

Current concepts in synchronization of estrus: Sheep and goats^{1,2}

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Abstract

Estrus synchronization (ES) in goats and sheep is achieved by control of the luteal phase of the estrous cycle, either by providing exogenous progesterone or by inducing premature luteolysis. The latter approach is not applicable during seasonal anestrus, whereas exogenous progesterone in combination with gonadotropin can be used to induce and synchronize estrus in anovular does and ewes. In the United States, ES in small ruminants is limited by the availability of appropriate pharmaceuticals, and there is a need for use of products designed and approved for the major livestock species (cattle and swine). The traditional product of choice for ES in goats and sheep is the intravaginal sponge impregnated with progestagen (e.g., flurogestone acetate or methyl acetoxypregesterone) for 9 to 19 d followed by PMSG injected -48 to 0 h from sponge removal. Alternative choices of progesterone/progestagen have been controlled internal drug release (CIDR) devices, supplying natural progesterone, norgestomet implants, and orally active melengestrol acetate. Other products used alone or in conjunction with progestagens are PGF_{2α} or an analogue (cloprostenol), a combination of PMSG/hCG, and zeranol. This review summarizes some of the research efforts in the 1990s to establish optimal dose levels and timing of administration, particularly for extra-label use products, achieve tighter synchrony in support of timed insemination, and use the male effect and short-term nutritional manipulation in nonpharmacological approaches to induce ovulation and enhance ovulation rate.

Key Words: Sheep, Goats, Estrus Synchronization, Progestagen, Prostaglandin, Male Effect

Introduction

Estrus synchronization (ES) in livestock focuses on the manipulation of either the luteal or the follicular phase of the estrous cycle. In does and ewes, the opportunity for control is greater during the luteal phase, which is of longer duration and more responsive to manipulation. Strategies can be employed to extend the luteal phase by supplying exogenous progesterone or to shorten this phase by prematurely regressing existing corpora lutea (CL). Successful techniques must not only establish tight synchrony, but also provide an acceptable level of fertility upon artificial insemination or natural mating. The latter is commonly accomplished through co-treatments using gonadotropin. After these conditions are met, ES becomes the basis for successful AI and embryo transfer programs.

A considerable amount of information was produced and published on ES in goats and sheep in the 1970s and 1980s and the foundation was established for much of the research conducted today. However, the scope of this review will focus on research reported on ES in sheep and goats during the past 5 to 10 yr. The purpose of this research was to improve the earlier ES systems to enhance ovulation rates, achieve tighter synchrony, and establish optimal doses of synchronizing agents, especially for systems requiring the extra-label use of pharmaceutical products.

Discussion

Considerations for Small Ruminants

In small ruminants, ES is affected by the seasonal breeding patterns in most temperate breeds of goats and sheep. In avovular does and ewes, estrus may not only have to be synchronized, but also initiated. Systems requiring the regression of an active CL will not be effective under these conditions. However, after cyclic activity can be induced in anovular goats and sheep, seasonal breeding can be manipulated and the production cycle can be shortened. A second opportunity in small ruminants is the propensity of many breeds to carry and raise multiple offspring, which can often be controlled by adjustments in dosage levels and nutritional manipulations as part of the ES regimen.

Estrus synchronization in sheep and goats in the United States is limited by their classification as minor livestock species. The availability of pharmaceuticals for ES is restricted, and most applications currently used require the extra-label application of products developed for the major livestock species (i.e., cattle and swine). As a result of extra-label use, there are not standardized protocols and doses, and a variety of synchronization protocols and product combinations have been described. Also curtailing the development of ES systems for small ruminants is the lack of large-scale application of AI. Whereas AI is used routinely in the dairy goat industry, this technology is usually restricted to use in expensive breeding stock or as part of an embryo transfer program in the sheep and meat goat industry. In sheep, AI is further impaired by problems in freezing

ram semen and problems in the transcervical deposition of semen.

Intravaginal Sponges

Intravaginal sponges have been the traditional treatment of choice for ES in small ruminants, during the breeding and anestrus seasons. They are impregnated with progestagens that are effective at lower dose levels than natural progesterone. Two types of sponges are currently commercially available, based on either flurogestone acetate (**FGA**), marketed as Chronogest (Intervet, Angers, France), or medroxyprogesterone acetate (**MAP**), marketed as Veramix (Pharmacia & Upjohn, Orangeville, Canada). Intravaginal sponges are usually inserted over periods of 9 to 19 d and used in conjunction with PMSG, particularly for out-of-season breeding, injected at time of sponge removal or 48 h prior to sponge removal. Intravaginal sponges have high retention rates (> 90%), and females usually exhibited estrus within 24 to 48 h after sponge removal.

Efficacy of Intravaginal Sponges. Estrus response and fertility vary greatly when intravaginal sponges are applied, dependent on species, breed, co-treatment, management, and mating system (Table 1). A comparison of intravaginal sponges containing 15, 30, 45, or 60 mg of MAP in seasonally anovular Corriedale ewes showed no differences between doses in the percentage of does ovulating (96.8%) or in ovulation rate (1.25) (Iglesias et al., 1997). These findings suggest that MAP doses of 25% of the commercial formulation (60 mg) may still be sufficient to induce estrus in this breed. Ewes in this experiment were induced to ovulate using the ram effect. A second experiment reported in the same paper indicated that no benefit was derived in lambing rate or number of lambs born by supplementing these ewes after estrus with an additional MAP sponge (30 mg) for 7 d; however, the percentage of ewes returning to estrus was reduced from 27 to 16% ($P < .05$). These latter observations are supported by an experiment in goats that evaluated the application of a second FGA sponge on d 7 or 9 of an 11-d treatment period (400 IU of PMSG and 50 µg of cloprostenol 48 h before sponge removal) for ES followed by exocervical AI with frozen semen in Alpine and Saanen does (Freitas et al., 1996b). No differences were observed in the percentage of does exhibiting estrus and ovulating, but fertility was lower ($P < .05$) in Alpine does supplemented with additional FGA on d 9 (87.5 vs 50.0%).

