred to fertile rams at the fourth estrus (no pregnancies occurred), again at the fifth estrus and necropsied 2 or 3 days later. In experiment II, ewes were necropsied 12 days after the first mating with fertile rams.

The results of analysis of variance of the lengths of estrous cycles for experiments I and II showed no significant differences between sham-operated and IUD-treated ewes. Of the 18 sham-operated ewes in experiments I and II, 17 conceived at the first mating with fertile rams. For all 18 IUD-treated ewes in experiments I and II, only one pregnancy resulted from the first mating. The proportion of ewes which became pregnant at the first mating was lower (P<.01 and P<.05 for experiments I and II, respectively) in the IUD-treated groups than in the sham-operated groups. If normal cycle lengths are a reflection of normal luteal function, then the results suggest that IUDs can exert a contraceptive effect in ewes without initiating the uterine luteolytic function. Ten IUD-treated ewes in experiment I failed to conceive at either the first or second mating. Eight ova were recovered from seven of these ewes 2 or 3 days after the third mating. Four ova from three ewes were fertilized. Histological examination of uteri did not reveal any significant differences between sham-operated and IUD-treated ewes for any of the characteristics studied.

(Key Words: Intrauterine Device, Estrous Cycle, Conception, Fertilization, Ewes.)

INTRODUCTION

The effects of intrauterine devices (IUDs) have been the subject of numerous reviews (Marston and Kelly, 1966; Hawk, 1968; Corfman and Segal, 1968; Sahwi and Moyer, 1970; Eckstein, 1970, 1971; Duncan and Wheeler, 1975). Although IUDs are contraceptive in a number of laboratory and domestic animals, the apparent mode of action varies widely. In rodents and primates, the presence of an IUD does not alter the sexual cycle to a significant degree and a major antifertility effect seems to be exerted between the time the embryo enters the uterus and the time of implantation (Marston and Kelly, 1966; Sahwi and Moyer, 1970; Eckstein, 1970, 1971; Duncan and Wheeler, 1975). In contrast, insertion of large diameter (uterus-distending) IUDs in sheep, cattle and guinea pigs results in an alteration of the estrous cycle by shortening the functional lifespan of the corpus luteum (Ginther et al., 1965, 1966a, b; Ginther, 1968; Hawk, 1968; Eckstein, 1970). In addition to decreasing the lifespan of the corpora lutea (CL), large diameter IUDs have been shown to inhibit sperm transport and fertilization in ewes (Hawk, 1965, 1967). Whether or not the effect on fertilization is dependent on a cycle-shortening...
effect has not been established.

While studying uterine motility in ewes, Cloud and Casida (1969) placed small rubber pellets into the uterine lumen 3 days after mating and noted that no embryos were found 11 days later. This raised the possibility that IUDs, much smaller than the plastic spirals used by other researchers, might exert a contraceptive effect in ewes. Furthermore, if the contraceptive effect involved an action on the embryo, then ewes with small diameter IUDs would provide an experimental model for studying embryonic mortality. Experiments utilizing ewes were conducted to evaluate the effect of small diameter IUDs on lengths of estrous cycles, fertility and uterine histology. It was hypothesized that small diameter IUDs would exert a contraceptive effect in the absence of a cycle-shortening effect.

MATERIALS AND METHODS

Two experiments were conducted utilizing a total of 40 ewes which had lambed the previous year. Estrous behavior was checked once daily with vasectomized rams and ewes to be bred were mated with each of two rams of proven fertility.

The IUDs utilized in both experiments were single strands of nylon suture, .3 mm in diameter. The uterus was exposed by midventral laparotomy on day three of the estrous cycle (estrus = day 0), and a long blunted surgical needle with a 15 cm length of suture attached was inserted through the uterine wall at a point midway between the internal and external bifurcations of the uterine horns. The needle was passed up the uterine lumen to a point approximately 1 cm from the uterotubal junction and then out through the uterine wall. The suture was then attached to the outside of the uterine wall with a single stitch. In place, the IUD consisted of a single strand of suture lying free in the uterine lumen except at its point of attachment near the uterotubal junction. In both experiments, IUDs were inserted bilaterally. Sham-operated animals were subjected to the same procedure except the IUD was removed immediately after insertion.

In experiment I, IUDs were inserted in 12 ewes, and 12 ewes were sham-operated. Two ewes in the sham-operated group and one in the IUD group died during the course of the experiment and were not replaced. Ewes were checked for estrus with vasectomized rams to determine the length of the cycle in which the operation was performed (first estrous cycle) and the length of the subsequent estrous cycle (second estrous cycle). All ewes were bred to fertile rams at the estrus beginning the third cycle. Ewes which returned to estrus after the first breeding were mated a second time. Ewes which failed to conceive after two matings to fertile rams were mated a third time and necropsied 2 or 3 days later and the oviductal flushings examined for the presence of fertilized ova.

