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Induction of accessory corpus luteum in goats and sheep: From physiological basis to reproductive effects

Indução de corpo lúteo acessório em caprinos e ovinos: Das bases fisiológicas aos efeitos reprodutivos

Jeferson Ferreira da Fonseca[1*], Gabriel Brun Vergani[2], Luana Rangel Côrtes[3], Juliana Nascimento Duarte Rodrigues[3], Luiz Gustavo Bruno Siqueira[4], Joanna Maria Gonçalves Souza-Fabjan[5], Maria Emília Franco Oliveira[2]

[1]Embrapa Caprinos e Ovinos e Ovinos, Rodovia MG 133, km 42, Coronel Pacheco, Minas Gerais, Brazil.
[2]Faculdade de Ciências Agrárias e Veterinárias, Universidade Estadual Paulista, Via de acesso Prof. Paulo Donato Castellane, s/n, CEP 14884-900, Jaboticabal, SP, Brazil.
[3]Departamento de Medicina Veterinária, Universidade Federal de Viçosa, Av. Peter Henry Rolfs, s/n, CEP 36570-000, Viçosa, MG, Brazil
[4]Embrapa Gado de Leite, Av. Eugênio do Nascimento, 610, Juiz de Fora, MG, Brazil
[5]Faculdade de Veterinária, Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brazil

Resumo

A identificação das ondas foliculares ovarianas e de seu padrão hormonal revelou que os folículos ovarianos dominantes da onda ovulatória (FDOO) crescem em ambiente hormonal com predominância crescente de estradiol, diferentemente daqueles da primeira (FDPO) e das ondas foliculares intermediárias (FDOI), que crescem sob forte impacto da progesterona (P4). O hormônio luteinizante (LH) é considerado o hormônio gonadotrófico decisivo para direcionar se um folículo dominante ovulará (↑ LH) ou não (↓ LH). Estratégias foram desenvolvidas para aumentar o LH endógeno (administração de GnRH) ou fornecer LH exógeno de origem suína (pLH) ou, ainda, gonadotrofinas semelhantes ao LH, como gonadotrofina coriônica humana (hCG). Estas medidas são capazes de disponibilizar LH para maturação final, ovulação e/ou luteinização de FDPO ou FDOI, formando corpos lúteos acessórios (CLa). Como consequência, a P4 aumenta e favorece o estabelecimento da gestação, sobretudo em condições em que a P4 for o fator limitante para a implantação e manutenção embrionária. Em ovelhas e cabras, em diferentes estudos, a hCG foi administrada de cinco a sete dias após o início do estro e revelou que o FDPO responde positivamente à administração de hCG, formando CLa e/ou promovendo a hipertrofia do CL formado originalmente, aumentando a área luteal. O incremento da P4 normalmente acompanha o aumento de área do tecido luteal. Como efeito final e mais desejável, a gestação e o nascimento de cordeiros/cabritos também aumentam. Esses conceitos serão discutidos na presente revisão sobre indução de CLa em ovinos e caprinos.

Palavras-chave: *CLa, gonadotrofinas, hCG, onda folicular ovariana, progesterona.*

Abstract

The identification of ovarian follicular waves and associated hormonal milieux has revealed that dominant follicles of the ovulatory wave (OWDF) grow in a hormonal environment where there is an increasing predominance of estradiol, unlike first-wave dominant follicles (FWDF) and intermediate-wave dominant follicles (IWDF), which grow under increasing progesterone (P4) concentrations. The luteinizing hormone (LH) is considered the decisive gonadotropic hormone to direct whether a dominant follicle will (↑ LH) or will not (↓ LH) ovulate. Based on this, strategies have been developed to either increase endogenous LH (GnRH administration) or provide exogenous LH of porcine origin (pLH) or LH-like gonadotropins, such as human chorionic gonadotropin (hCG). Such strategies are able to provide LH for final maturation, ovulation, and/or luteinization of the FWDF or IWDF, forming accessory corpora lutea (aCL). As a consequence, P4 increases and favors the establishment of pregnancy, particularly when P4 is the limiting factor for the success of the conceptus implantation and maintenance. In sheep and goats, previous studies have administered hCG five to seven days after the onset of estrus and revealed that FWDF positively respond to hCG administration by either forming aCLs and/or

[1]Correspondência: jeferson.fonseca@embrapa.br
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promoting hypertrofia of the original CL which, in turn, increases its luteal tissue area. Normally, P4 synthesis increases along with the increase in luteal tissue area. As a final and most desirable outcome, pregnancy and the birth of lambs/kids also increase. These concepts will be discussed in this review, focusing on aCL induction in sheep and goats.

