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Male-induced short oestrous and ovarian cycles in sheep and goats: a working hypothesis

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Abstract – The existence of short ovulatory cycles (5-day duration) after the first male-induced ovulations in anovulatory ewes and goats, associated or not with the appearance of oestrous behaviour, is the origin of the two-peak abnormal distribution of parturitions after the “male effect”. We propose here a working hypothesis to explain the presence of these short cycles. The male-effect is efficient during anoestrus, when follicles contain granulosa cells of lower quality than during the breeding season. They generate corpora lutea (CL) with a lower proportion of large luteal cells compared to small cells, which secrete less progesterone, compared to what is observed in the breeding season cycle. This is probably not sufficient to block prostaglandin synthesis in the endometrial cells of the uterus at the time when the responsiveness to prostaglandins of the new-formed CL is initiated and, in parallel, to centrally reduce LH pulsatility. This LH pulsatility stimulates a new wave of follicles secreting oestradiol which, in turn, stimulates prostaglandin synthesis and provokes luteolysis and new ovulation(s). The occurrence of a new follicular wave on days 3–4 of the first male-induced cycle and the initiation of the responsiveness to prostaglandins of the CL from day 3 of the oestrous cycle are probably the key elements which ensure such regularity in the duration of the short cycles. Exogenous progesterone injection suppresses short cycles, probably not by delaying ovulation time, but rather by blocking prostaglandin synthesis, thus impairing luteolysis. The existence, or not, of oestrous behaviour associated to these ovulatory events mainly varies with species: ewes, compared to does, require a more intense endogenous progesterone priming; only ovulations preceded by normal cycles are associated with oestrous behaviour. Thus, the precise and delicate mechanism underlying the existence of short ovulatory and oestrous cycles induced by the male effect appears to be dependent on the various levels of the hypothalamo-pituitary-ovario-uterine axis.

male-effect / ovulation / corpus luteum / cycle / oestrus / uterus

1. INTRODUCTION

The existence of a two-peak abnormal distribution of lambing and kidding five months after the re-introduction of males in sheep and goat flocks, was described

very early in the literature. In the 19th century, Girard [1], presented this technique as “being able to fertilise all adult ewes of the flock in the shortest time possible”. Underwood et al. [2] in ewes and Shelton [3] in goats carefully described the distribution of lambing and kidding induced by the voluntary re-introduction of males. They

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suggested that this re-introduction probably provoked induction of synchronous ovulations and oestrous behaviour, being able to induce such synchronisations of parturitions. However, the existence, in both species, of two peaks of lambing and/or kidding, clearly separated by some days, suggested that the underlying physiological mechanisms were probably not so simple.

Many authors have decorticated the short, medium and long-term response to the male effect conducting to a rationalisation in the understanding of female responses (see reviews in sheep [4–7], in goats [8–10]). However, to our knowledge, in spite of these important advances, the general mechanism to explain the existence of an abnormal (i.e. short) cycle after the first male-induced ovulation has not been carefully described, especially to explain the very constant duration of the short cycles and why some females experience it and other ones do not. The objective of the present review was to propose a working hypothesis for a global explanation of the underlying physiological mechanisms controlling these short cycles. It is now clear that a subtle dialogue between the hypothalamus-pituitary axis, the ovary and the uterus is probably responsible for the appearance and constant duration of these short cycles. We will also try to replace, within this global description, the mechanisms by which exogenous progesterone (P4) or progestagens are able to completely suppress short cycles and to provide a rationale explanation for the existence or not of oestrous behaviour associated with induced ovulations.

Thus, after a description of classical ovulatory and oestrous responses to the male effect in sheep and goats, we will focus on various experiments performed to demonstrate the implication of the different levels of the hypothalamus-pituitary-ovarian-uterine axis in the generation of

short cycles, and on the effects of P4 injections which suppress the short cycle.