A number of studies evaluated the effectiveness of timed insemination following intravaginal sponge treatment. In a large-scale trial using Merino ewes ($n = 2,304$), Moses et al. (1997) found no difference in pregnancy rates when laparoscopic AI with frozen semen was performed in mature ewes at 12 h after detected estrus (62.9%) or at a fixed time 60 h after sponge removal (59.1%). Pregnancy rates, however, were lower in 20-mo-old ewes, regardless of AI protocol (54.5 and 48.6%, respectively). Evaluation of the timing of PMSG injection (–48 h or 0 h in relation to MAP sponge removal) for fixed-time cervical insemination,

36 and 48 h for –48 h and 48 and 60 h for 0 h after sponge removal, with fresh semen in seasonally anestrus ewes suggested that lambing percentages (40 to 64%) could be achieved comparable to those obtained by “at-estrus” inseminations (50%) (Fukui et al., 1989). Optimum timing of insemination in this experiment was related to the timing of the injection of PMSG in relation to sponge removal.

In two experiments Freitas et al. (1997a) assessed the natural variability in the timing of estrus and ovulation following ES with intravaginal sponges to detect physiological limitations to the development of fixed-time insemination. They determined that the between-goat variation in the timing of events in an uninduced estrus was greater than that following a synchronized estrus. Furthermore, a considerable part of this variability was associated with delays occurring after the estradiol peak, thus removing these from events immediately associated with the progestagen treatment.

Gonadotropin Co-treatments. The use of gonadotropin is routinely incorporated into intravaginal device synchronization systems used in anovular does and ewes to induce ovulation. The most commonly used product is PMSG (eCG). One limitation of PMSG is its long-acting biological activity, causing it to continually recruit antral follicles, which results in a large number of unovulated follicles (Armstrong et al., 1983), particularly when given at dose levels to induce superovulation. Hence, various studies have evaluated different dose levels of PMSG, the timing of PMSG treatment, and alternative types of gonadotropins. To this end, three doses of PMSG (300, 450, and 600 IU) were evaluated for use with FGA (40 mg, 14 d) sponges during the anestrus season in ewes (Zaiem et al., 1996). All three PMSG dose levels yielded similar fertility rates (81.2 to 84.3%) that were higher ($P < .05$) than those in FGA-treated control ewes receiving no gonadotropin (57.5). Prolificacy was increased ($P < .05$) over that of controls (130.4%) at PMSG dose levels of 450 IU (155.5%) and 600 IU (176.9%), but not at 300 IU (133.3), suggesting that 450 to 600 IU PMSG are optimal levels in this scenario.

Another potential limitation of PMSG has been the recent discovery of declining fertility after long-term use (reviewed by Baril et al., 1998). In a project involving nine commercial flocks of dairy sheep, seven flocks were subjected to a standard FGA sponge treatment (40 mg, 14 d) with 500 to 550 IU PMSG injected at the time of sponge removal, and two flocks served as untreated controls (Bodin et al., 1997). Blood samples were collected at the time of sponge insertion and again 20 d after PMSG treatment and checked for the presence of anti-PMSG antibodies. Binding rates for PMSG in 95% of ewes in the two control flocks never treated with PMSG were below 1.5%. In contrast, the mean binding rate for treated flocks was 14.7%, but this was not immediately related to ewe age and number of previous PMSG treatments. Similar observations of anti-PMSG antibodies have previously been reported in goats, with elevated binding levels found in multiparous does in herds routinely using PMSG in conjunction with sponge-

based ES to facilitate AI during the anestrus season (Baril et al., 1992). In does with PMSG binding > 5%, a delay of the onset of estrus was noted in 37.9% of does, whereas only 7.4% of does with binding < 5% experienced a delay in onset of estrus past 30 h (Baril et al., 1996). This delay in timing of estrus has been suggested as one of the major causes of the reduction in fertility seen in does repeatedly treated with PMSG (Baril et al., 1993).

The use of pharmacological doses of GnRH in conjunction with intravaginal sponges to induce ovulation was evaluated by Robin et al. (1994) in dairy goats. A single injection of GnRH (125 µg) and a double injection (125 µg/injection in a 48-h interval) at sponge (MAP, 60 mg, 14 d) removal delayed ($P < .01$) onset of estrus and the timing of endocrine events associated with ovulation compared to PMSG-treated does. Pregnancy rate was also lower ($P < .05$) in does receiving single and double injections of GnRH than in does treated with PMSG (0 and 12% vs 57%, respectively). In Merino ewes treated with GnRH injection (100 µg) 24 h after sponge removal (MAP, 12 d), time to ovulation was advanced in the breeding season, but the treatment had no effect on the timing of ovulation in the anestrus season (Ryan et al., 1992). Similarly, shortening of the time to onset of estrus was observed in cyclic Merino when GnRH (100 µg) was injected 12 h after sponge removal (MAP, 12 d) (Jabbour and Evans, 1991). It seems doubtful that bolus injections of GnRH can stimulate ovulation to the same extent previously seen with sustained GnRH treatment protocols.