Keywords: aCL, gonadotropins, hCG, ovarian follicle wave, progesterone.

Introduction

Knowledge of ovarian follicular dynamics in ruminants has opened new and interesting windows for the control of the estrous cycle combined with assisted reproductive technologies (ARTs). In cattle (Sirois and Fortune, 1988), goats (Ginther and Kot, 1994), and sheep (Bartlewski et al., 1999), antral ovarian follicles emerge on the ovarian cortex in pools and grow in a wave-like pattern, in so-called follicular waves. Each follicular wave has dominant and subordinate follicles in cattle (Ginther et al., 1995), but it is common for sheep and goats to have more than one dominant follicle, a phenomenon referred to as “co-dominance” (Rubianes and Menchaca, 2003). Although there is often more than one ovarian follicular wave in a regular estrous cycle, normally only the last one develops sufficiently to allow the ovulation of one or more given dominant follicle(s) (Ginther et al., 1996), yet the dominant follicle of a previous wave can still ovulate (Bartlewski et al., 1999; Gibbons et al., 1999).

LH pulses and frequency vary during the estrous cycle and are decisive in determining whether the dominant follicle acquires ovulatory capacity or undergoes atresia (Campbell et al., 2007; Forde et al., 2011). Progesterone (P4) secretion starts after ovulation by a newly formed original corpus luteum (oCL), reaches a plateau at mid-cycle, and then declines due to the luteolysis process. In cattle, LH concentration changes are proportionally inverse to P4 concentrations during the estrous cycle (Wheaton et al., 1984). Thus, in the presence of an active CL, plasma LH pulse frequency is lower, preventing the dominant follicles from growing to the last stage and ovulating (Badinga et al., 1992). In addition, the negative effect of P4 on LH pulse secretion during the onset (early luteal phase) and end of the estrous cycle (follicular phase) allows the FWDF and ovulatory follicles to last longer and attain a larger diameter than the other IWDFs (Sirois and Fortune, 1988; De Castro et al., 1999).

Endogenous increase of plasma LH after the administration of gonadotropin-releasing hormone (GnRH; Rajamahendran et al., 1998) or exogenous supply of pLH or its analogues, such as hCG, has been used to induce the formation of aCL. Such aCL are derived from dominant follicles growing during the luteal phase (Price and Webb, 1989; Kerbler et al., 1997), from either FWDFs (Price and Webb, 1989; Schmitt et al., 1996a; Fonseca et al., 2000) or IWDFs (Wiltbank at al., 1961, Price and Webb, 1989). As a consequence, P4 may increase in response to hCG administration (Fonseca et al., 2001a). Although it is well known that P4 concentration is positively associated with uterine environment and, consequently, interferon-τ production by the conceptus (Kerbler et al., 1997; Lonergan and Sánchez, 2020), early embryo development and pregenancy survival (Lonergan et al., 2016) rates may increase (Vergani et al., 2020) or not (Fonseca et al., 2001b). In addition, P4 is known to be lower after ovulation in seasonally induced estrus than in cyclic ewes (Rhind et al., 1978), and this limiting factor can be minimized by administering gonadotropins at the beginning of the estrous cycle (Fonseca et al., 2006; Fonseca et al., 2018) in seasonal ewes (Balaro et al., 2014) and goats (Balaro et al., 2019). These strategies can lead to either the formation of an aCL or hypertrophia of the oCL, which is followed by a P4 increase and a potential positive impact on pregnancy rates.

It is well known that the early stages of gestation are the timepoints when most pregnancy losses occur (Rhind et al., 1978), and the most common causes are related to the insufficient production of P4, pre- and post-ovulation, which leads to a reduction in the growth and elongation of the conceptus and decreased production of interferon-τ (IFNT) (Forde and Lonergan, 2017), which is essential for proper maternal recognition of pregnancy. Therefore, the aim of this review is to discuss the physiological basis and potential effects of gonadotropin administration at the beginning of the estrous cycle to improve reproductive efficiency in sheep and goats.

Ovarian follicular dynamics in goats and sheep

Goats and sheep are seasonally polyestrous animals with ovulatory estrous cycles occurring in periods of shortening daylengths (Medan et al., 2005; Bartlewski et al., 2011). However, there may be greater or lesser seasonal effects depending, in particular, on the breed and the latitude where the animals are raised (Fatet et al., 2011). Antral ovarian follicular development occurs in a wave-like pattern, and there are typically three or four waves per interovulatory interval, that is, five- to four-day intervals between waves (Simões et al., 2006; Bartlewski et al., 2011). Although this pattern is generally observed, the day of follicular wave emergence is mainly influenced by the number/frequency of follicular waves in a given cycle (Oliveira et al., 2016), and it remains unclear what determines the number of follicular waves per estrous cycle.