2. OVULATORY AND OESTROUS RESPONSE TO THE MALE EFFECT

In both species, immediately after introduction of males (Day 0, D0), LH pulsatility increases and remains elevated if the male remains present among females in the flock. The gonadotropin stimulation of the ovarian follicles provokes an increase in plasma oestradiol 17β (E2) pulsatility, which centrally triggers the onset of the preovulatory surge of LH, around 20 h after D0, and females ovulate before D3 after introduction of males. The percentage of females ovulating is generally high (> 85%) all year round in Mediterranean breeds, or about one month and a half before and/or after the breeding season, in more seasonal breeds. In responding females, the delay between the introduction of males and ovulation is modulated by the intensity of anoestrus (indirectly estimated by the percentage of females cycling before D0).

If females are not mated by an entire male in the following days after introduction (especially in goats), a very specific pattern of ovulations and oestrous behaviour is observed afterwards (Fig. 1).

After the first male-induced ovulation, in one part of the females the corpora lutea (CL) develop and secrete P4 during the normal duration, leading to a second ovulation around day 19 in ewes and 23 in goats. The second group of females experience a very early luteolysis, after only 1.5 days (i.e. D4–D5) of low P4 secretion in the blood of the systemic circulation (between 0.5 and 1 ng.mL⁻¹, Fig. 2). After this short cycle of highly constant duration (5–6 days) in both species, these latter females re-ovulate a second time around

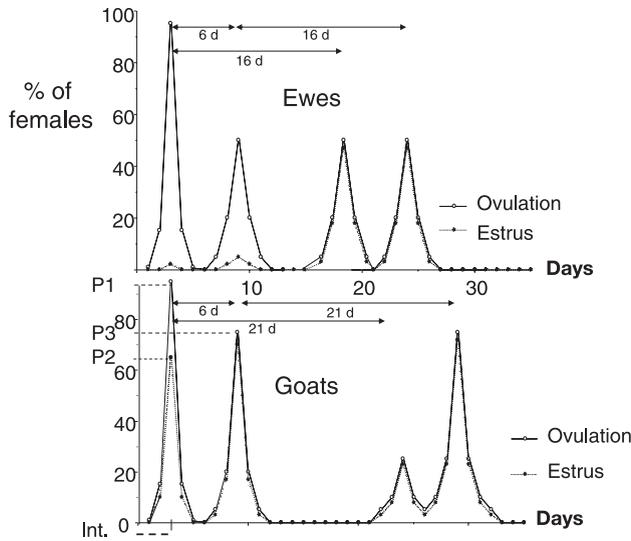


Figure 1. Schematic representation of the ovulatory and oestrous responses of ewes and goats to the male-effect (adapted from Thimonier et al., [6], for ewes). Int., P1, P2 and P3 varied with “intensity of anoestrus”.

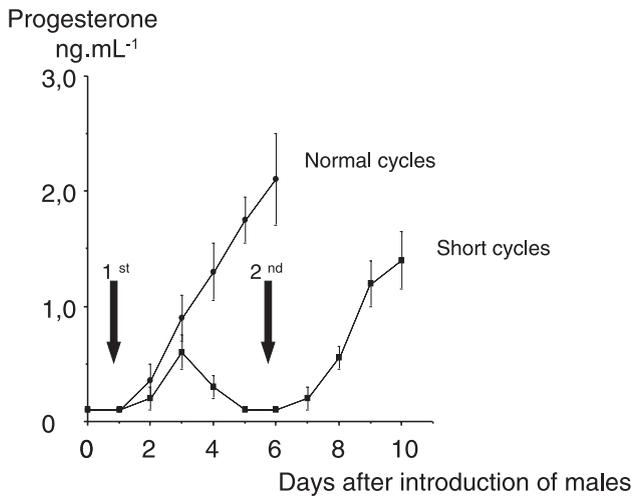


Figure 2. Plasma progesterone in Creole goats experiencing short lifespan and normal corpora lutea after introduction of bucks (adapted from Chemineau et al. [18]). First and second ovulation are indicated.

6–9 days after introduction of males. This second ovulation is always followed by a cycle of normal duration and females re-ovulate again around day 25 in ewes and 29 in goats.