Co-treatments to Enhance Ovulation Response to Synchronization. Short-term nutritional manipulation has resulted in increased ovulation rates following intravaginal sponge ES. Supplementing Merino ewes with lupin grain starting d 8 of a 14-d FGA (40 mg) treatment period resulted in a 64% increase ($P < .05$) in ovulation rate over that in unsupplemented ewes (Pearse et al., 1994). In another experiment feeding of lupin grain delayed ($P < .001$) the timing of ovulation in the breeding season but did not affect timing in the anestrus season (Ryan et al., 1992). To increase ovulation rate in anovular Corriedale ewes and mimic results previously seen with lupin feeding, Iglesias et al. (1996) incorporated an oral glucogenic cocktail containing glycerol (70%) and propylene glycol (20%) into a synchronization protocol with two MAP levels (10 and 60 mg). This protocol included ram exposure to induce ovulation, and the glucogenic cocktail (100 mL) was administered immediately before ram exposure. The results were variable: glucogenic treatment resulted in higher ($P < .01$) ovulation rates at the lower MAP levels (1.56 vs 1.31), but ovulation was depressed with glucogenic treatment at the higher MAP levels (1.30 vs 1.13). In this experiment the time from ram exposure to estrus was significantly longer for the 60-mg MAP group (54.8 h) than for the 10-mg MAP group (43.6 h). These results point to the potential of short-term nutritional modifications to increase ovulation rate in synchronized estrus.

Laliotis et al. (1998) incorporated melatonin implants into a MAP-based synchronization system (60 mg, 14 d,

500 IU PMSG at time of sponge removal) during the anestrus period in Greek dairy sheep. Melatonin implants (Regulin, 18 mg; Cambridge Animal and Public Health, Cambridge, U.K.) were inserted 35 d before sponge insertion and ewes were cervically time-inseminated at 48 and 60 h after sponge removal. Melatonin co-treatment resulted in higher ($P < .05$) lambing rates in the second estrus after treatment (60.4 vs 32.6%) and overall (83.3 vs 68.6%), and it increased ($P < .05$) overall litter size by .17 lambs. With a similar system (MAP + melatonin), Stellflug et al. (1994) were able to increase lambing rate in Targhee ewes lambing (67.9 vs 92.7%) over that of controls; treatments with MAP only or melatonin only yielded intermediate results. However, in the same experiment Columbia ewe lambs failed to respond to treatment.

Influence of Stage of Estrous Cycle and Ovarian Structures. In a recent study using MAP sponges for 12 d in cyclic Suffolk ewes, insertion was timed to occur on d 0 (ovulation), 6, and 12 of the estrous cycle and ovarian activity was monitored by ultrasonography and blood plasma analysis (Leyva et al., 1998). Estrus was synchronized prior to sponge insertion using a triple injection of cloprostenol (100 µL) 9 and 12 d apart, and synchrony following the final injection was confirmed by ultrasonography and a rise in progesterone. Insertion of sponges on d 6 and 12 extended ($P < .001$) the interovulatory interval from 16.4 to 22.8 and 28.4 d, respectively, and increased the number of follicular waves from three to four and five, respectively, over that seen in ewes on d 0. The return to basal endogenous progesterone was delayed ($P < .01$) by 3 d when sponges were inserted at d 6 and 12. Ovulation after sponge removal occurred earlier for d 0 (83.6 h) and d 12 (79.5 h) than d 6 (93.5 h). Hence, stage of estrus cycle at implantation has implications for timed insemination after ES.

Controlled Internal Drug Release (CIDR) Devices

These devices are made of progesterone-impregnated medical silicone elastomers and were developed in New Zealand. Types available for small ruminants are the CIDR-S and CIDR-G (InterAg, Hamilton, New Zealand); the latter is more commonly applied today. Their progesterone content ranges from 9 to 12% (330 mg progesterone). In early studies in ovariectomized ewes implanted with CIDR-S devices, plasma progesterone peaked within 2 h of insertion (5.5 ng/mL), with a rapid curvilinear decline thereafter (Ainsworth and Downey, 1986). However, subsequent work by Wheaton and coworkers (Hamra et al., 1986; Wheaton et al., 1993) with later versions of the device found peak plasma progesterone values of 2.1 ng/mL within 24 h and relatively stable levels between d 1 and 13 (1.9 ng/mL). Protocols for the use of CIDR devices are usually identical to protocols for intravaginal sponges.

The timing of endocrine events was evaluated in cyclic Suffolk ewes following the application of a single or two CIDR-G devices for 8 d by frequent blood sampling (Van Cleeff et al., 1998). The two-CIDR treatment increased the plasma progesterone concentration from 2.7 to 5.2 ng/mL at

the time of CIDR withdrawal and delayed the timing of the peak LH surge from 38.2 to 46.2 h ($P < .001$), but there were no other differences in endocrine variables. Both treatments synchronized LH and E_2 surges within 24 h in 92% of ewes. Other research suggests that the progesterone priming supplied by a CIDR device may not be sufficient to support desirable ovulation rates in superovulation and embryo transfer schemes (Thompson et al., 1990; Scudamore et al., 1993).

The timing of estrous activity following an 11-d CIDR treatment at the beginning of breeding was delayed ($P < .05$) by 10 h in younger (two-tooth) ewes than in mature ewes (33.3 to 34.5 h) (Fenton et al., 1997). In the same study, there was also evidence of a location effect on the mean interval to estrus following CIDR treatment. Other research indicated that the use of CIDR eliminated variations in ovulation rates usually observed under natural conditions during the breeding season in ewes (Scott and Montgomery, 1990).

