# EFFECTS OF MELATONIN AND PROGESTERONE ADMINISTERED TO EWES IN SPRING AND SUMMER[1,2]

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**ABSTRACT**

Melatonin (MEL) was evaluated for effects on LH, prolactin (PRL) and fertility in spring (Exp. 1, 2) and summer (Exp. 3 to 5). In Exp. 1, 17 ovariectomized ewes bearing estradiol implants were fed 3 mg MEL or vehicle for 44 d beginning May 1. Melatonin decreased ($P < .001$) PRL levels but had no effect on LH secretion and response to GnRH. In Exp. 2, 12 ewes each received a 40-d MEL ear implant or a sham implant on March 31. Progesterone-releasing pessaries (CIDR) were applied for 12 d and were withdrawn concomitant with ram joining on May 7. Neither treatment stimulated follicular development or induced estrus or ovulation. Exp. 3 and 4 were contemporary 2 × 2 factorial trials with 24 ewes at each of two locations. Melatonin implants were administered on June 29 and CIDR on July 22. The CIDR were removed and rams (Exp. 3, vasectomized; Exp. 4, fertile) were joined on August 3. Days from introduction of rams to estrus were reduced ($P < .05$) by CIDR but not by MEL. All ewes lambed in Exp. 4, and days to estrus and conception were reduced ($P < .001$) by CIDR but not by MEL. Exp. 5 was designed like Exp. 4 except that MEL implants were inserted June 20 and rams were joined August 8. Intervals from introduction of rams to estrus were reduced ($P < .01$) by both MEL and CIDR treatments. Days to conception were reduced ($P < .001$) by CIDR and tended ($P < .1$) to be decreased by MEL. In spring, MEL and CIDR failed to induce fertility, whereas in summer both treatments advanced onset of the breeding season. (Key Words: Melatonin, Progesterone, Sheep, Anestrus, Fertility.)

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## Introduction

Seasonal reproductive patterns of sheep are dependent largely on latitude and breed and are influenced to a lesser extent by other factors such as altitude, strain, age and nutrition (Hafez 1952). In Minnesota, meat-type and medium-wool breeds predominate; sheep of Suffolk, Hampshire and Columbia lineage are common. Crossbreeding with Finn often improves prolificacy. Ewes typically are anestrous in spring after lambing and lactating and remain so until late August or early September. Seasonal anestrus reduces reproductive efficiency and continues to hinder productivity. Out-of-season fertility is achieved with reasonable success using progestogens and pregnant mare serum gonadotropin (**PMSG**); however, these materials are not approved for commercial use in the U.S. In this regard, native ovine hormones, such as melatonin and progesterone, should be viewed more favorably by the Food and Drug Administration for future approval.

Extensive research with melatonin has led to its licensing in Australia for induction of

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fertility in anestrous ewes (Staples, 1988). Progesterone-releasing pessaries (**CIDR**) are marketed in New Zealand primarily for estrus synchronization, but also for advancement of the breeding season (Welch et al., 1984). A positive interaction may exist between these two treatments (Moore et al., 1988). Experiments reported herein were conducted to evaluate melatonin and progesterone treatments for ability to stimulate fertility in spring and summer under local genetic and environmental conditions.

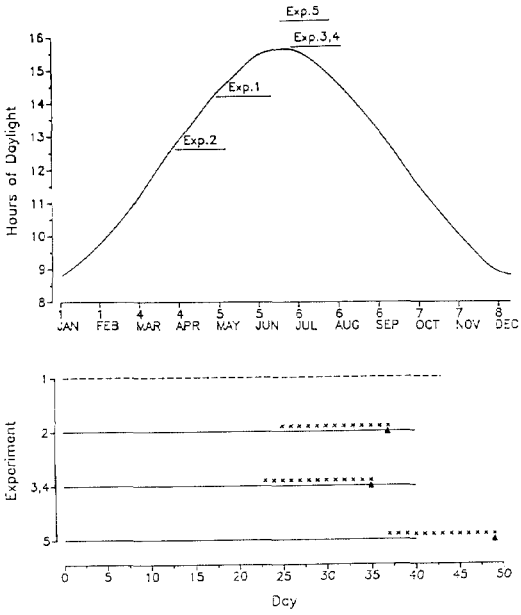


Figure 1. Top panel shows the relationship of melatonin treatments to the annual photoperiod cycle in St. Paul, MN. Bottom panel illustrates duration and timing of melatonin administration (---, ingestion; —— implants), progesterone-releasing pessaries (xxx) and joining of rams (▲).

