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Review paper

THE OESTRUS CYCLE IN THE BITCH: A REVIEW ARTICLE

Janoš Butinar [1*], Emir Mujagić [1], Sara Galac [2]

Addresses of authors: [1] Clinic for Small Animal Medicine and Surgery, Veterinary Faculty, Cesta v Mestni log 47, 1000 Ljubljana, Slovenia; [2] Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University, The Netherlands

*Corresponding author. E-mail: janos.butinar@vf.uni-lj.si

Summary: The regulation of the oestrous cycle in the bitch is quite unique among the various animal species commonly encountered in veterinary medicine. The cycle, which has an average length of about 3 months, consists of the pro-oestrus, oestrus and metoestrus phases and is followed by the anoestrus phase that varies in duration. The duration and regulation of the luteal phase is the same in both cyclic and pregnant bitches. In contrast to some other species, the uterus is not involved in the regulation of the cyclic corpus luteum. While the first stage of the luteal phase is completely autonomous, the second depends on pituitary factors, mainly prolactin. It is still unclear whether LH has luteotrophic properties in the bitch. Recent studies centred on the role that hormones play in the oestrous cycle have led to developments such as the FSH threshold concept, which could lead to the induction and manipulation of the oestrous cycle. They have also led to the use of progesterone-receptor antagonists to control some of the physiological consequences of the luteal phase, such as pseudopregnancy. This article presents a review of the new scientific insights concerning the oestrous cycle of the bitch, with the emphasis on the regulation and complications of the luteal phase, such as the cystic endometrial hyperplasia–pyometra syndrome, acromegaly, insulin resistance, diabetes mellitus and the incidence of mammary tumours.

Key words: oestrous cycle; luteal phase; bitch

Introduction

The oestrous cycle of the bitch consists of the pro-oestrus, oestrus, and metoestrus phases. After each oestrous cycle, which has a length of about 3 months, there is an anoestrus phase, which varies in duration. The mean interval from the onset of one oestrous cycle to the next is about 7 months, within a range of between 4 and 12 months. The inter-oestrous interval of individual bitches may be either regular or variable (1).

Pro-oestrus is defined as the period when the bitch has become sexually attractive but is rejecting the male's advances until the first signs of its willingness to accept the male. As early behavioural signs may be indistinct, the onset of a serosanguineous vaginal discharge and swelling of the vulva are used to mark the first day of pro-oestrus. The duration of pro-oestrus ranges from 3 to 17 days with an average of 9 days. Oestrus is the period when the female allows breeding and has an average duration of 9 days, within a range of 3 to 21 days. During oestrus the vulva begins to shrink and soften and the vaginal discharge generally diminishes. Metoestrus begins when the bitch will no longer accept the male and usually lasts about 70 days. The end of metoestrus can be defined in a number of ways such as when the progesterone secretions of the luteal phase subside, mammary development declines, progesterone secretions no longer effect the endometrium or when the plasma-progesterone concentration initially declines to a level of 1 μg/L or less (1, 2).

In addition to this behaviour-oriented classification of the oestrous cycle, a new and far more appropriate classification system has been introduced. It is based on the ovarian function and divides the oestrous cycle into four phases: the

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follicular, the pre-ovulatory luteinization and ovulation, the luteal and the anoestrus phases (3, 4).

Follicular phase

Tertiary follicles developing in the ovaries produce oestradiol. The increased concentration of oestradiol is responsible for external signs of prooestrus, such as hyperaemia and oedema of the vulva, the bloody vaginal discharge and for behavioural changes. It also causes a lengthening and hyperaemia of the uterine horns, an enlargement of the cervix and a thickening of the vaginal wall (1, 5). Plasma-oestradiol levels increase constantly throughout the follicular phase and reach peak plasma values 1 to 2 days before the pre-ovulatory LH surge (6, 7, 8). The oestrogen levels decline rapidly thereafter, while the level of plasma progesterone starts to increase as a result of the partial luteinization of the follicles (7). Both LH and FSH plasma concentrations are relatively low during the follicular phase (9, 10).