Efficacy of CIDR Devices. Estrous response and fertility levels in a number of experiments using CIDR in sheep and goats over the past 10 yr are summarized in Table 2. Ritar et al. (1990) reported large-scale trials ($n = 1,833$) with Cashmere does in Australia comparing CIDR-G devices with more traditional intravaginal sponges (FGA) for use in AI schemes during the breeding season. In these trials, does were treated intravaginally for 15 to 20 d and exposed to testosterone-treated wethers to avoid short cycles due to the male effect. At termination of intravaginal treatment PMSG (200 IU) was administered to all does. Their experiments suggested no differences between FGA sponges and CIDR devices; however, timing of insemination was advanced by 10 h for the CIDR-treated does to account for expected differences in the mean time to ovulation in the two intravaginal treatments. In these experiments pregnancy rates of 39% were achieved for cervical insemination and 52 to 64% for laparoscopic insemination using frozen-thawed semen. Pregnancy rates were significantly higher ($P < .01$) when timed to precede the estimated time of ovulation. For CIDR devices fecundity (fetus/doe pregnant) was higher ($P < .05$) when insemination occurred 39 h (1.27) rather than 45 h (1.20) after intravaginal treatment removal, although pregnancy rate was not affected by timing.

In 10 on-farm trials with mixed-breed ewes in Minnesota, CIDR-S sponges performed similarly to 30-mg FGA sponges after a 14-d treatment period and an injection of PMSG (750 IU) at the end of intravaginal treatment (Hamra et al., 1989). Conception rates and fecundity were 71% and 1.6 for CIDR-S and 85% and 1.5 for FGA sponges, respectively, and differences were not significant. In a second series of five on-farm trials during the breeding season, CIDR-S were applied for 12 d and rams were turned in with ewes 2 d after device removal (Carlson et al., 1989). A majority of ewes (91%) were bred within 5 d, and 7% expelled the device prior to the end of treatment.

In goats, advancing PMSG (200 to 400 IU) co-treatment from the time of CIDR removal to 48 h prior to

removal advanced ($P < .01$) ovulation (Ritar et al., 1989). However, time of PMSG treatment had no effect on kidding rates and litter size following either laparoscopic or timed cervical insemination. Using the CIDR-G in Spanish goats (16-d treatment), satisfactory pregnancy rates (61.1%) and prolificacy (168 %) in conjunction with PMSG (250 IU) 48 h before implant removal were achieved when does were inseminated laparoscopically using frozen-thawed semen during their natural breeding season (Waldron et al., 1999). In this study no benefit was derived when $PGF_{2\alpha}$ (5 mg) was administered at the time of PMSG injection.

Extra-label Use of Progestagens and PMSG

Norgestomet Implant Systems. Commonly used systems for ES in small ruminants in the United States are based on the norgestomet ear implant supplied with the Syncro-mate-B (SMB; Rhone-Merieux, Athens, GA) system developed for cattle. The cattle implant contains 6 mg of the synthetic progestagen norgestomet (17 α -acetoxy-11 β -methyl-19-pregn-4-ene-3,20-dione) but is commonly used as one-half or one-third of the original implant when used in sheep and goats (Mellado and Valdez, 1997). Implantation periods for both species usually extend from 9 to 14 d and often are combined with PMSG and(or) $PGF_{2\alpha}$ co-treatments at or 2 d before the end of the implantation period. The injectable component supplied for the cattle system (norgestomet and estradiol valerate) to inject at the beginning of implantation are rarely used in goats and sheep, because their action on a CL that may be present is not needed or desired.

A recent study evaluated the timing of estrus and ovulation in norgestomet-implanted (6 mg) Dorset and Rambouillet \times Dorset ewes by use of a telemetric HeatWatch estrus detection system and transrectal ultrasonography (Cardwell et al., 1998). Estrus was detected in 84% of ewes in the study. Season (spring vs fall) had no effect on the timing of events; however, co-treatment with PMSG (500 IU) advanced ($P < .01$) ovulation from 79.8 to 68.6 h and the onset of estrus from 46.0 to 32.6 h, compared to ewes implanted only. The timing of the occurrence of the LH peak following norgestomet implantation (3 mg for 11 d with 400 IU PMSG and 50 μ g cloprostenol 48 h before implant removal) was delayed ($P < .05$) when two or more CL were present on d 9 of implantation (46.9 h) compared to 0 and one CL (42.5 and 42.2 h, respectively) but was not affected by the number of CL on d 0 of treatment (Freitas et al., 1996a). The number of CL on d 0 of treatment had no effect on the onset of estrus, nor did follicle populations on either day affect timing of estrus and the LH surge.

The estrus response following norgestomet-based ES systems in a number of experiments ranged from 62 to 100%, depending on dose, season, and co-treatment; similarly, fertility varied greatly (27 to 83%) depending on the same variables and the mating system employed (Table 3). In comparing norgestomet implants (3 and 1.5 mg for 11 d with 400 IU PMSG and 50 μ g cloprostenol 48 h before end of treatment) to FGA sponges (45 mg) for use in dairy

goats, Freitas et al. (1996b) found no differences in the percentage of does exhibiting synchronized estrus but observed a decrease ($P < .05$) in the percentage of does ovulating (98.2 to 81.8%) in one experiment and a shortening ($P < .05$) in the onset of estrus in a second experiment when comparing FGA to the 1.5-mg dose of norgestomet.

A dose-response study for PMSG associated with norgestomet implantation (6 mg for 10 d, PMSG administered 24 h before implant removal) in cyclic Pelibuey ewes suggested a decreased ($P < .05$) estrus response at dose levels of 500 and 1,000 IU; however, dose levels of $\geq 2,000$ IU produced a superovulatory response (> 5 CL) and large numbers of unovulated follicles (Gonzalez-Reyna et al., 1999). Another study in Mexico evaluated the use of recycled norgestomet implants, used previously in cattle and goats, for ES in Criollo goats (Mellado and Valdez, 1997). Implants (1.2 to 2 mg norgestomet) previously used in goats did not perform significantly differently from new implants of similar size (52.7 vs 66.7% does in estrus, respectively), but estrus response was lower (42.7 vs 61.9%; $P < .05$) and time to estrus was delayed (52 vs 48 h; $P < .05$) for implants used in cattle, suggesting a reduced release of norgestomet in these implants.