## Materials and Methods

*Experiment 1.* Seventeen Suffolk ewes weighing 77 ± 10 kg (SD) were fed melatonin or control pellets in spring of 1985 (Figure 1). Ewes were 4 yr of age and had been ovariectomized (**ovx**) for 2 yr. Ewes were kept in a barn and exposed to natural photoperiod (45°N) through numerous windows. Light intensity was 175 lux measured 1 m from the floor at midday during the latter part of May. Rams were excluded from the barn. Estradiol implants constructed of a 1-cm length of silastic[5] tubing (3.35 mm i.d., 4.65 mm o.d.) packed with estradiol-17β ($E_2$), were inserted s.c. on April 10. From May 1 to June 13, nine ewes were each hand-fed three melatonin pellets once daily at 8 h ± 10 min after sunrise. Fresh melatonin pellets were prepared daily by dissolving 1 mg melatonin[6] in 50 μl absolute ethanol and absorbing it into individual alfalfa-corn pellets. Eight ewes were fed ethanol-treated control pellets. Blood samples were taken at 3-d intervals beginning April 25. On blood collection days, samples were drawn via venipuncture at 20-min intervals during two 1-h periods, one beginning 2 h after sunrise and the other 2 h following feeding of melatonin pellets. Blood samples were drawn into chilled heparinized tubes (8 IU/ml) and centrifuged soon thereafter. Jugular vein cannulas were inserted on June 11; on the last 2 d of melatonin treatment, blood samples were obtained at 15-min intervals for 7 h starting 1 h after melatonin feeding on June 12 (1430 to 2130) and 1 h after sunrise on June 13 (0630 to 1330). Gonadotropin-releasing hormone (GnRH, 2.5 μg) was injected i.v. at 1430 on June 13, after which blood samples were taken at 5- or 10-min intervals for 2 h. Plasma was stored at −20°C until it was assayed for LH and prolactin.

*Experiment 2.* Twelve multiparous, predominantly Suffolk ewes 3 to 8 yr of age and weighing 66 ± 10 kg were implanted on March 31, 1986 with 40-d melatonin implants[7] inserted s.c. in the left ear. Twelve animals received sham implants. Melatonin implants were cylindrical in shape, measured 2 mm in diameter and 4 mm in length, and were not removed. They elevated plasma melatonin concentrations for about 40 d, followed by a gradual decrease (Howse et al., 1987). All ewes were treated on April 25 with 366 mg progesterone type G controlled internal drug release dispensers[8] (CIDR). Progesterone-releasing devices were removed 12 d later at 0900, after which ewes were checked twice daily for estrus. Blood samples were taken at 0900 at 3-d intervals from March 23 to CIDR removal, followed by 6-and 24-h spacings for 2 and 7 d, respectively. Laparoscopy was

[5]Dow Corning, Midland, MI.
[6]Sigma Chemical Co., St. Louis, MO.

performed 8 d after CIDR withdrawal to examine ovaries for corpora lutea and surface follicles. Ovaries from four ewes selected randomly from each treatment group were removed 24 h after CIDR removal and weighed, the diameter of surface follicles was recorded, and ovaries were fixed in Bouin's fluid. Cross-sections (7 μm) were stained with hematoxylin-eosin and follicles were classified as primordial (one layer of flattened cells), primary (one layer of cuboidal cells), secondary (granulosa cell proliferation) or tertiary (antrum present).

*Experiment 3.* Twenty-four multiparous Columbia ewes, 4 to 6 yr of age and weighing 88 ± 8 kg, were assigned randomly to four treatment groups in a factorial arrangement: 1) control (**CON**), 2)melatonin implant (**MEL**), 3) CIDR and 4) melatonin implant and CIDR. Forty-day melatonin ear implants were inserted on June 29, 1987 and CIDR on July 22. The latter were removed after 12 d at which time three vasectomized rams were joined and ewes were checked daily for estrus. Blood samples were obtained at 3-d intervals from June 26 to September 9.

*Experiment 4.* Twenty-four multiparous, crossbred ewes (50% Suffolk, 25% Finn, 25% Targhee), 3 to 4 yr of age and weighing 79 ± 11 kg, were treated contemporarily with those in Exp. 3. Sheep were located at the University of Minnesota Experiment Station at Crookston (48°N) and were maintained in a lot with an open-faced shelter. Rams were kept in a shelter 154 m away until August 3, when three Finn rams were placed into the flock. Breeding and lambing dates and number of lambs born were recorded.

