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Review article

Synchronization of time of development of ovarian follicular waves in South American Camelids

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ABSTRACT

South American camelids (SAC) are induced ovulating animals. In unmated females, ovarian follicle development occurs in waves of growth and regression, while mating when there is the presence of a mature follicle leads to ovulation. The capacity to respond to an ovulatory stimulus depends on the stage of the follicular wave development. Treatments to control ovarian follicular development have been performed to synchronize timing of wave emergence and development of the dominant follicle at a predictable time. Thus, synchronization of the time of follicular wave development allows for performing fixed time mating or artificial insemination, and super-estimulatory treatments for multiple follicule development. Protocols are based on removal of the suppressive effect of the dominant follicle, that can be achieved by physical ablation or by inducing ovulation (with LH or GnRH) or atresia (with progesterone or progestagens alone or combined with estradiol) of this follicle. Differences between treatments should be taken into consideration when choosing a protocol for fixed time mating or artificial insemination, especially when applying the use these technologies for SAC production by commercial enterprises. Furthermore, the objective of applying synchronization protocols should be considered, because not all of these are effective in inhibiting follicular growth before initiation of a super-estimulatory treatment for multiple follicle development.

1. Introduction

South American Camelids (SAC) are induced ovulating animals and physiologically similar to old world camelids (Skidmore et al., 2013), requiring a mating stimulus when there is a mature follicle to induce the ovulatory process (Bravo et al., 1990; Aba et al., 1995). In unmated females, ovarian follicular development occurs in waves where there is a group of follicles that start to develop and there is subsequent regression of all follicles except for one follicle which becomes dominant, grows to maturity and finally regresses (llama: Adams et al., 1989, 1990; Cavilla et al., 2013; alpaca: Bravo and Sumar, 1989; Vaughan et al., 2004; vicuna: Agüero et al., 2001; Miragaya et al., 2004; guanaco: Riveros et al., 2008); so that waves of follicular development may be classified in three phases: growth, mature and regression (Adams et al., 1990; Bravo et al., 1990; Aba et al., 1995; Chaves et al., 2002). Waves of follicular development usually overlap, so that as one follicle is regressing, another group of follicles are developing with one eventually becoming dominant. Females, therefore, are sexually receptive most of the time and there is not an association between estrous behavior and the time of ovulation, as occurs in spontaneous ovulating animals (Bravo, 1994; Vaughan et al., 2003; Cavilla

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et al., 2013). Differing from spontaneous ovulating species, when mating occurs and there is a mature follicle, this mating stimulus leads to ovulation and corpus luteum development (Aba et al., 1995; Vaughan, 2011). The capacity to have an ovulation in response to mating depends on the size of the dominant follicle at the time of mating. Females with follicles ≥7 mm in diameter that are in the growth phase of development and with static follicles during the mature phase (8–12 mm) have ovulations after mating or ovulation induction (GnRH or LH), while females with small growing follicles (< 7 mm) or a regressing dominant follicle do not have ovulations as a result of mating (Bravo et al., 1991; Sumar et al., 1993; Ratto et al., 2006). It has been reported, however, that alpacas mated when there are small growing follicles or regressing follicles may have ovulations as result of mating (Ratto et al., 2011). Llamas with regressing follicles that were treated with a GnRH analog had lesser ovulation rates than those with growing follicles (Bianchi et al., 2018). Nevertheless, growing or early static dominant follicles might contain greater quality oocytes and consequently mating at these stages of follicular wave development would lead to greater pregnancy rates (Vaughan et al., 2003).

Several protocols to control ovarian activity have been performed in SAC with two final objectives: to synchronize the time of emergence of a new wave of follicular development and consequently predict the time when a dominant follicle is present, and to perform superstimulatory treatments for multiple follicle development to the ovulatory stage that must be initiated when there is a not a dominant follicle present (Trasorras et al., 2017; Bianchi et al., 2018). The effectiveness of these methods is based on the removal of the suppressive effect of the dominant follicle, which inhibits subordinate follicle development and development of a subsequent wave of follicle emergence (Cavilla et al., 2013). This can be achieved by physical follicular ablation or by inducing ovulation or atresia of the dominant follicle (Ratto et al., 2003; Trasorras et al., 2017).

