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A simple mathematical model of the progesterone curve during the estrous cycle in Canindé goats (*Capra hircus*)

Modelo matemático simples da curva de progesterona durante o ciclo estral em cabras Canindé (Capra hircus)

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Abstract

A mathematical model of the estrous cycle could help in understanding the dynamics of this complex biological system. This study aimed to use a mathematical model that accounts for the variations of progesterone during the estrous cycle in Canindé goats. Five adult (3-6 years old) and six young (1-2 years old) healthy and cyclic goats were used. The females were submitted to a hormonal estrus synchronization treatment, and blood samples were collected for progesterone dosage from the day of synchronized estrus until the subsequent natural estrus. Plasma progesterone concentrations were then compared across different age groups. The progesterone curves were fitted to mathematical models for both the luteal and luteolytic phases. It is concluded that the proposed model, simple and efficient, can describe the evolution of progesterone during the estrous cycle of Canindé goats using few parameters, which can be employed to investigate other effects

Resumo

A modelagem matemática do ciclo estral pode auxiliar na compreensão da dinâmica desse complexo sistema biológico. Este estudo teve como objetivo utilizar um modelo matemático que leve em conta as variações de progesterona durante o ciclo estral em cabras Canindé. Foram utilizadas cinco cabras adultas (3-6 anos) e seis jovens (1-2 anos) saudáveis e cíclicas. As fêmeas foram submetidas a um tratamento de sincronização hormonal do estro e amostras de sangue foram coletadas para dosagem de progesterona do dia do estro sincronizado até o próximo estro natural. Os níveis plasmáticos periféricos de progesterona foram comparados entre as faixas etárias. As curvas de progesterona foram ajustadas a modelos matemáticos para as fases lútea e luteolítica. Conclui-se que o modelo proposto, simples e eficiente, consegue descrever a evolução da progesterona durante o ciclo estral de cabras Canindé com poucos parâmetros, que podem ser utilizados para investigar outros efeitos.

Palavras-chave: equações diferenciais; fertilidade; hormônio; reprodução.

1 | Introduction

Goats are widespread worldwide, being the first dairy species to be domesticated, possibly in the Middle East (Zheng et al., 2020). In Brazil, different breeds of goats developed from those brought by Portuguese settlers shortly after arriving in the country in the 16th century. Currently, this species exhibits characteristics adapted to environmental conditions. Specifically, in the Northeast of Brazil, after hundreds of years of adaptation, locally adapted goat breeds such as Canindé, Moxotó, Marota, Gurguéia, Azul, and Graúna (Menezes et al., 2020) together with exotic breeds form the livestock that provides milk, meat and other products, boosting the local economy (Da Rocha et al., 2016).

Considering economic and social importance, it is essential to achieve good breeding indexes to ensure rapid genetic advance and increase herd productivity. Regarding the Canindé breed, different aspects of reproduction have been investigated, including the effect of heat stress on reproduction (Lima et al., 2022) and the application of reproductive biotechnologies (Souza-Fabjan et al., 2013).

It is essential to note that a set of biological systems work together. Therefore, it is essential to understand these systems to achieve appropriate reproductive indices. In this sense, it is crucial to evaluate how the various components of a biological system function together rather than investigating only individual parts. Thus, mathematical models allow transforming a conceptual biological model into a set of mathematical equations representing the relationships between the different components of the system, enabling the interpretation of the functioning of these biological systems (Boer et al., 2017; Zaheri and Hassanipour, 2020). Some models have been developed to improve the understanding of the biological processes involved in reproduction, whether to describe the biological mechanisms of the bovine estrous cycle (Boer et al., 2011), understand ovarian follicular dynamics (Clément and Monniauxou, 2021) or to better understand ovarian function in sheep (Clément et al., 2002).

The corpus luteum is a temporary endocrine gland whose primary function is progesterone secretion (Wuttke et al., 1998), which regulates the release of Gonadotropin Release Hormone (GnRH) and, consequently, gonadotropins. The luteolysis or corpus luteum regression is characterized initially by a decrease in plasma progesterone concentration. It involves many processes triggered by the lack of maternal recognition and increased pulsatile release of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). In this context, using a mathematical model, it is possible to equate different biological events that culminate in a main event. Due to the complexity of progesterone synthesis and luteolysis, this study aimed to use a mathematical model that considers the variations in progesterone during the estrous cycle in Canindé goats. Furthermore, we investigated potential differences between females of varying age groups.

2 | Materials and methods

2.1 | Local of experiment

The experiment was conducted at the State University of Ceará in Fortaleza, Brazil, at 3°43'47''S and 38°30'37''W. The locality is at an average altitude of 16m above sea level and has a tropical climate (Aw), as classified by Köppen and Geiger. The average annual temperature and rainfall are 26.7°C and 1042mm^3, respectively.