Melengestrol Acetate (MGA) Feed Supplement. This product is an orally active, synthetic progestagen developed and used for the suppression of estrus in feedlot heifers, but it has also been used for the induction of a fertile estrus in seasonally anovular ewes. The use of this product requires the feeding of a supplement containing MGA (Pharmacia & Upjohn, Kalamazoo, MI) once or twice daily for a duration of 8 to 14 d. Protocols for ES with MGA have usually included co-treatments of PG-600 (PMSG/hCG; Invervet, Millsboro, DE) and/or Ralgro (zeranol; Pittman-Moore, Terre Haute, IN). Zeranol, a commercially available growth promotant for cattle and sheep with estrogen-like effects on LH and FSH concentrations, has been administered both at the beginning (Jabbar et al., 1994) and the end (Powell et al., 1996) of MGA feeding.

Results from ES experiments using MGA feeding are summarized in Table 4. During seasonal anestrus, the estrus response ranged from 13 to 96% and was usually higher when a co-treatment with PMSG or zeranol was applied. Similarly, fertility after MGA feeding was variable (10 to 75%) depending on co-treatment and the male effect (Umberger et al., 1994). Although zeranol, when administered at the end of the MGA feeding period, tended to increase the synchronized estrus response at higher doses, fertility was depressed ($P < .05$) at these higher dose levels (5 mg) (Powell et al., 1996). This depression in fertility was not observed when zeranol was administered at the beginning of MGA feeding (Jabbar et al., 1994).

Use of PG-600 as a Source of PMSG. Currently PG-600 represents the only veterinary-grade source of PMSG readily available in the United States. The product contains a combination of 400 IU PMSG and 200 IU hCG per described dose of 5 mL and is approved for the induction of estrus in pubertal gilts. The product has found extra-label use in progestagen-based ES systems for sheep, usually at

the 5-mL dose level prescribed for swine. Estrus response and fertility following its use in conjunction with norgestomet and MGA were described above (Safranski et al., 1992; Jabbar et al., 1994; Umberger et al., 1994).

In goats, the use of PG-600 has not been as extensively reported. Rowe and East (1996) compared the efficacy of PG-600 to a reagent-grade source of PMSG, following norgestomet implantation (3 mg, 9 to 13 d) of lactating dairy goats. The two sources of gonadotropin were injected at dose levels of 300 IU PMSG 36 h before implant removal, followed by an injection of cloprostenol (125 μ g) at implant removal. Estrus response was not significantly different between PG-600 and reagent-grade PMSG (97 vs 89%, respectively), but the percentage of does pregnant and kidding was higher ($P < .05$) in PG-600 treated does (90 and 83% vs 76 and 70%) at similar litter sizes. These authors suggest that this difference may be mediated through a synergistic effect of the PMSG with the hCG. Our lab evaluated the estrus and ovarian response to graded doses of PG-600 following norgestomet implants (3 mg, 12 d) during the breeding and anestrus season (Wildevus, 1997). Dose levels of 0, 80, 160, 320, 640, and 1,280 IU PMSG were used and administered at the time of implant removal. Estrus response and time to estrus were not affected by PG-600 dose level, but the number of CL increased with increasing dose levels in both seasons. Doses of > 160 IU PMSG resulted in ovulation rates > 3 , suggesting a superovulatory effect, but only at the highest dose (1,280 IU) was there a significant ($P < .05$) increase in the number of large follicles (> 5 mm). These data suggest that PG-600 dose levels lower than those applicable for swine may be sufficient in ES protocols for goats.

Prostaglandin (PGF_{2 α})-Based Systems

Prostaglandin-based ES systems control the estrous cycle by terminating the luteal phase through regression of the CL. This approach is only applicable in cyclic females and hence prostaglandin-based systems are restricted for use during the breeding season in sheep and goats. The two commonly used products are PGF_{2 α} (Lutalyse; Pharmacia & Upjohn) and the prostaglandin analogue cloprostenol (Estrumate; Bayer, Shawnee Mission, KS). Because not all stages of the estrous cycle are similarly receptive to treatment, a double injection system 11 d apart is the most widely used approach in goats and sheep.

No difference was observed in estrus response and timing of estrus and LH surge in dairy goats treated with cloprostenol (125 μ g) on d 6 and 12 of the estrous cycle (Nuti et al., 1992). The mean time from injection to behavioral estrus was 46 to 48 h, with 95 to 100% of does responding, and the LH surge occurred at 62 to 64 h after injection. Furthermore, no difference was observed between a dose of 62.5 and 125 μ g cloprostenol in the onset and duration of estrus in Nubian goats injected once between d 8 and 15 of the estrous cycle (Romano, 1998a). Zamiri and Hosseini (1998) evaluated the use of hCG to improve fertility, prolificacy, and lambing performance in fat-tail ewes synchro-

nized with cloprostenol 8 d apart. Ewes were injected with doses of 125, 250, and 500 IU hCG or saline 24 h after the second injection of cloprostenol. The higher doses of hCG increased ($P < .05$) prolificacy but depressed fertility and conception rate, suggesting that hCG is not a viable source or gonadotropin for this type of synchronization system. Feed restriction for 19 d had no significant effect on the estrous response in dairy goats following an injection PGF (10 mg) on d 16 of the estrous cycle (71.0 and 87.5 % for restricted and control group, respectively), but ovulation and pregnancy rate were reduced ($P < .05$) in the feed-restricted group (Mani et al., 1992).