Control of follicular function would allow for performing fixed time artificial insemination or natural service in a herd. In addition, it would allow for synchronizing the timing of donor follicle development and development of gonadotropin receptors for performing superstimulatory follicular treatments in embryo transfer programs (Trasorras et al., 2017; Bianchi et al., 2018). All of these procedures are focused on improving reproductive efficiency in these species (Trasorras et al., 2009; Carretero et al., 2010) and thus fulfil the increasing demand of SAC meat and fibre production; which is around 15,000 and 3700 tons per year, respectively, in the Andean region (Cristofanelli et al., 2004; Mamani-Linares et al., 2014; Avilés Esquivel et al., 2018). Furthermore, it is estimated that there are about 7 million animals in South America and more than 500,000 families that are residents of South America are dedicated to SAC production; being an economic activity of great importance in this region (Avilés Esquivel et al., 2018).

2. Follicular wave synchronization

2.1. Physical methods

2.1.1. Follicle ablation

In cattle, synchronization of the timing of ovarian follicular development has been performed using physical ablation methods that induce synchronous timing of follicular wave emergence, such as ultrasonic-guided transvaginal follicle ablation (Bergfelt et al., 1994, 1997). Ablation of all follicles ≥5 mm or the two largest follicles present in the ovaries at random stages of the estrous cycle leads to follicular wave emergence 1–2 days later; when a superstimulatory follicular treatment can be performed that results in development of multiple large and functional follicles (Bergfelt et al., 1997; Baracaldo et al., 2000). Thus, with this method there is the advantage of initiating a superstimulatory follicular treatment immediately after follicle ablation, and application of the ablation technique can be performed at any time of the estrous cycle without knowledge of the stage of ovarian follicular wave development.

As in cattle, in SAC ultrasonic-guided transvaginal follicle ablation had previously been used as a method for oocyte collection (Brogliatti et al., 1996). Afterwards, this procedure was used in llamas to elicit development of a new wave of follicular emergence before a superstimulatory follicle treatment is imposed (Ratto et al., 2002, 2005; Berland et al., 2011). In these studies, ablation of all follicles ≥5 mm regardless of ovarian status was useful to induce follicular wave emergence. Ratto et al. (2003) reported that follicle ablation in llamas led to follicular wave emergence and development of follicles ≥7 mm in diameter in 2 and 5 days, respectively; thus, this procedure was more effective for inducing synchronization in timing of follicular wave development than hormonal treatments (17β-estradiol combined with progesterone). In alpacas, ultrasonic-guided transvaginal follicle ablation was used to synchronize stage of follicular wave emergence to perform a pre-scheduled mating (Ratto et al., 2011). Although this method has proven to be useful for control of ovarian follicular development and functions, it should be considered that there is the requirement of an epidural anesthesia that must be performed by trained professionals; thus, it is difficult to implement in field conditions.

In addition, ablation of dominant follicles by rectal manipulation of ovarian position has been described in llamas before initiation of a superstimulatory treatment for multiple follicle development (Sansinena et al., 2003, 2007). Information concerning this method is, however, limited.

2.2. Hormonal control of follicular function

2.2.1. Parenteral progesterone or progestagens

Progesterone secretion resulting from presence of a corpus luteum and treatment with exogenous progesterone or progestagens exert a negative effect on follicular function. When there are optimal concentrations of progesterone or progestogens in blood, the number of follicles and maximum diameter of dominant follicles are relatively less than that when there are lesser concentrations of these hormones in blood. Also there is a less prominent day-to-day growth and regression profile of dominant follicles and lesser follicular estradiol production when progestogens are in concentrations that inhibit LH stimulation of follicular development (Adams et al., 1990; Aba et al., 1997, 1999; Chaves et al., 2002). Luteal phase progesterone concentrations or supra-luteal progesterone

Table 1
Treatments performed in South American Camelids to synchronize time of follicular wave maturation among animals.