2.2 | Animals

Eleven Canindé goats were used, five of which were adults (3-6 years old) and six were young (1-2 years old) with an average weight (± SD) of 27.5 ± 7.2kg. The females were examined previously to confirm health and cyclicity. All the animals were maintained in a semi-intensive system, receiving capim elefante (*Pennisetum purpureum*) and daily access (4h) to the pasture of this grass variety. Additionally, supplemented with 0.1kg/day of commercial concentrate (minimum of 20% crude protein) and had free access to water and mineralized salt licks.

2.3 | Hormonal estrus synchronization

Goats received routine treatment for estrus synchronization (Freitas et al., 1997). This treatment consisted of an intravaginal sponge impregnated with 60mg medroxyprogesterone acetate (MPA) (Progespon, Syntex, Buenos Aires, Argentina) for 11 days, associated with intramuscular injections of 120IU of equine chorionic gonadotrophin (eCG, Novormon, Syntex) and 50µg of cloprostenol (Ciosin, MSD, São Paulo, Brazil) 48h before sponge removal. The onset of estrus was tested twice a day for 60h

after sponge removal, with the aid of a vasectomized buck. Five days after estrus, the number of ovulations was determined by transrectal ultrasonography using a 7.5MHz linear probe (DP-10 Vet Power, Mindray, Shenzhen, China).

2.4 | Blood samples and progesterone dosage

Blood samples were collected by jugular venipuncture using 4ml tubes containing EDTA (BD Vacutainer, Becton Dickinson and Company, Holdrege, NE, USA) to determine the plasma progesterone concentration. Samples were obtained every 48h from the onset of estrus until the subsequent estrus or up to 21 days after the first estrus. The tubes were immediately placed on ice until centrifugation at 2000 × *g* for 15 min. Samples were stored at -20°C until the hormone assay. The progesterone concentrations were measured using a commercial, solid-phase radioimmunoassay kit (Coat-A-Count; Diagnostic Products Corporation, Los Angeles, CA, USA). The mean intra- and inter-assay coefficients of variation were 8.8% and 9.7%, respectively, and the analytical detection limit was 0.08ng/mL.

2.5 | Mathematical modeling

To schematize the curves (n = 11), the mathematical model was used describing the evolution of the amount of progesterone during the cycle. The model developed for the cow by Yenikoye et al. (1981) and Boer et al. (2017) allows objective and precise evaluation of the profiles. The onset of estrus (t = 0) corresponds to the instant when estrus is observed. The first expression of the model is a logistic function, and the second is a decreasing exponential function. All the experimental points of a curve of progesterone can be represented by a model with two trends.

If we call ϕ the moment when the decrease in the level of progesterone begins, the equations of the model are as follows:

$$t < \phi \quad f(t, \theta) = \theta_1 / 1 + \theta_2 \, e^{-\theta 3 \, t}$$

$$t = \phi \quad f(\phi, \theta) = \theta_1 / 1 + \theta_2 \, e^{-\theta 3 \, \phi}$$

$$t > \phi \quad f(t, \theta) = f(\phi, \theta) \, e^{-\theta 4 \, (t - \phi)}$$

Thus, it was calculated, for each animal, the following parameters of the curve, in which: f(0) is the progesterone level at synchronized estrus; θ_1 is the value of the upper limit of the logistic function and is expressed in nanograms; and ϕ is the moment of reversal of the phenomenon or time of rupture expressed in days.

2.6 | Statistical analysis

All calculations for determining the individual curves were performed using the Casio fx-CG50 calculator (Casio Computer Co., Tokyo, Japan). The values (mean ± SD) between age groups concerning the length of estrous cycle, number of ovulations, and all parameters of the model of progesterone curve were compared by unpaired *t* test using the Statistica software (StatSoft, Hamburg, Germany).

3 | Results

All females in both groups showed estrus and ovulation after hormonal synchronization treatment, approximately 36 hours after removing the sponge. In all parameters studied before the use of modeling data, no statistical difference ($p > 0.05$) was observed between the age groups. In the 1-2 years age group, the mean length of the estrous cycle was 20.7 ± 0.8 days, and the number of ovulations was 1.1 ± 0.7. In the 3-6 years age group, the mean length of estrous cycle and the number of ovulations were 21.2 ± 0.5 days and 1.0 ± 0.0, respectively.

Two distinct phases could be observed in the evolution of the plasma progesterone level in both age groups: i) a growth phase or luteal secretion, which begins four days after estrus, and which characterizes the functional state of the corpus luteum and ii) a decrease phase which characterizes the involution of the corpus luteum (Figure 1).