*Experiment 5.* Design of this experiment was similar to that of Exp. 4. Differences were that two groups of 24 crossbred ewes were used, one like that described above (3 to 4 yr of age, 73 ± 6 kg) and the other composed of 50% Finn and 50% Targhee ewes (3 to 4 yr of age, 79 ± 10 kg). Melatonin implants were inserted June 20, 1988, and CIDR application and removal were on July 27 and August 8, respectively. Rams were joined August 8.

*Hormone Analyses.* Plasma LH and prolactin were measured using double antibody RIA described previously (Niswender et al., 1969; Butler et al., 1972). Respective components were NIH-LH-S19 and NIH-P-S13 for reference, LER-1056-C2 and LER-860-2 for radioiodination and GDN #15 and DJB-7-0330 antisera. Sensitivity of the LH RIA was .3 ng/ml and intra-assay and interassay CV were 10 and 13%, respectively. Sensitivity of the prolactin RIA was 3.9 ng/ml and intra-assay and interassay CV were 13 and 15%, respectively. Progesterone was quantitated using a solid phase RIA validated for ovine plasma (Hamra et al., 1986) Sensitivity was .1 ng/ml and intra-assay and interassay CV were 8 and 10%, respectively. This assay has been used previously to measure plasma progesterone concentrations in ewes bearing type S and G CIDR (Hamra et al., 1986; Carlson, 1987).

*Statistical Analyses.* Hormonal concentrations and numbers of ovarian follicles in different size categories were analyzed in a split-plot design for repeated measures. The Pulsar computer program was used to identify LH pulses occurring during 7-h bleeding periods (Merriam and Wachter, 1982). Ovarian weights and total numbers of follicles were compared for treatment differences using a *t*-test. Estrus, conception, luteal activity and lambing responses from Exp. 3, 4 and 5 were analyzed for effects of melatonin and CIDR treatments and their interaction in a 2 × 2 factorial design. Data from each experiment were analyzed separately. A seasonal difference in incidence of estrus following withdrawal of CIDR was examined statistically by comparing responses of ewes treated with CIDR in Exp. 2 and 5. Data were grouped into a 2 × 2 contingency table and analyzed using a chi-square test. Incidence of estrus in ewes treated with melatonin implants in these two studies were compared in the same manner. Animal weights are presented in text as mean ± SD; treatment data are given as mean ± SE.

## Results

*Experiment 1.* Plasma LH concentrations were similar in ovx-$E_2$-treated ewes fed melatonin or control pellets for 43 d. Mean LH levels were 1.4 ng/ml in animals fed melatonin and 1.7 ng/ml in control animals. Luteinizing hormone levels also were similar 2 to 3 h after sunrise and 2 to 3 h after melatonin feeding, as well as among blood sampling days. Likewise, melatonin treatment was without effect on LH levels, frequency or amplitude of LH pulses and magnitude of secretory response to GnRH

[7]Regulin, Gene Link Australia Ltd., Victoria.
[8]Eazi-breed, AHI Plastic Moulding Co., Hamilton, NZ.

TABLE 1. OVARIAN FOLLICULAR DEVELOPMENT IN CONTROL (CON) AND MELATONIN-TREATED SHEEP (MEL)

| Surface follicles/ovary | | | Internal follicles/cm$^2$ | | |
|---|---|---|---|---|---|
| Diameter, mm | CON | MEL | Class | CON | MEL |
| <2 | 4.4 ± .9[a] | 2.0 ± .7 | Primordial | 6.1 ± 3.4 | 3.3 ± 1.2 |
| 2–3 | 10.7 ± 3.0 | 11.4 ± 2.5 | Primary | .3 ± .1 | .6 ± .3 |
| 4–5 | 1.1 ± .4 | .5 ± .2 | Secondary | .2 ± .0 | .3 ± .1 |
| ≥6 | 0 | .4 ± .1 | Tertiary | .3 ± .1 | .4 ± .1 |

[a]Mean ± SE, n = 4. Data from both ovaries of an animal were averaged to give one value/ewe.

during extended blood sampling periods at the end of the treatment period. Most ewes had 0 or 1 LH pulse/7 h and had GnRH-induced peak levels of 8.4 ± 1.0 (CON) and 6.9 ± 0.5 (MEL) ng/ml 15 min postinjection.