Treatment	Minimum mean value of follicular size reached (mm)	Mean time elapsed from beginning of treatment until minimum follicle size is reached (days)	Mean time elapsed from beginning of treatment until development of a mature follicle (days)	Species	Reference
Daily IM progesterone 50 mg for 12 days	< 5	7	19	Llama	Alberio and Aller, 1996
Single IM dose of progesterone 25 mg and 17β-estradiol 1 mg	4	4.5	8	Lama	Ratto et al., 2003
Daily IM progesterone (100 or 150 mg) for 5 days plus single dose of EB 1 mg	≤5.5	3	7–8[b]	Llama	Carretero et al., 2010
Single IM dose of progesterone BioRelease® LA 150 mg	5.5 to 8.8[a]	10	10	Llama	Veiga et al., 2018
MPA 120 mg, intravaginal sponge for 8 days	No detailed	No detailed	14	Llama	Aba et al., 1999
MPA 120 or 240 mg, intravaginal sponge for 13 days	No detailed	No detailed	No detailed	Llama	Ferrer et al., 1999
MPA 60 mg, intravaginal sponge for 7 days plus single IM dose of EB 2 mg	No detailed	No detailed	No detailed	Vicuna	Aller et al., 2002
MPA 150 mg, intravaginal sponge for 8 days plus single IM dose of MPA 5 mg and EB 2 mg	4	6.5	13	Llama	Aller et al., 2010
CIDR® (0.33 g of progesterone) for 8 days	3.7–5.2[a]	5 to 7[a]	No detailed	Llama	Chaves et al., 2002
CIDR® (0.33 g of progesterone) for 5 days	1.85	5	10	Vicuna	Aba et al., 2005
Cue-Mate® (780 mg of progesterone) for 8 days	3	2–5[a]	14	Llama	Cavilla et al., 2016
CIDR® (0.33 g of progesterone) for 5 days plus single IM dose of EB 1 mg	< 5	5	No detailed	Llama	Trasorras et al., 2009
Cue-Mate® (780 mg of progesterone) for 8 days plus single IM dose of EB 2.5 mg	3	7	14	Llama	Cavilla, 2014

Treatments performed in SAC to synchronize stage of wave of ovarian follicular development with progesterone or progestagens alone or combined with estradiol. IM: intramuscular, MPA: medroxiprogesterone acetate, EB: estradiol benzoate.

[a] Based on the stage of the phase of the follicular wave development at the beginning of treatment.

[b] According to progesterone dose, mean time elapsed from beginning of treatment until development of a mature follicle was of 7 (100 mg dose) or 8 days (150 mg dose).

concentrations resulting from treatment with this hormone suppresses the frequency of LH pulses and consequently induces follicular regression and atresia of the dominant follicle and hastens the emergence of a new wave of follicular development (Ireland and Roche, 1982; Cavilla et al., 2016). Progesterone and progestagens, therefore, have been used in several species to control ovarian function (cattle: Bo et al., 2006; goat: Knights and Singh-Knights, 2016; ewe: Viñoles et al., 2001). Progesterone is also useful in controlling ovarian follicular development and functions in llamas (Table 1). Alberio and Aller (1996) reported that animals that were treated 50 mg/day progesterone for 12 days had follicles < 5 mm in diameter on the seventh day of treatment, regardless of the stage of follicular development at the beginning of treatment. Also a follicle < 7 mm (considered ovulatory for this species) was observed 7 days after the end of the treatment period. Thus, use of this protocol would result in suppression of follicular development before superstimulatory follicular treatments are imposed or to perform pre-scheduled mating in a herd. Alternatively, the use of an injectable progesterone treatment regimen that results in a longer period of progestin activity might be used in llamas to control ovarian functions (Veiga et al., 2018). Progesterone BioRelease® LA was administered in a single dose of 300 or 150 mg with the smaller dose being more effective in synchronizing time of follicular wave emergence, regardless of the stage of follicular development at the beginning of treatment. The average diameter of the largest follicle at the end of treatment was variable depending on the ovarian status at the time of the progesterone injection. Thus, this must be considered when using this protocol for pre-scheduled mating or artificial insemination. Although this treatment inhibited follicular growth, follicles did develop to a size that is necessary to perform a superestimulatory follicular treatment (Trasorras et al., 2009, 2017). Nevertheless, the long action progesterone treatment regimen has the advantage of requiring a single injection (instead of several injections as is the situation with other treatment regimens), therefore, the use of this treatment regimen results in less animal stress and is easier to perform in field conditions.