Concerning the modeling data, the logistic function has these two phases. Following the growth phase, a gradual decline in progesterone levels was observed in both age groups (Figure 2). Also, regarding the three parameters studied by the mathematical model, statistical differences ($p < 0.05$) were observed for some parameters when compared to the two age groups. Thus, older females presented statistically higher values for progesterone maximum level after synchronized estrus and an upper limit of the logistic function (Table 1).

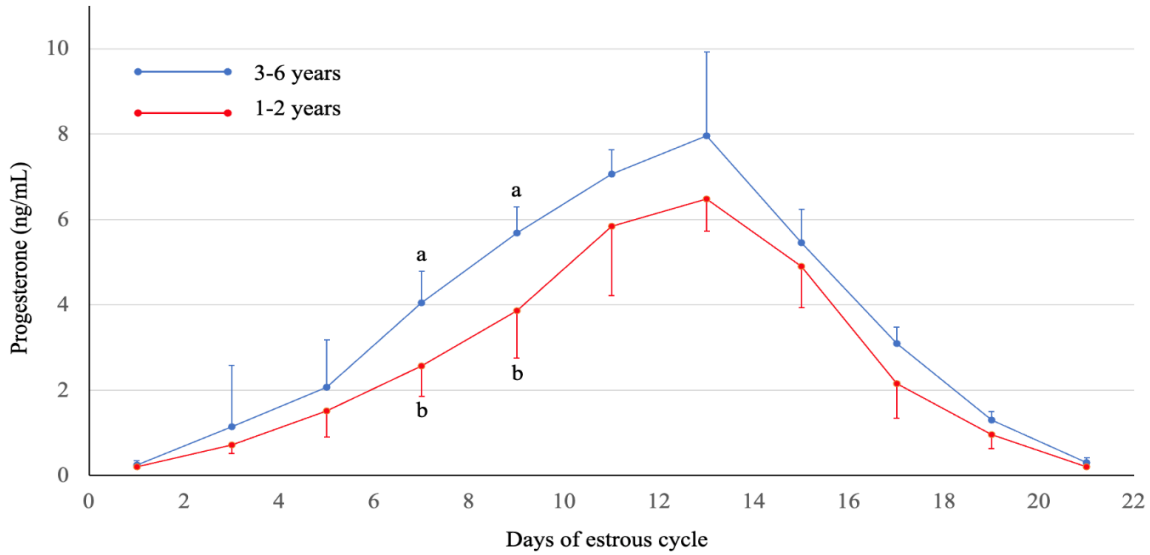

Figure 1. Progesterone (mean ± SD) curves during the estrous cycle in Canindé goats in different age groups. a,b: Different lowercase letters on each day of the cycle indicate statistical difference between groups ($p < 0.05$).