In experiment II, IUDs were inserted into uteri of eight ewes and eight ewes were sham-operated. One ewe in the IUD group never returned to estrus and was excluded from the experiment. The lengths of the first and second estrous cycles were determined as in experiment I. All ewes were bred to fertile rams at the estrus beginning the third cycle. Twelve days later the ewes were necropsied, and the uterine flushings were examined for embryos.

Segments of uterine tissue were obtained from the middle of the uterine horn, fixed in neutral formalin, and processed for light microscopy. The following characteristics were evaluated: (1) lymphocytes in the lumens of the endometrial glands, (2) lymphocytes in and immediately beneath the epithelium of the uterine lumen, and (3) polymorphonuclear cells in and immediately beneath the epithelium of the uterine lumen. Each characteristic was scored on a 4-point scale with a score of 1 indicating few to no cells present, and a score of 4 indicating large numbers of cells present. Scoring was done without knowledge of which treatment the uterus had received.

Treatment effects on lengths of estrous cycles were evaluated by analysis of variance. Differences in pregnancy rates were analyzed by Chi-square tests. The effects of treatment on uterine histology were analyzed by transforming the scores for each characteristic to $\sqrt{X+1}$ and subjecting the transformed data to a Student's $t$ test.

RESULTS

The results of analysis of variance of the lengths of the estrous cycles for experiment I and experiment II (table 1) showed no significant effect of IUDs, first vs second estrous cycle or interaction of treatment and cycle. However, in both experiments there was heterogeneity of the within subgroup variances as
shown by Bartlett's test (Snedecor and Cochran, 1967). An examination of the data indicated that for both the sham-operated and IUD-treated ewes there was greater variability in the lengths of first estrous cycles (cycle in which surgery was performed) than in the lengths of second estrous cycles. Cycle lengths in animals with IUDs tended to be more variable than in sham-operated animals. The greater variability in the first estrous cycle was due to a few abnormally short and abnormally long estrous cycles. In the first estrous cycle of the 18 IUD-treated ewes, there were four short cycles (6, 7, 10 and 14 days in length) and two long cycles (25 and 26 days in length). The first estrous cycle of ewes in the sham-operated group included four long cycles (21 to 27 days in length) but no short cycles. During the second cycle, there was one 14 day and one 21 day estrous cycle in the IUD-treated ewes. The remaining 16 animals in the IUD-treated group and all 18 animals in the sham-operated group had estrous cycle lengths of 16 to 19 days.

The proportion of animals which became pregnant at the first mating (table 1) was lower (P<.01 and P<.05 for experiments I and II, respectively) in the IUD-treated groups than in the sham-operated groups. After the first mating to fertile rams, the 10 sham-operated ewes from experiment I failed to return to estrus and subsequently lambed. Seven of eight sham-operated ewes in experiment II had normal-appearing embryos 12 days after mating. Of the 18 sham-operated ewes in experiments I and II, 17 became pregnant after the first mating. One of 11 IUD-treated ewes in experiment I failed to return to estrus after the first mating. A normal-appearing embryo with the fetal membranes surrounding the IUD was found 40 days after mating. No embryos were recovered 12 days after mating from seven IUD-treated ewes in experiment II. For all 18 IUD-treated ewes in experiments I and II, only one pregnancy resulted from the first mating to fertile rams.

The 10 IUD-treated animals from experiment I which failed to conceive at the first breeding (at the third estrus) were bred to fertile rams at the fourth and fifth estrus. No pregnancies occurred at the fourth estrus. The lengths (X ± SE) of the third and fourth estrous cycles were 16.8 ± .4 days and 17.0 ± .4 days, respectively. Two or 3 days after the fifth estrus, eight ova were recovered from seven ewes. Four ova from three ewes contained two to eight blastomeres. The remaining four ova were not fertilized, but one did have sperm attached to the zona pellucida.

Histological examination of the uteri from experiment II (table 2) did not reveal any significant differences between the sham-operated and IUD-treated groups for any of the characteristics studied.

**Discussion**

In analyzing the contraceptive effects of IUDs in mammals, sheep are usually classed with cattle and guinea pigs because insertion of IUDs in these species alters the length of the estrous cycle. The cycle-shortening effect of IUDs in ewes appears to be related to the size of the IUD. Nalbandov et al. (1955) found that

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Lengths of estrous cycles (X ± SE)a</th>
<th>Conception at first matingb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Second</td>
</tr>
<tr>
<td>Experiment I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham-operated</td>
<td>17.6 ± 1.0</td>
<td>16.8 ± .2</td>
</tr>
<tr>
<td>IUD</td>
<td>16.1 ± 1.5</td>
<td>17.2 ± .6</td>
</tr>
<tr>
<td>Experiment II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham-operated</td>
<td>19.1 ± 1.3</td>
<td>17.9 ± .4</td>
</tr>
<tr>
<td>IUD</td>
<td>16.1 ± 2.1</td>
<td>17.4 ± .5</td>
</tr>
</tbody>
</table>

aThe results of analysis of variance showed no significant effects of treatment in experiment I and experiment II.
bConception rates were different. Chi square for experiment I and experiment II were 8.2 (P<.01) and 6.1 (P<.05), respectively.
TABLE 2. EFFECTS OF IUDs ON SELECTED ASPECTS OF UTERINE HISTOLOGY