In both species, the percentage of females experiencing short cycles among responding females varies with the depth of anoestrus and is modulated by body con-

dition and/or previous nutrition of females. A significant negative relationship was observed between the percentage of females cycling before male introduction and the percentage of females experiencing a short male-induced cycle in both species (ewes [11], goats [12]). The frequency of short cycles is significantly higher in Barbarine ewes which have been underfed around

lambing, 5 months before introduction of rams, than in females correctly fed (67 vs. 21 %, 13). Interestingly, this negative effect of underfeeding is not compensated for by a "flushing" applied during the 3 weeks before introduction of males, in spite of a significant increase in ram-induced ovulation rate (1.31 vs. 1.65 [13]).

The very specific pattern of response of these two groups of females after D0, one experiencing a normal cycle and the other one a short then a normal cycle after the first male-induced ovulation, is complicated by the variability in the expression of oestrous behaviour at each one of these ovulation times. This expression depends mainly on the species and on the previous priming by P4.

In ewes, which require a sufficient presence of endogenous P4 so that E2 may be able to trigger oestrous behaviour [14], no oestrous behaviour is generally observed at any ovulation if not preceded by a luteal phase of normal duration [11, 15]. Thus, first induced ovulation is never associated with oestrus, and in the group of ewes experiencing a short luteal phase, oestrus is not observed at the second one. On the contrary, oestrous behaviour is observed at the second induced ovulation in ewes experiencing a normal cycle and at the third one in ewes experiencing short cycles. This situation explains the two peaks of oestrous behaviour observed around days 18–20 and 24–26 in ewes [6].

In goats, which do not require such priming [16], about 60% of the females show oestrous behaviour as early as the first male-induced ovulation (i.e. D2–D4) and almost all females show oestrus at the second one, around D8–D10 (group experiencing a short cycle) or D23 (group experiencing a normal cycle). This explains the difference between species when watching at the time schedule of distribution of oestrus after introduction of males. The expression of oestrous behaviour also varies with anoestrous intensity, especially

in goats: in deep anoestrus, fewer females experience oestrus at the first ovulation [12].

Of course, in field conditions, it frequently occurs that the flock is constituted of a mixture of females previously in anoestrus (which respond as exposed earlier) and of already cycling females. Thus, the situation described above is complicated by the presence of these latter females which show oestrus between day 0 and 17 after introduction of males. Thus, in flocks where around 50% of the females are cycling on D0, it may be difficult to clearly see the response of anovulatory females to the introduction of males.

The duration of this first male-induced ovulatory cycle is remarkably constant in both species and between breeds within each species. In other situations where short cycles are also observed, like resumption of post-partum activity or onset of puberty, the duration of these short cycles is not as constant as it is after induction by the males.

The intriguing question of this constant duration of the male-induced short cycle and of the reason why some females are experiencing it while other ones show a cycle of normal duration were not explored completely. One reason of the few number of experiments done so far could be that adequately designed experiments are difficult to perform in this field. But various experiments were done in this area and we propose hereafter a working hypothesis for the underlying mechanisms involved. One interesting point to mention, coming from the laparoscopic examinations performed on the male effect, is that one given ewe doing twin ovulations, experiences either a normal cycle, or a short cycle on both CL, but quite never one short CL and one normal CL. Thus, this strongly suggests the existence of a general control of cycle duration, involving the general physiology of females.

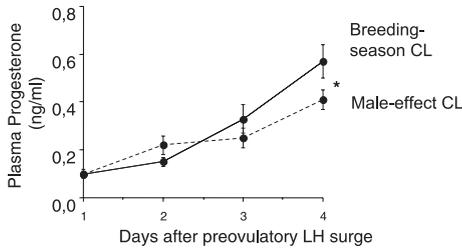


Figure 3. Jugular plasma progesterone in Prealpe ewes induced by the male effect during anestrus season or cyclic during the breeding season (adapted from Chemineau et al. [19]).