The initial growth of antral follicles is associated with elevations in FSH concentrations and, later, growing follicles synthesize inhibin and estradiol, which, in turn, suppress FSH secretion (Medan et al., 2005). Follicular deviation and dominance in small ruminants is still unclear (Medan et al., 2005; Bartlewski et al., 2011); however, in general, at around 1.5 days after emergence (Evans, 2000) one or more follicles are selected to dominate and acquire LH receptors in granulosa cells to continue their growth. These follicles with LH receptors are the focus to induce the formation of aCL by exogenous supply of LH or hCG. According to Driancourt (2001), follicles with a diameter >4 mm in sheep already have LH receptors; however, Vergani et al. (2020) suggest that slightly smaller follicles (≥ 3.5 mm) may already be responsive to aCL development.

The length of the follicular dominance period (i.e., the period of the follicular wave in which follicles with LH receptors are present on the ovaries) varies between non-ovulatory and ovulatory waves, as does the maximum diameter reached by the dominant follicles. These differences are associated with variations in hormonal profiles among follicular waves that occur during the luteal phase relative to those occurring at the follicular phase of the estrous cycle. The main difference is due to the fact that P4 and estradiol are acting in concert to modulate the frequency and amplitude of LH pulses (Barrett et al., 2007) and, consequently, restrict the final growth of the follicles, preventing them from reaching a preovulatory size and, thus, from ovulating. Conversely, the continuous increase in estradiol secretion during the follicular phase of the estrous cycle is reflected in an increase in LH receptor density in preovulatory follicles (Bartlewski et al., 2011).

Therefore, when focusing on the induction of aCL, it is essential to consider the administration of luteotrophic agents at a timepoint when responsive follicles are present on the ovaries, whether from the first or second follicular wave. Thus, understanding the follicular dynamics of different breeds of sheep and goats under different environmental influences will certainly allow greater efficiency in the induction of aCL.

Induction of aCL in sheep

The use of luteotropic agents, such as hCG and GnRH, to induce the formation of aCL and, consequently, to increase the P4 and the conception rate has been widely investigated in sheep (Khan et al., 2009; Fonseca et al., 2018; Vergani et al., 2020), as listed in Table 1. In this regard, hCG seems to give better results than GnRH, since GnRH is not always able to produce a functional aCL and may even not affect P4 concentrations (Fernandez et al., 2018). The hCG dose previously used has differed among studies, varying from low (100 IU, Nephew et al., 1994) through intermediate (250–300 IU, Catalano et al., 2015; Fernandez et al., 2018; Fonseca et al., 2018; Vergani et al., 2020) to high (600 IU, Colenson et al., 2015). These studies aimed to increase P4 concentrations and promote greater percentages of aCL formation, which ranged from 71% to 100% (Table 1). These findings suggest that there is a positive effect in the oCL and from the aCL to increase the P4 concentration profile.

One of the most important criteria to implement a protocol for induction of aCL is the moment of administration of the luteotropic agent, considering the already-mentioned need for the presence of LH-responsive follicles (Driancourt, 2001). Other factors to consider are the moment of the maternal recognition of pregnancy in ewes and the influence of IFNT production at high P4 levels (Satterfield et al., 2006), improving embryonic survival and providing better chances for embryonic development. Furthermore, hCG improved the crown-rump length, amniotic sac length, and number of caruncles in ewe lambs (Khan et al., 2007), including a high number of placentomes in ewes, in addition to increasing progesterone concentrations, presumably providing better survivability and developmental condition for the embryos.

Although several studies have investigated aCL induction in ewes, few have obtained an increase in pregnancy rates (Catalano et al., 2015; Fernandez et al., 2019). In a recent study of aCL induction during the transitional period (from the end of the anestrus season to the beginning of the breeding season), a greater pregnancy rate was observed in ewes that successfully formed at least one .