2.2.2. Parenteral progesterone combined with estradiol

Protocols combining the use of progesterone and estradiol have also been utilized in llamas and can be effective in controlling ovarian functions (Table 1). Lactating and non-lactating llamas that received a single dose of 17β-estradiol (1 mg) and progesterone (25 mg) had a new wave of follicular development within 4.5 days of treatment initiation and a development of a follicle < 7 mm in diameter at about 8 days after treatment initiaton, regardless of ovarian status at the beginning of treatment (Ratto et al., 2003). Variability in the interval to the initiation of a new wave of follicular development was greater when there was use of other protocols in the same study such as LH injections or follicle ablation. Similarly, llamas that were treated with a single dose of estradiol benzoate (EB) (EB, 1 mg) on the first day of imposing the protocol and 100 or 150 mg of progesterone daily for 5 days had follicles ≤ 5.5 mm at the third day of treatment in 70% (100 mg) to 80% (150 mg) of the animals (Carretero et al., 2010). It must, however, be considered that suppressive effects of this treatment regimen was different depending on the stage of ovarian follicular development before treatment initiation; with the protocol where there was use of 150 mg progesterone being more effective in early growing phase of follicular development and the 100 mg dose being more effective when there was a static phase in follicular development. Time elapsing between the end of treatment and development of a dominant follicle was 7–8 days, allowing for imposing of a fixed time mating regimen.

2.2.3. Parenteral estradiol

In alpacas, different doses of 17β-estradiol (0.5 or 2 mg) proved to be useful in synchronizing the time of emergence of a new wave of follicular development between 6 to 8 days after treatment cessation, regardless of the phase of the follicular wave development at the beginning of treatment (D'Occhio et al., 1997). Vaughan (2001), however, reported that treatments with 1 mg of 17β-estradiol or 2 or 5 mg of EB were ineffective in inhibiting follicular growth or synchronizing timing of follicular wave emergence in this species. Similarly, Trasorras et al. (2005) reported the use of 1 or 2 mg of EB would not be useful in inhibiting ovarian functions in llamas, because the range in day of detection of follicles smaller than the size of the dominant follicle was from 2 to 17 days with use of the 1 mg dose and from 5 to 14 days with use of the 2 mg dose.

2.2.4. Intravaginal devices and sponges containing progesterone or progestagens

The use of intravaginal devices and sponges for administration of progestagens has also been described in SAC (Table 1; Aba et al., 1999; Chaves et al., 2002) and in other animals (mare: Lübbecke et al., 1994; buffalo: Neglia et al., 2003). The use of these devices involves less labor than the daily injections and these devices can be reused successfully reducing the costs of treatments (Vilariño et al., 2011), although some of these devices are currently unavailable in certain markets (Trasorras et al., 2017). Progestagens such as medroxiprogesterone acetate (MPA) have been used to induce follicular regression in llamas (Aba et al., 1999). Intravaginal sponges containing MPA (120 mg) were inserted and left in the vagina for 8 days; and 6 days after removal ovulation induction or mating was performed. Although an ultrasonic assessment of ovarian follicles was not performed in this study, it was reported that there were ovulations in all females, therefore there must have been an ovulatory follicle present in an ovary at the time of the pre-ovulatory surge of LH release. Ferrer et al. (1999), however, performed ultrasonic monitoring of follicular dynamic after treatment with intravaginal sponges containing different doses (120 and 240 mg) of MPA, and reported there was not any beneficial effect on synchronization of stage of follicular growth as compared with that of control animals.