In Boer goats synchronized outside the normal breeding season, the estrous response was lower ($P < .01$) in a double PGF injection system (13 to 20%), compared to sponges and sponges plus PGF (87 to 100%), regardless of co-treatment with 500 IU PMSG (Greyling and Van Niekerk, 1991), confirming the lack of efficacy of PGF during the anestrus and transitional season. No difference was observed in cyclic Menze ewes in the estrus response (83%) following PGF (2.5 mg, 12 d apart) and sponge (FGA, 40 mg for 12 d) treatment, but PGF-treated ewes exhibited estrus ($P < .05$) earlier (-6 h) than sponge-treated ewes (Mutiga and Mukasa-Mugerwa, 1992). An earlier onset of estrus after PGF (10 mg, 11 d apart) compared to sponge (MAP, 60 mg for 14) treatment was also observed in West African Dwarf sheep (41.2 vs 77.7 h; $P < .05$) (Oyediji et al., 1990). In contrast, Romano (1998b) found an earlier ($P < .01$) onset of estrus in Nubian does after synchronization with FGA sponges (32.6 h) than with cloprostenol (48.0 h) and MAP sponges (50.4). In cyclic Nubian goats a double injection of PGF induced estrus in a higher ($P < .05$) percentage of does (100%) than in sponge-treated does (70%) (Ahmed et al., 1998).

Beck et al. (1993) compared the double injection system (125 µg cloprostenol 11 d apart) with a single injection and a combination of short-term progestagen treatment (MAP, 5 d) with a cloprostenol injection at sponge removal in Clun Forest ewes. They found a 100% estrus response in the double injection and MAP-PGF combination treatment, whereas estrus response was reduced in the single injection group (52.9%; $P < .05$). Return rate to estrus was similar for all three treatments (14.2 to 17.4%). In a follow-up experiment, Beck et al. (1996) compared the same double injection regimen with the combination of a 4-µg busserelin (GnRH agonist; Hoechst UK Ltd., Milton Keynes, U.K.) injection followed by a 100-µg cloprostenol injection 5 d later. Treatment groups had similar percentages of ewes exhibiting synchronized estrus (94 and 91%) and lambing (92.5 and 88.8%). These experiments suggest that combination treatments may successfully reduce the treatment period for ES from 11 to 5 d.

The Male Effect

In both goats and sheep, estrus can be induced with the strategic exposure of anestrus does (Chemineau, 1987) and ewes (Martin et al., 1986) to intact males or androgen-

treated castrates. This response is dependent on the depth of seasonal anestrus (Scott and Johnstone, 1994) and associated with a first ovulation in 2 to 3 d. This effect is mediated through changes in pulsatile GnRH release from the hypothalamus, selectively increasing tonic LH. The first ovulation is usually silent and of low fertility, with a premature regression of the first CL. The second ovulation 5 d later is accompanied by a fertile estrus with a luteal phase of normal length. The response to the male effect is influenced by such factors as the serving capacity and sexual aggressiveness of the buck (Walkden-Brown et al., 1993a) and ram (Perkins and Fitzgerald, 1994), the intensity of the stimulation, with immediate contact resulting in a greater response than fence-line contact or intermittent contact (Walkden-Brown et al., 1993b), and body condition (Walkden-Brown et al., 1993c).

Attempts to identify specific olfactory, tactile, visual, and even auditory stimuli have not been successful, which suggests that a complete response may require the interaction of a number of stimuli (Pearce and Oldham, 1988). Olfactory responses, however, seem to be important, as evidenced by a depressed response of anosmic does (Chemineau et al., 1986). The responsible pheromones are present in wool clippings and buck hair, but not in urine (Walkden-Brown et al., 1993b), and are not associated with buck odor during the breeding season.

Effect of Male Stimulation on Timing and Duration of Estrus. The primary limitation to the use of the male effect for ES is the reduced fertility of the first cycle and the loss of synchrony in subsequent cycles. The short life span of the male effect-induced CL may be associated with a different cellular composition than in CL developing after a FGA-synchronized estrus during the breeding season (Chemineau et al., 1993). Exogenous progesterone (20 mg) at the time of male introduction significantly reduced the number of short estrus cycles and extended the period from male induction to ovulation from 20.5 to 58.8 h in sheep and increased ovulation rate in goats (Lassoued et al., 1995, 1997). The uterus is also implicated in the premature regression of the CL after the male effect; both hysterectomy (Chemineau et al., 1993) and inhibitors of PGF_{2α} suppressed short cycles (Lassoued et al., 1997).

There has been some indication that continuous exposure to a buck following synchronized estrus by either cloprostenol or intravaginal sponges reduced ($P < .05$) the interval to estrus in Nubian does from 48 to 38 h (Romano, 1998b). Research by the same group also suggested that the duration of estrus was reduced when bucks were allowed to service the does, as opposed to be merely mounting the does (Romano, 1993, 1994a), and that this response was mediated through mechanical action of the penis against the vagina (Romano, 1994b). This variation in the timing of estrus may need to be taken in consideration when teaser bucks are used for estrus detection for AI following ES.

Incorporation of the Male Effect into ES Protocols. Umberger et al. (1994), using synchronization systems based on norgestomet and MGA, with or without gonad-

otropin treatment (PG-600), in anovular Dorset, Hampshire, and Suffolk ewes found that ram exposure was as effective in inducing ovulation as PG-600. In Dorset ewes in Canada, the male effect increased fertility following the use of FGA sponges only in July but had no beneficial effect at other times of the year (Rajamahendran et al., 1993), suggesting that the male effect for ES is most effective in anovular ewes. A comparison of two ram:ewe ratios (1:6 vs 1:12) for induction of ovulation and estrus following a 9-d MAP intravaginal sponge implantation period found no effect on the number of Corriedale ewes ovulating or on ovulation rate. However, the percentage of ewes marked by rams was higher ($P < .001$) at the lower ram:ewe ratio (Iglesias et al., 1997). In view of the lack of availability of gonadotropins for use in sheep and goats in the United States, the use of the male effect represents a viable and inexpensive alternative as a co-treatment in progesterone-based synchronization schemes for anestrus females.