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. ewes</th>
<th>Mean scores&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lymphocytes in glandular lumens</td>
<td>Lymphocytes in and beneath epithelium of uterine lumen</td>
<td>Polymorphonuclear cells in and beneath epithelium of uterine lumen</td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>8</td>
<td>1.5 (1.6)</td>
<td>2.0 (1.7)</td>
<td>1.1 (1.4)</td>
<td></td>
</tr>
<tr>
<td>IUD</td>
<td>7</td>
<td>2.0 (1.7)</td>
<td>2.4 (1.8)</td>
<td>1.4 (1.5)</td>
<td></td>
</tr>
<tr>
<td>SE of the difference</td>
<td></td>
<td>(.16)</td>
<td>(.08)</td>
<td>(.09)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Each characteristic was scored on a 4-point scale as described in the Materials and Methods. The scores were transformed to the $\sqrt{X+1}$ for analysis. Values in parentheses are based on transformed scores. There were no significant differences.

insertion of 8 mm or 11 mm, but not 2 mm, diameter plastic beads into the uterus on day three of the estrous cycle resulted in a significant reduction in estrous cycle lengths. Estrous cycles in ewes with large diameter plastic spiral IUDs are commonly 5 to 12 days in length as compared to 16 or 17 days in control ewes (Hawk, 1965; Ginther, 1968).

The IUDs utilized in experiments I and II (.3 mm diameter) did not distend the uterus and appeared to have had only minor effects on estrous cycle lengths. Most of the disturbance in estrous cycle lengths occurred during the cycle in which the IUDs were inserted. Since uterine distention was not involved, the short estrous cycles observed may have been the result of other undetermined actions of the devices. Shortened estrous cycles have been reported to occur in ewes after injection of irritating chemicals or suspension of bacteria into the uterus during the first 4 days after estrus (Brinsfield and Hawk, 1968; Woody et al., 1969). The abnormally long estrous cycles observed in some sham-operated and IUD-treated ewes may represent a combination of a short interovulatory interval without overt estrus followed by a normal interovulatory interval accompanied by estrus (Inskeep et al., 1962). Despite the disturbances in lengths of the first estrous cycle, nearly all animals had one estrous cycle of normal length (second estrous cycle) before the first mating with fertile rams. In addition, all 10 IUD-treated animals from experiment I which did not conceive at the first mating had third and fourth estrous cycles of normal duration.

Although a major effect of large diameter IUDs in sheep is to initiate a uterine luteolytic function and cause a shortening of the estrous cycle, Hawk (1965, 1967) has shown that these devices also inhibit sperm transport and block fertilization. However, with large diameter IUDs it cannot be determined to what extent the inhibition of sperm transport and fertilization is due to initiation of the uterine luteolytic function.

The IUDs used in experiments I and II were contraceptive in the absence of any consistent effects on the lengths of estrous cycles. If normal cycle lengths are a reflection of normal luteal function, then the results of experiments I and II indicate that IUDs can exert a contraceptive effect in ewes without initiating the uterine luteolytic function.

Moor and Rowson (1966) have shown that the presence of embryos in the uterus from days 12 to 13 of pregnancy followed by their removal on day 14 frequently resulted in interestrous intervals of 25 days or more. Removal of embryos before day 12 resulted in normal interestrous intervals of 16 to 19 days. The failure to observe extended cycles after breeding (experiment I) and the failure to recover any embryos 12 days after mating (experiment II) indicates that the presence of IUDs blocked fertilization or caused early embryonic death. When compared to the high fertility in the sham-operated groups at the first mating, the finding that the ova from only three of the seven IUD-treated ewes were cleaved is indicative of an inhibitory effect on fertilization. However, sperm transport and fertilization were not blocked completely. It should be noted that the fertilized ova were recovered after the third mating, and it is possible that the contraceptive effects of the IUDs decreased with increasing length of exposure to the devices. Although the results suggest
that the IUDs used in experiments I and II have an inhibitory effect on fertilization, the exact stage or stages of the reproductive process affected cannot be determined adequately.

The rationale for the histological characteristics studied was based on examinations of sheep uteri containing large diameter plastic spiral IUDs. The characteristics and scoring method used were thought to be reflective of the moderate to severe inflammatory response which is associated with the presence of large diameter plastic spiral IUDs (L. R. French, unpublished data; Hawk, 1967). The small diameter IUDs used in experiments I and II seemed to produce minor but statistically non-significant changes in uterine histology. The mean score for each characteristic measured was higher in the IUD-treated ewes than in the sham-operated ewes. However, histological changes which were consistently associated with the absence of pregnancy were not observed. Sham-operated animals which had normal-appearing embryos, frequently had scores which were greater than those from IUD-treated animals which were not pregnant.

LITERATURE CITED