Pre-ovulatory luteinization and ovulation

The pre-ovulatory LH surge starts 1 to 2 days after the oestradiol peak and coincides with the declining oestradiol and rising plasma-progesterone concentrations (6, 7). It has been suggested that the pre-ovulatory LH surge is triggered by a decline in the plasma oestrogen: progesterone ratio in the latter stages of the follicular phase (7, 11). The pre-ovulatory LH surge, which lasts from 24 to 72 hours and produces a rapid and final enlargement and luteinization of the mature follicles, causes ovulation and in the process transforms oestrogen-secreting follicles into progesterone-secreting corpora lutea (7). Thus the LH surge represents the transition from the follicular phase to the luteal phase. Ovulation appears to occur synchronously about 36 – 48 hours after the LH peak (7, 12). Most ova in the bitch are ovulated in an immature state as primary oocytes (13) and cannot be fertilized until they undergo the first meiotic division to become secondary oocytes, which usually occurs about 60 hours after ovulation (12, 14). By this time the ova have descended through two thirds of the oviduct. Plasma-progesterone concentrations are between 2 and 4 µg/L at the LH peak and by the time ovulation occurs, usually 36 to 48 hours later, they rise from 5 to 8 µg/L (15). Concurrent with the LH peak, there is also a pre-ovulatory surge of FSH that reaches its peak concentration 1 to 2 days later (9).

Luteal phase

The concentration of progesterone, which originates from the corpora lutea, increases in the peripheral blood during the latter stage of oestrus and the onset of metoestrus and reaches its maximum level 10 to 30 days after the LH peak. Thereafter, in non-pregnant bitches, the progesterone secretion slowly declines and reaches a basal level of 1 µg/L for the first time about 75 days after the start of the luteal phase (15). The transition from oestrus to metoestrus takes place during the initial stage of the luteal phase.

Regulation of the luteal phase

In many species, the regulation of the cyclic corpus luteum is influenced by both luteotrophic and luteolytic factors. Prostaglandin F2? originating from the endometrium, which is the causative factor for luteolysis in the cow and sheep, is not present during the luteal phase of the cyclic dog (15). This is demonstrated by the fact that a hysterectomy does not influence the length of the luteal phase. Therefore the uterus is not involved in the regulation of the cyclic corpus luteum (15). Moreover, in the initial stage of the luteal phase the canine corpus luteum functions completely autonomously. Studies of dogs that had undergone hypophysectomy demonstrated that the canine corpus luteum functions independently of pituitary support for 24 to 28 days from the onset of the luteal phase (16).

Administering aglepristone in the early part of the luteal phase does not effect its duration (17). During the second half of the luteal phase, pituitary luteotrophic factors – prolactin and possibly LH – are necessary to sustain the luteal function (16, 18, 19, 20). Whether LH has luteotrophic properties in the bitch is still unclear. Concannon et al. (1987) reported that passive immunization against LH caused a decline in the progesterone concentration. However, the luteotrophic role of LH has been brought into question by studies in which LH-inhibition had no effect on the plasma-progesterone concentration, whereas prolactin-inhibition caused it to fall abruptly, indicating that only pro-