Implications

Although progress has been made toward characterizing and manipulating the endocrine events associated with estrus synchronization and their timing, there are still opportunities to improve the efficiency of current systems and address some of their limitations. This holds true especially in the United States, where there is a limited availability of pharmaceutical products and a need to develop more standardized procedures and dose levels and to validate these in large-scale trials. However, unless improvements are made in artificial insemination procedures for small ruminants, especially sheep, that lead to a more widespread use of artificial insemination beyond the dairy goat industry, there is a limited incentive to improve on existing technologies.

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Notes

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Table 1. Estrus response within 96 h and fertility in does and ewes synchronized with FGA and MAP intravaginal sponges during anestrous and the breeding season not designed to achieve superovulation

Type	Duration, d	Dose, mg	Associated treatment	Breed	n	Estrus, %	Mating system	Fertility, %	Litter size	Reference
Anovular does										
FGA	11	45	400 IU PMSG and 100 µg cloprostenol 48 h before sponge removal	Saanen	169	80.7	Hand-mating AI	49.5 62.8	— —	Baril et al., 1992
FGA	14	45	FSH 12 mg, 8 injections at sponge removal	Dairy	17	88	—	—	—	Pendleton et al., 1992
MAP	14	60	None	Boer	15	53.5	—	—	—	Greyling and Van Niekerk, 1991
	8		62.5 µg cloprostenol at sponge removal		15	86.7	—	—	—	
	8		500 IU PMSG and 62.5 µg cloprestenol at sponge removal		15	86.7	—	—	—	
FGA	16	40	None 300 IU PMSG at sponge removal	Nubian	10 10	70.0 77.7	Cervical AI	40 33	1.5 1.6	Ahmed et al., 1998
FGA	11	45	400 IU PMSG and 50 µg cloprostenol 48 h before sponge removal	Dairy	640	98.1	Timed AI	65	1.9	Baril et al., 1993
FGA	11	45	400 IU PMSG and 50 µg cloprostenol 48 h before sponge removal	Alpine Saanen	15 17	93.8 100	Cervical AI	87.5 58.8	2.3 1.6	Freitas et al., 1996b
MAP	17	60	400 IU PMSG 48 h before sponge removal	Dairy	76		Natural	53.9	2.3	Robin et al., 1994
FGA		45			78			43.6	2.2	
Cyclic does										
FGA	18	45	200 IU at sponge removal	Cashmere	198 279	— —	Cervical AI Laparo. AI	37.4 62.7	1.92 1.73	Ritar et al., 1990
MAP	12	60	None	Nubian	10	100	—	—	—	Romano, 1998b
FGA		30			14	100	—	—	—	
MAP	17	60	400 IU PMSG 48 h before sponge removal	Saanen	6	100	Cervical AI	50	—	Menegatos et al., 1995

Continued on next page

Type	Duration, d	Dose, mg	Associated treatment	Breed	n	Estrus, %	Mating system	Fertility, %	Litter size	Reference
Anovular ewes										
MAP	14	60	500 IU PMSG at sponge removal	Mixed	167	94.1	Natural	65.0	1.67	Tritschler et al., 1991
FGA	12	40	500 IU PMSG at sponge removal	Dorset	12	77.0	Natural	53.0	1.01	Rajamahendran et al., 1993
FGA	14	40	None	Black Thibar	40	—	—	57.5 ^a	1.30 ^a	Zaiem et al., 1996
			300 IU PMSG at sponge removal		32	—	—	84.4 ^b	1.33 ^{ab}	
			450 IU PMSG at sponge removal		32	—	—	84.4 ^b	1.55 ^b	
			600 IU PMSG at sponge removal		32	—	—	81.2 ^b	1.77 ^b	
MAP	9	15	Ram introduction	Corriedale	58	90.7	—	81.8	—	Iglesias et al., 1997
		30			58	98.1	—	70.9	—	
		45			58	94.1	—	76.0	—	
		60			58	96.4	—	76.0	—	
Cyclic ewes										
MAP	14	60	None	Dwarf	6	100	—	—	—	Oyediji et al., 1990
FGA	12	40	None	Menze	12	83.3	Natural	75	1.11	Mutiga and Mukasa-Mugerwa, 1992
			200 IU PMSG at sponge removal		12	100		75	1.22	
			300 IU PMSG at sponge removal		12	75		75	1.55	
MAP	14	60	200 IU PMSG at sponge removal	Merino	1824	80.1	Laparo. AI	61	—	Moses et al., 1997
FGA	14	30	400 IU PMSG at sponge removal	Merino	116	96.7	AI frozen AI fresh	39.3 80.4	— —	Tekin et al., 1992

^{a,b}Values with unlike superscripts within same column and reference differ ($P < .05$).