Chaves et al. (2002) reported that treatment with a progesterone-releasing intravaginal device (CIDR®, containing 0.33 g of progesterone) for 8 days was useful to suppress follicular development and functions in llamas. The smallest follicular diameters were present between day 5 and 7 after the beginning of treatment and there were basal plasma 17β-estradiol concentrations, regardless of stage of follicular development before CIDR® insertion. In vicunas the use of a CIDR® containing 0.33 g of progesterone for 5 days inhibited follicular development and functions, at the end of treatment with all females having follicles < 3 mm in diameter (Aba

et al., 2005). There, however, was a great variability among individuals in the time elapsed for a follicle to become dominant and the end of the treatment period. In vicunas, therefore, this treatment would be useful when imposing superstimulatory follicular development protocols but not to perform pre-scheduled mating. Although intravaginal devices containing progesterone have been useful in controlling ovarian development and functions, the size of dose administered must be considered because 160 mg of progesterone were not as effective in suppressing follicular growth as 780 mg of progesterone (persistence of follicles present at the start of treatment were observed with the smaller dose; Cavilla et al., 2016). Results of this study indicated the use of intravaginal devices (Cue-mate®) containing the larger dose of progesterone (780 mg) suppressed follicular development and hastened the emergence of a new wave of follicular development in all females regardless of the stage of follicular development at the time of device insertion. Additionally, this device was useful to effectively concentrate the timing of appearance of ovulatory follicles with a newly developed and viable oocyte being present 6 days after the end of treatment (Cavilla et al., 2016). This treatment regimen would be useful to perform fixed time mating or artificial insemination in a herd. Emergence of the new wave of follicular development depended on follicular status at the beginning of treatment; occurring earlier when a follicle in the mature phase was present at the time of device insertion. Thus, this protocol would not be useful before a superstimulatory treatment for multiple follicle development, unless an ultrasonic assessment is performed.

2.2.5. Intravaginal devices containing progesterone or progestagens combined with estradiol

Protocols combining intravaginal devices that contain progesterone or progestagens and estradiol injections have been used in SAC (Table 1). In llamas, the use of a CIDR® containing 0.33 g of progesterone for 5 days plus a single 1 mg dose of EB the first day of the imposing the protocol was useful to suppress follicular development and functions, as the diameter of all follicles was < 5 mm at the end of treatment (Trasorras et al., 2009). Cavilla (2014) reported that llamas treated with a single dose of 2.5 mg EB administered the first day of imposing the protocol plus an intravaginal device containing 780 mg of progesterone resulted in a marked inhibition of follicular development and functions because follicular wave emergence was observed 7 days after beginning of treatment; while the same treatment without EB lead to follicular wave emergence 3 days after device insertion. Also, results of this study indicated the use of a combination of progesterone plus an EB injection resulted in synchronization in the timing of emergence of the new wave of follicular development in a shorter interval than with administration of progesterone alone (between days 5–8, and 1–6 after the beginning of treatment, respectively; Cavilla, 2014). Thus, the combined treatment was useful to inhibit follicular growth and to concentrate the timing of development of a new dominant follicle between days 4 and 7 after device removal; being more effective than with the use of progesterone alone (Cavilla, 2014).

The use of intravaginal sponges containing progestagens such as MPA plus estradiol have also proven to be useful in inhibiting follicular development (Aller et al., 2002, 2010). In llamas that were treated with a single dose of 5 mg MPA and 2 mg EB the first day of imposing the treatment protocol plus administration of an intravaginal sponge containing 150 mg of MPA for 8 days, there was suppression of follicular development, with a new wave of follicular development occurring 6.5 days after treatment initiation (Cancino et al., 2005; Aller et al., 2010). The same treatment without the use of estradiol lead to follicular wave emergence 4 days after treatment initiation (Aller et al., 2010). Similarly, in vicunas it was reported that the combined treatment with intravaginal sponges containing 60 mg of MPA for 7 days and a single 2 mg EB injection the first day of imposing the protocol resulted in suppression of the follicular functions; being useful as a pre-treatment for imposing a superstimulatory protocol for follicular development (Aller et al., 2002).