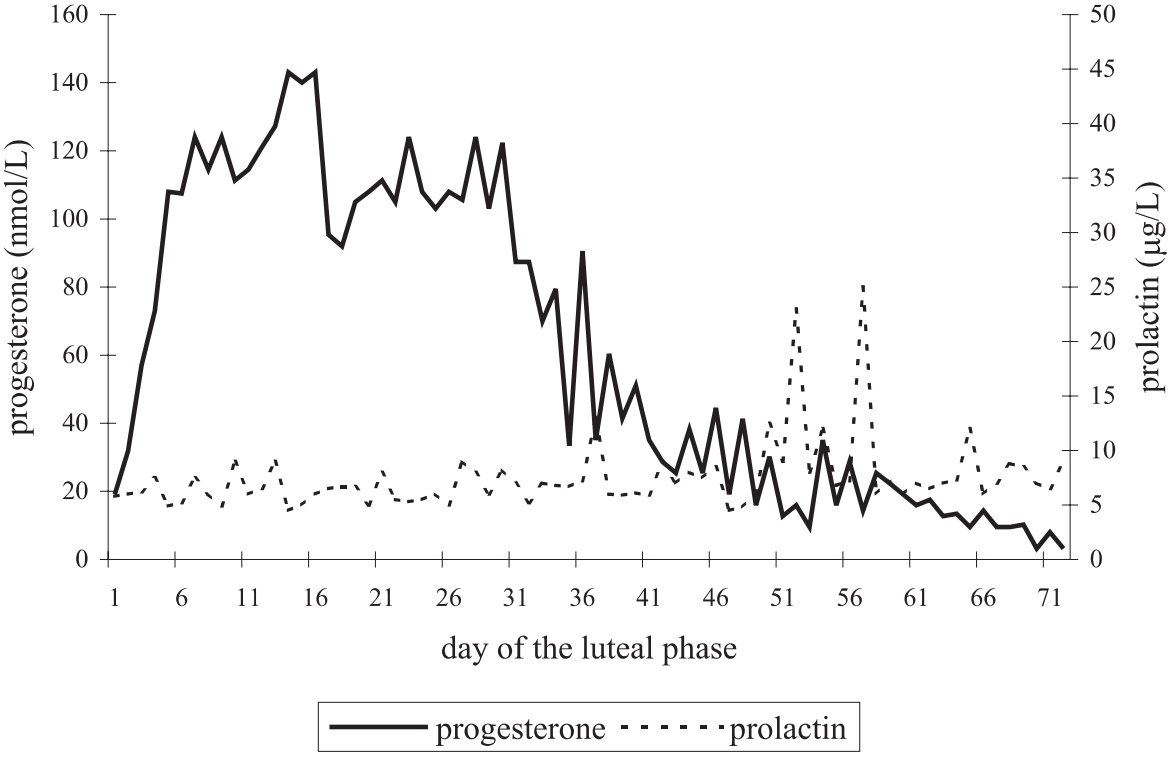

Figure 1: Mean plasma concentrations of progesterone and prolactin in 3 healthy beagle bitches, starting from the day of ovulation (Day 1) to the end of the luteal phase. (From Galac S. The effect of aglepristone, the progesterone receptor antagonist, on the hypothalamic-pituitary-ovarian axis, pregnancy and luteal phase in bitches. In: doctoral thesis. Ljubljana, 2001. Reproduced with the author's permission)

lactin is luteotrophic in cyclic dogs (19). It is possible that LH has an indirect luteotrophic role that is mediated by the secretion of prolactin (21).

Anoestrus

The transition from the luteal phase to anoestrus is gradual and varies considerably among bitches. The onset of anoestrus depends on which criteria are being used to define the end of the luteal phase. It can be defined as the period when mammary development subsides, which is usually after 2 to 3 months, or when the plasma-progesterone concentration reaches a level below 1 µg/L for the first time or as the moment that the influence of progesterone on the endometrium is no longer evident (1, 22). In anoestrus, the normal bitch is neither attractive nor receptive to the male, the mucoid vaginal discharge is minimal and the vulva is small (5).

Although anoestrus seems an inactive part of the oestrous cycle in the bitch, neither the ovaries nor pituitary are quiescent (9). From early to late anoestrus, the hypothalamus releases increasing amounts of GnRH (23), which the pituitary becomes increasingly sensitive to (24). Additionally, increases in ovarian responsiveness to gonadotrophins (25) and the level of basal LH-concentrations towards the end of the anoestrus (9), as well as a brief period of increased LH pulsatility (26) have been reported as important determinants of the initiation of a new follicular phase. It has even been suggested that changes in the LH secretion may be more important than changes in the FSH secretion in the initiation of the follicular phase leading to ovulation (11). In line with this, the administration of pharmacological doses of LH can terminate anoestrus in bitches by inducing the follicular phase (27). However, the progression from early to late anoestrus is associated with an increase in the basal plasma-FSH concentration, suggesting that in the bitch an increase in circulating FSH levels is a critical event in the initiation of ovarian folliculogenesis (10). In this respect, there are similarities with the situation in primates. Observations during gonadotrophin-indu-