Table 1. Summary of studies on the effects of exogenous gonadotropins administered after breeding on reproductive efficiency in goats and sheep at different reproductive seasons

Breed (n)	**Reproductive Season**	**Day of treatment*/ dose of hormone**	**aCL* (%)**	**Positive effect/increase (yes or no)**				**Authors**
				P4*	Pregnancy	TLA*	MVA*	
Goats								
Alpine and Saanen (24)	Transitional / Breeding	D5 / 250 IU hCG	---	No	No	---	---	Fonseca and Torres (2005)
Alpine (81)	Breeding	D5 / 250 IU hCG	---	---	No	---	---	Fonseca et al. (2005a)
Alpine (18)	Transitional / Breeding	D5 / 250 IU hCG	---	Yes (D45)	No	---	---	Fonseca et al. (2005b).
Alpine and Saanen (76)	Non-breeding / Transitional	D5 / 250 IU hCG	---	No	No	---	---	Maffili et al. (2005)
Alpine (64)	Breeding	D5 / 250 IU hCG	---	Yes (D13 to 21)	---	---	---	Fonseca et al. (2006)
Toggenburg (43)	Transitional	D7 / 300 IU hCG	46.5	No	Yes	No	No	Côrtes et al. (2021)
Sheep								
Targhee (90)	Breeding	D11.5 / 100 IU hCG / 12 mg P4	---	Yes	No	---	---	Nephew et al. (1994)
Karayaka (132)	Breeding	D12 / 150 IU hCG / 4 µg GnRH	---	---	Yes	---	---	Cam & Kuran (2004)
Welsh Halfbred (445)	Breeding / Non-breeding	D12 / 200 IU hCG	71.4	---	No	---	---	Khan et al. (2009)
Western Whiteface (19)	Breeding	D4 / 600 IU hCG	---	Yes	---	---	---	Coleson et al. (2015)
Corriedale (103)	Non-breeding	D12 / 300 IU hCG	100.0	Yes	No	---	---	Catalano et al. (2015)
Merino (12)	Breeding	D4 / 300 IU hCG	91.6	Yes	---	---	---	Fernandez et al. (2018)
Merino (12)	Breeding	D4 / 4 µg GnRH	---	No	---	---	---	Fernandez et al. (2018)
Santa Inês (7)	Non-breeding	D7 / 250 IU hCG	85.7	Yes	No	Yes	---	Fonseca et al. (2018)
Merino (92)	Breeding	D4 / 300 IU hCG	---	---	No	---	---	Fernandez et al. (2019)
Merino (99)	Breeding	D4 / 4 µg GnRH	---	---	Yes	---	---	Fernandez et al. (2019)
Morada Nova (55)	Non-breeding	D7.5 / 300 IU hCG	81.5	Yes	No	Yes	No	Vergani et al. (2020)

*Days (D) after the onset of estrus; aCL: accessory corpus luteum; P4: progesterone; TLA: total luteal area; MVA: mean vascular area; ---: not assessed in the paper;

aCL, and there was an increase in the number of lambs born as a function of the number of treated ewes (Vergani et al., 2020).

Considering all reports on the effects that hCG can have on embryonic survival and development, besides increasing P4 concentrations and improving the uterus milieu, further studies are still required to adjust aCL induction protocols, with the ultimate goal of increasing pregnancy rates in ewes.

Induction of aCL in goats

hCG has also been used to improve reproductive efficiency in goats, stimulating the elevation of P4 concentrations (Fonseca et al., 2005b, 2006) and inducing the formation of aCL (Côrtes et al., 2021), as shown in Table 1. During the breeding season, nulliparous and lactating Alpine females received 250 IU of hCG five days after natural mating; although the plasma P4 concentrations increased from Days 13 to 21 in hCG-treated goats, regardless of parity (Fonseca et al., 2006), there was no difference in pregnancy outcomes, kidding, or prolificacy (Fonseca et al., 2005a, 2006). When the same dose was tested in nulliparus Saanen and Alpine goats after estrus, but in the transitional period, no difference was observed in most variables assessed, except for plasma P4 concentration, which only increased on the 45th day of pregnancy (Fonseca and Torres, 2005; Fonseca et al., 2005b). Similarly, treatment with hCG (250 IU) on the 20th day of the estrous cycle had no effect on the reproductive performance of multiparous females (Maffili et al., 2005).