Table 2. Estrus response within 96 h and fertility in goats and sheep synchronized with CIDR devices

Type	Duration, d	Associated treatment	Breed	Season	n	Estrus, %	Ovulation rate	Mating system	Fertility, %	Litter size	Reference
Sheep											
CIDR-S	12	None	Mixed	Breeding	129	91	—	Natural	95.0	—	Carlson et al., 1989
CIDR-S	14	750 IU PMSG at removal	Mixed	Anestrus	165	92	—	Natural	64.0	1.00	Hamra et al., 1989
CIDR-G	15–20	200 IU PMSG at removal	Mixed	Breeding	204	—	—	Cervical	40.7	1.75	Ritar et al., 1990
					290	—	—	laparosc.	64.5	1.84	
					479	—	—	Laparosc. – 39 h	51.6	1.27	
					383	—	—	Laparosc. – 45 h	52.7	1.20	
CIDR-G	12	None	Mixed St. Croix	Breeding	29	—	1.40	Natural	72.0	1.20	Godfrey et al., 1997
					14	—	—	Natural	100	2.20	
Goats											
CIDR-G	16	250 IU PMSG 48 h before removal 250 IU PMSG + 5 mg PGF 48 h before removal	Spanish	Breeding	59	—	—	Laparosc.	64.5	1.70	Waldron et al., 1999
					59	—	—	Laparosc.	59.5	1.67	
CIDR-G	16–20	200 IU PMSG at removal 200 IU PMSG 48 h before removal	Cashmere	Breeding	22	55	2.18	—	—	—	Ritar et al., 1989
					22	95	2.68	—	—	—	
CIDR-G	16–18	200–400 IU PMSG at removal	Cashmere Angora	Breeding	14	92	2.15	—	—	—	Ritar et al., 1994
					6	50	1.33	—	—	—	

Table 3. Estrus response within 96 h and fertility in goats and sheep synchronized in norgestomet implant-based systems not designed to achieve superovulation

Dose, mg	Duration, d	Associated treatment	Breed	Season	n	Estrus, %	Mating system	Fertility, %	Litter size	Reference
Sheep										
2	14	500 IU PMSG at removal	Mixed	Anestrus	128	96	Natural	59	1.44	Tritschler et al., 1991
3	14	6 mg FSH-P, graded doses	Mixed	Anestrus	25	48	Natural	40		Youngs, 1992
3	10	None	Mixed	Anestrus	14	93	Natural	50	1.83	Umberger et al., 1994
		400 IU PMSG/200 IU hCG at removal			14	71		50	1.90	
3	10	None	Mixed	Anestrus	29	72	Natural	45	1.71	Jabbar et al., 1994
		400 IU PMSG/200 IU hCG at removal			29	90		59	1.88	
Goats										
3	11	500 IU PMSG and 50 µg cloprostenol 24 h before removal	Dairy	Anestrus	62	97	Natural Cervical AI	60 27		Bretzlaff and Madrid, 1989
3	9	None	Dairy	Breeding	6	100	Natural	83		Bretzlaff et al., 1991
3	9	250 IU PMSG 48 h before removal	Dairy	Transition	45	93	Hand-mating	64		East and Rowe, 1989
2	9	1.25 mg estradiol at implantation	Criollo	Breeding	42	62				Mellado and Valdez, 1997
1.5					42	62				
1.2					42	55				
3	11	400 IU PMSG and 50 µg cloprostenol 48 h before removal	Dairy	Breeding	43	97				Freitas et al., 1997b
1.5					39	98				
3				Anestrus	56	98	Cervical AI	75 ^a	1.9	
1.5					55	98		45 ^b	1.8	
3	9–13	300 IU PMSG 36 h before and 50 µg cloprostenol at removal	Dairy	Transition	67	89	Hand-mating	70	2.1	Rowe and East, 1996
3	11	400 IU PMSG and 50 µg cloprostenol 48 h before removal	Dairy	Breeding	39	97				Freitas et al., 1996a

^{a,b}Values with unlike superscripts in same column within study differ ($P < .05$).

Table 4. Estrus response within 96 h and fertility in sheep synchronized with the use of daily feeding of an MGA supplement

Daily dose, mg	Feeding duration, d	Associated treatment	Breed	Season	n	Estrus, %	Mating system	Fertility, %	Litter size	Reference
.25	14	None 5 mg Zeranol 30 h after end of feeding	Mixed	Anestrus	20	80.0	Natural	75.0 ^a	1.33	Powell et al., 1996
					23	95.7		43.5 ^b	1.10	
.25	8	None	Rambouillet	Anestrus	20	90.0	Natural	65.0	1.46	Powell et al., 1996
	11				21	71.4		61.9	1.39	
	14				26	92.3		57.7	1.27	
.25	8	None .315 mg Zeranol 30 h after end of feeding 1.25 mg Zeranol 30 h after end of feeding 5 mg Zeranol 30 h after end of feeding	Mixed	Anestrus	51	21.6 ^a	Natural	47.1 ^a	1.58	Powell et al., 1996
					48	33.3 ^a		39.6 ^{ab}	1.63	
					48	70.8 ^b		29.2 ^{ab}	1.29	
					50	94.0 ^c		12.0 ^b	1.17	
.3	10	None 400 IU PMSG/200 IU hCG at end of feeding	Mixed	Anestrus	14	57.0	Natural	64.0	1.33	Umberger et al., 1994
					14	43.0		50.0	1.40	
.3	10	None 2.5 mg Zeranol at beginning of feeding 400 IU PMSG/200 IU hCG at end of feeding	Mixed	Anestrus	27	13.0	Natural	26.0	1.65	Jabbar et al., 1994
					28	20.0		50.0	1.61	
					30	14.0		36.0	1.68	
.25	10	None 400 IU PMSG/200 IU hCG at end of feeding	Mixed	Anestrus	39	55.2	Natural	40.5	1.91	Safranski et al., 1992
					38	69.8		41.2	1.89	
.22	14	None	Mixed	Breeding	48	74.0	AI fresh	27.7 ^a	1.3	Quispe et al., 1994
					44		AI frozen	11.6 ^b	1.3	

^{a,b,c}Values with unlike superscripts within same column and reference differ ($P < .05$).