Plasma prolactin levels were decreased ($P < .001$) by melatonin treatment. Concentrations averaged 227 (CON) and 86 (MEL) ng/ml and became different ($P < .05$) 9 d after melatonin feeding began. Prolactin levels in morning and evening plasma samples were uniform.

*Experiment 2.* In ewes with melatonin implants, mean LH levels were 1.3 ng/ml during the 40-d treatment period, unchanged from that in control animals (1.2 ng/ml). Levels were similar before, during and after progesterone administration. No animals had a preovulatory LH surge following CIDR withdrawal nor were any corpora lutea observed during laparoscopy. Progesterone concentrations averaged 1.2 ng/ml the day CIDR were removed and .7 ng/ml the next day. Thereafter, levels were low or undetectable. Ovarian weights (CON = 1.1 ± .1; MEL = 1.4 ± .1 g/ovary) and follicular development were equivalent in ewes of both treatment groups (Table 1).

Plasma prolactin concentrations were lower ($P < .01$) in melatonin-implanted ewes (84 ng/ml) than in control ewes (139 ng/ml). Daily means varied ($P < .05$) on d 10 postimplantation and on most days thereafter.

*Experiment 3.* Following introduction of vasectomized rams on August 3, estrus was detected at similar times in ewes that had received melatonin implants and in those that had not (Table 2). Twelve-day application of CIDR preceding joining of rams reduced ($P < .05$) intervals to estrus. Onset of plasma progesterone levels ≥ 1 ng/ml for six consecutive days was advanced ($P < .001$) by both melatonin and CIDR treatments, corresponding to endogenous and exogenous progesterone, respectively (Table 2). Time of progesterone onset in ewes having a melatonin implant and a CIDR was similar to those animals with only a CIDR, producing a significant treatment interaction. The CIDR raised progesterone levels to 1.6 ng/ml while in place, after which spontaneous estrous cycles occurred.

Luteinizing hormone levels were similar among ewes in the four groups during the experimental period. Treatment means ranged from .9 to 1.2 ng/ml. Prolactin levels were

TABLE 2. INTERVALS FROM MELATONIN IMPLANTATION TO INCREASED PROGESTERONE LEVELS, AND FROM INTRODUCTION OF RAMS TO ESTRUS AND CONCEPTION, AND FECUNDITY

| | Experiment 3 | | Experiment 4 | | |
|---|---|---|---|---|---|
| Trt[a] | MEL-impl to prog[b] | Rams-in to estrus | Rams-in to estrus | Rams-in to conception | Fecundity |
| CON | 47 ± 1[c] | 16 ± 3 | 21 ± 5 | 21 ± 5 | 1.8 ± .2[d] |
| MEL | 30 ± 2 | 11 ± 5 | 21 ± 2 | 21 ± 2 | 1.8 ± .3 |
| CIDR | 21 ± 2 | 7 ± 2 | 2 ± 0 | 4 ± 3 | 1.7 ± .2 |
| CIDR-MEL | 22 ± 2 | 6 ± 3 | 1 ± 0 | 7 ± 4 | 2.0 ± 0 |

[a]Treatments were control (CON), melatonin (MEL) and progesterone-releasing pessaries (CIDR).

[b]Plasma progesterone ≥ 1 ng/ml for 6 d.

[c]Days, mean ± SE.

[d]Lambs born/ewe, mean ± SE.

TABLE 3. INTERVALS FROM INTRODUCTION OF RAMS TO ESTRUS AND CONCEPTION IN EXP. 5, AND FECUNDITY

| Trt[a] | Rams-in to estrus | Rams-in to conception | Fecundity, % Finn | |
|---|---|---|---|---|
| | | | 25% | 50% |
| CON | 21 ± 1[b] | 21 ± 1 | 2.0 ± .3[c] | 2.3 ± .2 |
| MEL | 13 ± 2 | 16 ± 2 | 1.8 ± .2 | 2.3 ± .2 |
| CIDR | 1 ± 0 | 11 ± 4 | 1.8 ± .2 | 2.0 ± .3 |
| CIDR-MEL | 2 ± 1 | 6 ± 2 | 2.0 ± 0 | 2.8 ± .5 |

[a]Treatments were control (CON), melatonin (MEL) and progesterone-releasing pessaries (CIDR).

[b]Days, mean ± SE.