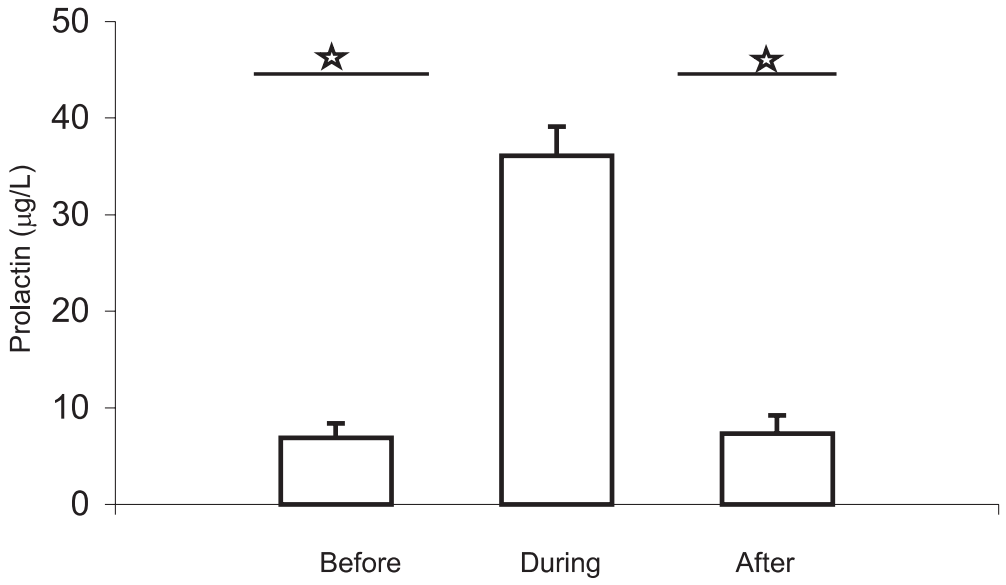

Figure 2: The average (± SEM) of the mean plasma prolactin concentrations in 6 beagle bitches before, during and after treatment with aglépristone. Asterisks indicate significant difference. (From Galac S. The effect of aglépristone, the progesterone receptor antagonist, on the hypothalamic-pituitary-ovarian axis, pregnancy and luteal phase in bitches. In: doctoral thesis. Ljubljana, 2001. Reproduced with the author's permission)

ced ovulation in women have emphasized that plasma FSH must exceed a certain concentration before preantral follicles reaching the FSH-dependent stage can progress to maturation (28). This has been labelled the FSH threshold concept. An increase of only 10 to 30 % above the threshold concentration of plasma FSH is sufficient to stimulate normal follicular development in women (29). The threshold for FSH may vary among individuals, and each follicle also has its own sensitivity to FSH (28). The study of Kooistra et al. (1999) indicate that the FSH threshold concept, as anticipated for women, could hold true for the dog as well.

The oestrous cycle can begin at any time throughout the year and there appears to be little, if any, seasonal influence. Breed differences and strains within breeds can form the basis of variation in mean inter-oestrous intervals. Environmental factors can also affect the inter-oestrous interval: the onset of pro-oestrus in an anoestrus bitch can be brought forward by several weeks by placing her in close proximity to a bitch in oestrus. Furthermore, bitches housed together often have synchronous oestrous cycles (11, 30).

Consequences of the oestrus cycle

The relatively long exposure to high levels of progesterone circulating during each oestrous cycle may result in disorders such as cystic endometrial hyperplasia-pyometra syndrome (31), acromegaly, insulin resistance, diabetes mellitus, (32) and an increased incidence of mammary tumours.

Cystic endometrial hyperplasia involves proliferation of the glandular epithelium and cystic dilatation of the endometrial glands with endometrial fluid accumulated in their lumen. These conditions provide an excellent environment for bacterial growth, which can lead to the development of pyometra. Pyometra is often caused by entering the progesterone phase of the sexual cycle with an abnormal endometrium, which can result in an overgrowth of bacteria that is normally isolated from this area of the anatomy. Surgery is the preferred treatment for pyometra unless the owner adamantly wants to breed with the bitch. The medical treatment consists of administering antibiotics and prostaglandins. If the bitch is still in the luteal phase, progesterone-receptor blockers may also be administered to diminish the influence of progesterone (33).

Acromegaly occurs as a consequence of excess secretion of the growth hormone (GH). Progesterone-induced GH secretions originate from the foci of hyperplastic ductular epithelium of the mammary gland (34, 35). In contrast to the GH from the pituitary gland, GH from the mammary gland is not pulsatile and cannot be stimulated by the GH-releasing hormone (GHRH) and nor can it be inhibited by somatostatin (34, 36). The progesterone-induced GH excess may lead to insulin resistance, exhaustion of the pancreatic ?-cells and consequently diabetes mellitus (32). If diabetes mellitus is diagnosed while there is a high level of progesterone secretion, it might have a reversible nature. However, the source of progesterone must be removed as early as possible. Therefore, an ovariectomy is advised if diabetes mellitus occurs during the luteal phase, although it is difficult to predict whether the pancreatic insulin production will completely recover. In any case, supportive therapy with insulin is recommended after the surgery. In order to prevent hypoglycaemia and to achieve the right dosage of insulin, daily blood glucose measurements are needed and the insulin dose adjusted accordingly (37).