The dominant follicle of the first follicular wave in goats reaches its maximum diameter (~6.3 mm) (De Castro et al., 1999; Côrtes et al., 2021) on the sixth day after ovulation or seven days after the onset of estrus (De Castro et al., 1999) and, by this time, is able to respond to the gonadotropic stimulus of hCG. This fact allows us to understand the lack of success in the development of accessory luteal structures in the studies described above, which administered hCG on the fifth day. Goats in the transition period to the breeding season submitted to treatment with 300 IU of hCG, seven days after estrus, were able to develop accessory luteal structures and improve pregnancy rates (Côrtes et al., 2021). The dose of 300 IU of hCG was compared with 100 IU administered seven and 14 days post-artificial insemination (AI) in multiparous and anovulatory goats (Bustamante-Andrade et al., 2021). The study confirmed the efficiency of the 300 IU dose in increasing reproductive efficiency (fecundity rate, corpus luteum area, and embryo implantation rate), although the formation of aCL was not evaluated.

Despite the results observed in the studies conducted to date, where hCG was able to increase P4 concentrations, pregnancy, fecundity rate, and embryo implantation rate, as well as to induce the formation of aCL, further research is needed to adjust these protocols and thus increase the reproductive efficiency of goats.

Effects of gonadotropins on oCL function and aCL formation

When administering gonadotropins or their analogues between Days 5 and 12 of the estrous cycle in small ruminants, some studies have reported an increase in P4 concentration and/or success in inducing aCL (Table 1). It is noteworthy that, in addition to the induction of aCL, as in heifers (Fonseca et al., 2001a), these hormones also act on the oCL, since the CL of small ruminants reaches its maximum size around Day 9 of the estrous cycle in goats (Balaro et al., 2017) to Day 12 of that in sheep (Figueira et al., 2015), and small luteal cells have LH receptors and may be stimulated with a possible increased production of P4 (Niswender et al., 1985). Administration of 120 µg of intravenous LH every 6 h from Day 5 to Day 10 of the estrous cycle (estrus = Day 0) decreased the proportion of small to large luteal cells of the oCL (Farin et al., 1988), reinforcing the hypothesis that LH stimulates small luteal cells to differentiate into large luteal cells, and this luteotrophic action may be important in oCLs. In addition, the administration of 100 IU of hCG on Day 11.5 of the estrous cycle in sheep led to aCL formation, although oCLs at Day 13 were larger in treated animals (Nephew et al., 1994).

In large ruminants, there are some more concrete reports on the action of these hormones on the oCL. hCG given daily from Day 2 to Day 7, or as a single administration on Day 1 or 3 of the estrous cycle, in cows caused a significant increase in the size of the oCL between Days 9 and 11 in all treated groups (Veenhuizen et al., 1972). Schmitt et al. (1996) studied the cellular and endocrine effects of hCG or a GnRH-agonist treatment on Day 5 upon both aCL and oCL in Holstein cows. They observed an increased mean size of small luteal cells, further evidence of the luteotrophic action of LH/hCG on oCL.

On Day 17 of the estrous cycle, there was a greater amount of P4 in luteal tissue (mg/CL) in oCL treated either with hCG or GnRH agonist than in the control group (Schmitt et al., 1996).

More recently, it has been possible to study this luteotrophic effect with the aid of ultrasonography to evaluate the effects of hCG administered on Day 5 after estrus detection on the characteristics of the CL in cows. hCG treatment promoted a significant increase in oCL area from Day 7 to Day 13 in treated animals compared with the control group (Rizos et al., 2012). In buffaloes, the administration of buserelin acetate or hCG on Day 5 after ovulation demonstrated a luteotrophic action of these hormones on the oCL at Day 12, which maintained a larger diameter until the end of the cycle (Day 21). Plasma P4 concentrations from Day 12 to Day 21 post-ovulation did not differ between treated buffaloes, whether or not they had an aCL, suggesting that this luteotrophic action on the oCL may be the main source of P4 for treated animals (Pandey et al., 2015).

Finally, data from our research group, studying the effects of hCG administration on Day 7 of the estrous cycle in dairy goats, showed the induction of aCL in 100% of the goats. Interestingly, a significant increase was detected in total luteal area and mean cross-sectional area of the oCL on Day 10 in the treated group, and both variables remained greater until Day 21. Moreover, circulating P4 concentrations were greater in hCG-treated goats from Days 13 to 21 and were directly related to total luteal and oCL area for the duration of the study (Rodrigues et al., 2022).

Final Considerations

The potential advantageous effects of the strategic administration of gonadotropins appear to be dependent on ovarian status at the time of hormone administration, reproductive cyclicity, and limiting factors for pregnancy establishment. Both increased P4 concentration profile and other unknown mechanisms have been reported as responsible for pregnancy increases. hCG is the most commonly used gonadotropin to induce aCL, but the consolidation of this strategy for reproductive management in sheep and goats will depend on the repeatability of positive effects on pregnancy rates.

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