[c]Lambs born/ewe ± SE.

decreased ($P < .001$) by melatonin treatment (CON = 299; MEL = 192 ng/ml). A clear difference was evident 15 d after melatonin implantation.

*Experiment 4.* Melatonin implants did not alter the time ewes exhibited estrus after joining of rams (Table 2). Intervals to estrus were reduced ($P < .001$) by CIDR. Conception resulted from matings at first estrus in 21 ewes and at second estrus in 3 sheep. Days to conception were less ($P < .001$) in the 12 CIDR-treated ewes. Gestation lengths ranged from 146 to 152 d and were unaffected by treatment. Fecundity was similar among ewes in the four treatment groups and 42 of 44 lambs survived the periparturient period.

*Experiment 5.* Responses, excluding fecundity, were similar ($P > .4$) in 25 and 50% Finn ewes; therefore, combined results are presented except for fecundity (Table 3). Melatonin implants reduced ($P < .01$) intervals from ram introduction to estrus, as did CIDR ($P < .001$). Onset of estrus following CIDR withdrawal was rapid, occurring within 2 d in most animals. This provided insufficient time to detect any further shortening of intervals by melatonin treatment and produced a significant interaction. Melatonin treatment tended ($P < .1$) to shorten and CIDR definitely shortened ($P < .001$) intervals to conception. Fecundity was unchanged by treatment but was greater ($P < .05$) in 50% than in 25% Finn ewes. Incidence of lamb mortality (7 of 108 lambs), gestation lengths (148.5 ± .3 d), lamb birth weights and vigor, lambing difficulty and dam's body condition and udder size and condition were independent of treatment and crossbreed groupings.

Incidence of estrus following CIDR and melatonin treatments was different ($P < .01$) between Exp. 5 and Exp. 2. In Exp. 5, control ewes expressed estrus from 17 to 27 d after introduction of rams on August 8. Twelve of 12 ewes administered CIDR were detected in estrus before 17 d, as were 7 of 12 melatonin-treated ewes. In Exp. 2, 0 of 8 ewes that had received CIDR and 0 of 8 ewes that had been treated with melatonin implants and CIDR exhibited estrus within 17 d of joining of rams on May 7.

## Discussion

Melatonin was administered by ingestion in Exp. 1 because at the time of the experiment the implants were in a developmental stage. Melatonin is readily absorbed from the digestive tract and a 3-mg dosage rapidly raises serum melatonin levels and sustains the increase for 7 h (Kennaway et al., 1982). A 7-h elevation would raise melatonin levels from the time pellets were fed, 8 h after sunrise, to dusk, when endogenous melatonin secretion occurs (Rollag et al., 1978). In this way, ewes were exposed to elevated melatonin levels for 16 h/d. Melatonin ingestion and implants have been compared and found to be equally effective (Arendt et al., 1988; Kennaway, 1988; Stellflug et al., 1988). Exogenous melatonin decreases prolactin levels (Symons et al., 1983; Poulton et al., 1986); this effect was evident in Exp. 1, 2 and 3, verifying that biologically active melatonin reached the circulation.

Bittman et al. (1983) reported that melatonin profiles characteristic of short days promote LH secretion by reducing the potency of estradiol negative feedback. Melatonin profiles characteristic of long days have the opposite effect. Melatonin was administered to ovx- $E_2$-treated sheep in Exp. 1 to determine the length of time needed to affect LH secretion. Melato-

nin was fed from May 1 to June 13 and had not effect on LH levels, pulsatility and response to GnRH. Robinson and Karsch (1988) indicated that the prevailing melatonin pattern is discontinuously processed, attributable to manifestation of an endogenous circannual rhythm. Such a phenomenon probably accounts for unresponsiveness of ewes to melatonin treatment in late spring when Exp. 1 was conducted. Results of Nett and Niswender (1982) and English et al. (1986) are consistent with a period of unresponsiveness to melatonin in spring.