2.2.6. Progestagens subcutaneous implants

In addition to the use of intravaginal devices, norgestomet subcutaneous implants (Crestar®) have been used in llamas before superstimulatory treatments for follicle development (Bourke et al., 1992, 1995). In these studies, most females had a mature follicle 6 days after implant removal, when mating was performed. Superovulation occurred independent of ovarian status at insertion of the implant, although this affected the response to superstimulatory treatment for multiple follicle development.

2.2.7. LH and GnRH: ovulation induction

Control of follicular functions in cattle has been performed with hormonal treatments that include the use of LH and GnRH (Pursley et al., 1995; Bó et al., 2008). The effectiveness of these treatments is based on the removal of the suppressive effect of the dominant follicle on subordinate follicles by inducing ovulation of the dominant follicle. Based on the protocols previously used in cattle, there are several studies in camelids where there are reports of the use of GnRH, LH and hCG to induce ovulation (Adam et al., 1992; Taylor et al., 2000; Ratto et al., 2006). These studies, however, were focused on ovulation rate and there was not evaluation of the hormone´s effect on follicular development and functions. Nevertheless, there is one study in llamas where there was an analysis of the effect of LH treatment on follicular wave dynamics (Ratto et al., 2003). Results indicated that administration of 5 mg LH was useful in controlling ovarian functions regardless of follicular status at the beginning of the treatment. Follicular wave emergence and presence of a dominant follicle were observed 2 and 5 days after treatment, respectively. Furthermore, LH treatment was more effective in synchronizing the timing of ovarian development and functions than treatment with estradiol plus progesterone.

Bianchi et al. (2018) evaluated a protocol in llamas based in the use of a GnRH analog (8.2 µg of Buserelin acetate) combined with the administration of a $PGF_{2\alpha}$ analog (105 µg of d-cloprostenol) 7 days later, to synchronize timing of follicular wave emergence, regardless of follicular status at the beginning of the treatment. This protocol had been previously used in camels and was effective in synchronizing time of ovulation in 80% of females 14 days after the GnRH injection (Skidmore et al., 2009). In llamas, the effectiveness of this protocol to synchronize the timing of development of a new dominant follicle on day 10 after the beginning of treatment was highly dependent on the number of females that had ovulations after the first GnRH analog injection (Bianchi et al.,

2018). Use of this protocol, however, would be effective to implement pre-scheduled matings or inseminations in a herd. The follicular wave emergence occurred between days 1 and 3 after initiation of treatment and was dependent on the follicular status on the day of GnRH analog injection; occurring earlier when the largest follicle was in the regression phase at the beginning of treatment (Bianchi et al., 2018). Similarly, Ferrer et al. (2002) reported the outcomes after use of a single dose of a GnRH analog (8.2 μg of Buserelin acetate) to synchronize timing of follicular wave emergence in llamas. Almost all females had follicles with a maximum size < 7 mm on the third day post treatment initiation with these follicles being maintained until the sixth day post treatment initiation, independent of follicular stage at the beginning of treatment. It was suggested that a superstimulatory protocol of follicular development stimulation could be initiated between days 3 and 5 post-treatment. Although time elapsed between buserelin injection and development of a follicle ≥ 7 mm in diameter was not different when there was consideration of follicular stage at the beginning of treatment, there was variability among females in time to development of a follicle ≥ 7 mm in diameter.

3. Conclusion

Several treatments are effective in controlling follicular functions and enabling synchronization in time of follicular wave emergence in SAC. There are differences in the need for ultrasonic assessment, requirement of anesthesia, use of daily injections, commercial availability of hormones, hormone and anesthesia costs, and time elapsed between treatment and follicular wave emergence, among others. These factors should be considered when choosing a treatment protocol for use, especially if procedures for control of ovarian development and functions is performed in field conditions because some protocols are not practical for commercial use. In addition, the purpose of applying a protocol for synchronization of timing of ovarian follicle development and functions should be taken into consideration, as most treatments are useful for inducing the development of a dominant follicle at a predictable time; but effective and practical protocols to inhibit follicular development in the field before the use of a superstimulatory protocol for follicular development stimulation are scarce. Further research, therefore, would be useful to more effectively accomplish the latter objective and consequently improve the results of superestimulatory treatments for multiple follicule development.

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