Pseudopregnancy is a syndrome that accompanies the extended luteal phase of all the non-pregnant ovarian cycles in the bitch (38). An important precipitating factor for pseudopregnancy appears to be a rapid decline in the plasma progesterone concentration, which is assumed to be the trigger for the release of prolactin, which in turn would give rise to pseudopregnancy (39). Correspondingly, an ovariectomy performed in the luteal phase often induces an overt pseudopregnancy. Studies using the progesterone-receptor antagonist aglépristone, have suggested that a sudden decline in the plasma progesterone concentration induces an increase in the concentration of prolactin (40, 41).

The development of mammary gland tumours in the bitch is clearly hormone dependent. The role of progestins in the pathology of the mammary gland was revealed in 1969, when Schneider et al. published a study about the protective effect of an ovariohysterectomy on mammary tumour development. They estimated that in comparison with intact dogs, bitches that had been spayed prior to their first oestrus had a 0.05 % risk of developing malignant tumours. This increased to 8 % if spayed following their first oestrus and rose to 26 % if spayed after their second oestrus. The spaying of older dogs does not reduce their risk of developing malignant tumours, although an ovariectomy does appear to reduce their risk of developing benign tumours (42). The protective effect of an early pregnancy, which is well known in the human, has not been demonstrated in the dog. As in the normal mammary gland, GH receptors have been demonstrated in neoplastic tissue (43). It has been speculated that the maximal effect of progestins on the mammary gland might be facilitated by the additional local action of GH. Yet, it must still be proven whether progestin-induced GH acts as an intermediate in the progestin-stimulated development of canine mammary tumours.

Conclusion

Being familiar with the endocrinological events associated with the oestrous cycle in the bitch could help the clinician to understand any complications that may eventuate during the luteal phase and to provide the best possible treatment for them. Applying this knowledge to breeding management, which is based on the hormonal changes in the oestrous cycle, will provide better results than those produced by using the empirical, behaviour-oriented approach. Canine female reproduction is a rapidly developing field in veterinary medicine and the pharmaceutical industry has provided us with several new possibilities to improve breeding programmes or to treat maladies associated with the oestrous cycle. Therefore it is of great importance that the small animal clinician keeps up to date with newly emerging information and developments regarding the endocrinology of the oestrous cycle in the bitch.

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POJATVENI CIKLUS PRI PSICI: PREGLEDNI ČLANEK

J. Butinar, E. Mujagić, S. Galac

Povzetek: Regualacija pojatvenega ciklusa pri psici, ki ga sestavljajo proestrus, estrus in metestrus in traja približno 3 mesece, sledi pa mu različno dolg anestrus, je med živalskimi vrstami v veterinarski medicini edinstvena. Trajanje in regulacija lutealne faze se ne razlikujeta pri ciklični in breji psici. V nasprotju z nekaterimi drugimi živalskimi vrstmi maternica ni vpletena v regulacijo cikličnega rumenega telesa. Prav tako je prvi del lutealne faze popolnoma avtonomen, v nasprotju z drugim, ki je odvisen od hipofiznih dejavnikov, predvsem prolaktina. Še vedno ni pojasnjeno, ali ima LH pri psici luteotropno vlogo ali ne. V zadnjem času so prišli do nekaterih novih spoznanj o hormonskih dogajanjih, na primer uveljavljanje koncepta praga FSH, ki lahko sprožijo pojatveni ciklus. Prav tako so bile nedavno v raziskavah z antagonisti progesteronskih receptorjev osvetljene nekatere fiziološke posledice lutealne faze, na primer navidezna brejost (psevdogravidnost). Dajanje aglépristona, antagonista progesteronskih receptorjev, v zgodnji lutealni fazi ni vplivalo na njeno trajanje. Članek predstavlja pregled novih znanstvenih spoznanj o pojatvenem ciklusu pri psici, s poudarkom na urejanju in zapletih lutealne faze, kot so cistična hiperplazija, sindrom endometrija – piometra, akromegalija, inzulinska odpornost in sladkorna bolezen ter povečano pojavljanje tumorjev mlečne žleze.

Ključne besede: estrus; lutealna faza; psica