In Exp. 2, melatonin implants were inserted March 31. Under production conditions in Minnesota, most ewes would be in mid- to late lactation at this time and a melatonin-induced fall in prolactin levels would not be expected to affect galactopoiesis (Tucker, 1981). Progesterone was given to condition the reproductive tract and, upon withdrawal, to stimulate a series of LH spikes. Such spikes stimulate estradiol secretion, but during anestrus this steroid blocks further LH spiking and thereby prematurely terminates follicular development and estradiol secretion (Legan and Karsch, 1979). It was postulated that 40-d melatonin treatment would reduce strength of estradiol feedback and thereby allow continued LH pulsing and full follicular growth and estradiol secretion, culminating in estrus and ovulation. Withdrawal of CIDR was not followed by preovulatory follicular development or estrus and ovulation in either melatonin-implanted or nonimplanted ewes. Use of CIDR without PMSG has been reported previously to be ineffective in spring (Hamra et al., 1989). Thus, application of 40-d melatonin implants to Suffolk ewes in early spring does not permit exogenous progesterone to stimulate out-of-season fertility.

Melatonin administration has been used successfully to achieve spring breeding (Stellflug et al., 1988; Wallace et al., 1988; Waller et al., 1988; Williams and Ward, 1988). In each case, however, circumstances differed from those of Exp. 2 in that either treatment was begun in winter and sheep were of breeds that exhibit considerable spontaneous reproductive activity in spring or much longer treatment periods were used that produced late spring and early summer matings.

Exp. 3, 4 and 5 were similar and were designed to compare melatonin and progesterone treatments to advance onset of the breeding season. Exp. 3 and 4 were contemporary trials; the former was conducted to determine time of onset of estrus and luteal function and whether spontaneous estrous cycles follow treatment-induced estrus, and the latter assessed fertility. Rams were joined August 3 in anticipation of January lambing, which on a commercial basis would allow early finishing of lambs to gain higher market prices. Although trials were performed at separate locations with different breeds of sheep, results showed that relationships among treatments at the two sites were consistent. Melatonin implants did not advance estrus under the experimental design employed. Broader extrapolation is limited by two factors: melatonin-implanted ewes may have expressed estrus before joining of rams, and sudden introduction of rams may have stimulated estrus earlier than normal in control animals (Pearce and Oldham, 1984). These possibilities are bolstered by appearance of cyclic luteal activity in melatonin-implanted ewes 10 d prior to joining of rams, and in control ewes 7 d after rams were brought in. Advanced luteal function does not necessarily imply that ewes exhibited estrus. In a study in which rams were present from the beginning of melatonin treatment, melatonin stimulated early luteal function but not estrus (Luhman and Slyter, 1986). The mechanism by which exogenous melatonin elicits ovarian activity is unclear. Alterations in gonadotropin secretion were not evident in the present experiment or in others (Kennaway et al., 1982; Poulton et al., 1987; Wallace et al., 1988).

The CIDR were withdrawn coincident with ram joining and estrous cycles followed soon thereafter. Estrus, conception and lambing dates (December 29 to January 19) were advanced by CIDR but were unaffected by the superimposed melatonin treatment. Comparison of results from Exp. 2 and 5 suggests a seasonal shift in response to CIDR. This supports past research that has shown that the number of ewes responding to progesterone treatment increased markedly after the summer solstice (Cunningham et al., 1980). The ram effect increases in potency as well (Nugent et al., 1988).

Unlike in Exp. 4, in Exp. 5 intervals from the time that rams were brought in to estrus were reduced by melatonin implants. Two changes in experimental design probably account for the difference. First, melatonin

implants were inserted on June 20 instead of on June 29, providing more exposure to continuous melatonin during a time of photoperiod transition. Observations from cited references make it tempting to speculate that photoperiod transitions encompass periods of responsiveness to melatonin. Second, a later date of ram introduction, August 8 vs August 3, appeared to push back dates of estrus in control animals. Estrus was detected 21 d after joining of rams in both trials, consistent with a ram effect. The tendency for melatonin treatment to decrease days to conception needs to be confirmed with more animals.

As in Exp. 4, CIDR removal was followed closely by estrus and conception. Higher fecundity seen in 50% than in 25% Finn ewes paralleled the lambing history of these sheep. Neither melatonin nor CIDR affected fecundity. Melatonin has been reported to increase fecundity to a mid-breeding season level. Above-average fecundity of the Crookston flock may have masked this action.

## Implications

Melatonin implants and progesterone pessaries imposed in spring were ineffective. Success may come from initiation of treatment in winter or from longer melatonin treatment producing summer breeding dates. Neither circumstance, however, has the potential to achieve two lambings per year in consecutive years. Melatonin and progesterone treatments each advanced the onset of the breeding season. Experiments were designed to produce January lambing, approximately 1 mo ahead of peak lambing in Minnesota. Commercial availability of either product could benefit producers with adequate lambing facilities and feed supplies.

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