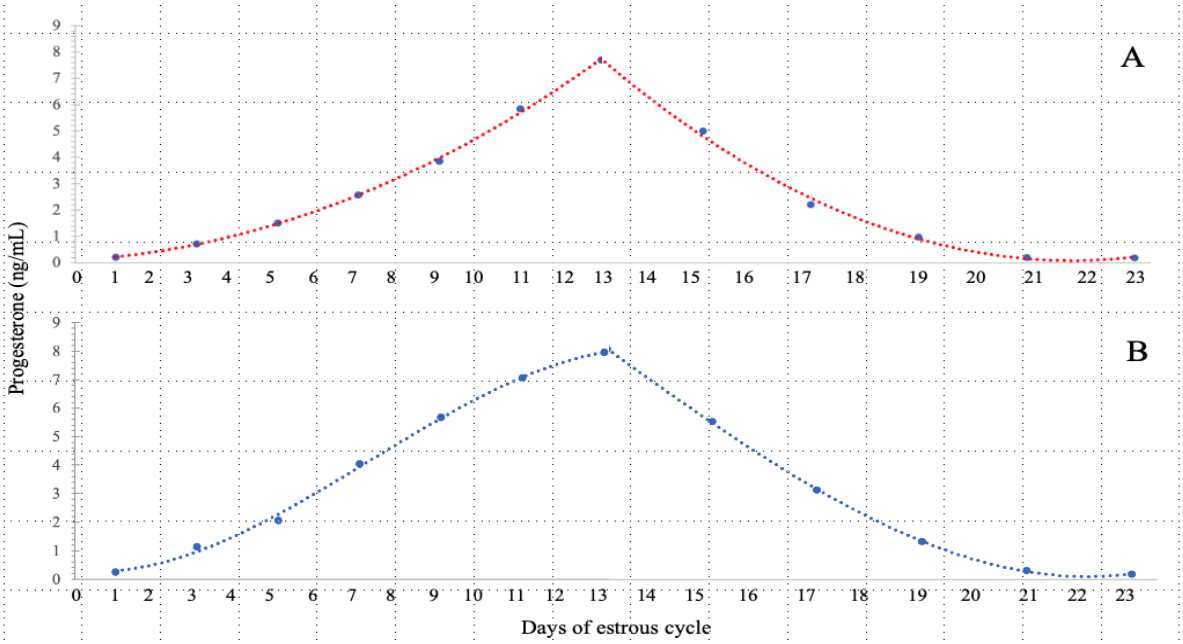

Figure 2. Adjustment of the progesterone curve in Canindé goats by the optimization method in different age groups: A: 1-2 years old and B: 3-6 years old.

Table 1. Mean and standard deviation of progesterone secretion curves in Canindé goats with different age groups

Group	Number of goats	Parameters		
		f(0) (ng/mL)	θ_1 (ng/mL)	Φ (days)
1-2 years	6	0.03 ± 0.37[a]	7.74 ± 1.87[a]	12.81 ± 0.71[a]
3-6 years	5	0.14 ± 1.01[b]	8.01 ± 1.95[b]	13.01 ± 1.01[a]

f(0): progesterone level at estrus; θ_1: maximum progesterone level; and Φ: length of luteal phase. Columns followed by different letters represent statistical difference ($p<0.05$).

4 | Discussion

In the current study, a mechanistic mathematical model of the Canindé goat estrous cycle was parameterized for an independent data set comprising progesterone measurements of females into two groups of different ages.

The hypothalamic-pituitary-gonadal axis plays a central role in female fertility, regulating hormones and coordinating reproductive processes such as ovarian follicle maturation, ovulation, and sex hormone production (Xie et al., 2022). Among these hormones, progesterone plays a crucial role in maintaining the cycle as well as maintaining pregnancy. However, its synthesis involves numerous factors, including age (Hori et al., 2019). Therefore, this work proposed to evaluate characteristics of the estrous cycle, as well as to use a mathematical model that described the variations in progesterone during the estrous cycle, considering different age groups of Canindé goats.

Concerning the length of estrous cycle, it was found that the values were similar to those observed in other studies with the Canindé breed (Souza-Fabjan et al., 2013). Regarding the number of ovulations, slightly lower values were observed in our experiment when compared to other studies, which reported averages of 1.2 to 1.3 (Nogueira et al., 2011; Souza-Fabjan et al., 2013). Progesterone concentrations determined during the estrous cycle were comparable to those obtained by other authors (Vázquez et al., 2010; Souza-Fabjan et al., 2013; Alves et al., 2018), with its basal level, during induced hormonal estrus, similar to that verified in ovariectomized goats (Freitas et al., 1997).

When considering the three parameters chosen to design the mathematical model of the progesterone curve (progesterone level in synchronized estrus, upper limit of the logistic function, and the moment of reversal of the phenomenon), it is possible to verify the similarity between the age groups. However, surprisingly, the curve after luteolysis shows a slow downward trend. This result is quite different from similar studies in cattle (Yenikoye et al., 1981; Boer et al., 2017) and even in goats of European breeds, such as Saanen and Alpine (Freitas et al., 1997), which showed a more pronounced curve. Luteolysis is a physiological process reflecting the increase in the pulsatile release of $PGF_{2\alpha}$, resulting from the increase in endometrial receptors for oxytocin and estrogen. When high concentrations of $PGF_{2\alpha}$ bind to receptors in the corpus luteum, trigger a series of changes in the gene expressions of angiogenic factors and vasoactive, which directly or indirectly influence corpus luteum activity (Pokharel et al., 2020). This observation deserves further studies that could elucidate this unexpected behavior in the Canindé breed.

The originality of the model presented lies in the fact that the evolution of progesterone levels over time is represented by a small number of parameters. An initial difficulty is the choice of these parameters, since they must have a biological meaning. However, it is possible that other parameters, analytically dependent or independent of those studied, but directly related to the model, may allow showing other aspects of progesterone secretion during the estrous cycle and performing another type of physiological evaluation.

5 | Conclusion

In conclusion, the proposed model, which is simple, enables the characterization of progesterone level evolution during the estrous cycle of Canindé goats using a few parameters. In addition, it was possible to use these parameters to verify the effect of age.

6 | Conflict of Interest Statement

The authors declare that there is no conflict of interest.

7 | Ethics Committee

This work was performed in accordance with the regulations of the Ethics Committee in the Use of Animals (CEUA) of the State University of Ceará (UECE), under nº 03550443/2022.

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