3. IMPORTANCE OF THE CL CHARACTERISTICS ISSUED FROM MALE-INDUCED OVULATIONS

Systemic plasma P4 concentrations were initially described as being roughly identical between females experiencing normal cycles and those showing short cycles up to D4–D5, after which luteolysis occurs in the latter group (ewes [17], goats [18], Fig. 2). However, when carefully comparing the evolution of plasma P4 between Prealpe ewes FGA-treated during the breeding season (BS ewes) and male-induced ewes (MI ewes) during anoestrus (Fig. 3, [19]), or between Barbarine ewes experiencing normal vs. short cycles (11), a significant difference appeared at day 4 after the LH surge or D5–D6, i.e. immediately prior to luteolysis in short-cycle females for which ovulation was induced by males. This difference is always in favour of normal CL which secrete more P4 than short-lifespan CL. The fact that various authors did not find significant differences may also originate from the fact that ovulation rate may vary from one female to another.

This difference, when observed, is very probably due to substantial differences in CL composition and function. When Prealpe ewes previously synchronised by an

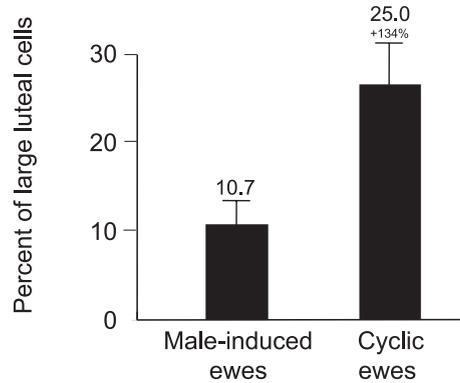


Figure 4. Percentage of large and small luteal cells and progesterone secretion by corpora lutea collected in male-induced versus breeding-season ewes (adapted from Chemineau et al. [19]).

FGA treatment during the breeding season (BS ewes) were compared to male-induced ewes (MI ewes) during anoestrus, their individual CL surgically collected 82 h after the LH surge from twin CL, had the same weight but contained a higher proportion of large luteal cells (139.1 vs. 142.1 mg and 25 vs. 11%, in BS vs. MI ewes, respectively, Fig. 4 [19]). These large luteal cells, which at this stage of the cycle derive directly from granulosa cells of the preovulatory follicle, secrete the majority of P4. On the contrary, the small luteal cells, which derive from thecal cells of the follicle, secrete the minority of P4 released by the CL in the blood [20–27]. In vitro, these BS-ewe CL, after enzymatic dispersion, secrete a higher quantity of P4 than MI-ewe CL in the absence of any LH stimulation (13.8 vs. 7.3 ng/10⁵ cells/3 h [19]). In this experiment, P4 in vitro secretion of MI-ewe CL collected from females in which the twin CL left intact was of short duration, seems lower than that of CL collected from females in which the remaining CL was of normal duration (2.9 vs. 10.3 ng/10⁵ cells/3 h respectively), but

the low number of samples (3 vs. 2) impaired any statistical comparison.

Thus, it is very probable that the cellular composition of the CL at this early stage of its development, reflects either the cellular composition of the follicle when recruited by the sudden introduction of males, or the changes which occurred within the CL between the onset of luteinisation and day 4. Thus, the difference observed here between the two groups in the ratio of large/small luteal cells could either reflect a similar difference in the granulosa/thecal cell ratio of the preovulatory follicle, or may reveal a difference in the processes of development of the large and/or small luteal cells between D0 and D4. The hypothesis of a seasonal difference in follicular composition is not supported by the results of Cahill et al. [28, 29] who did not find any difference in granulosa cell content of the follicle of the breeding season compared to the anoestrous season. On the contrary, the hypothesis of a difference in the evolution of the luteal cells between D0 and D4 is supported by the description of an inadequate luteal function due to poor response to the LH surge during the final maturation of the anoestrous follicle in ewes [30, 32]. In rats and women, if intrafollicular concentration of P4 is low, luteal development is abnormal [33]. In the few hours following the LH surge, P4 may act to mediate, as a paracrine factor, the survival rate of granulosa cells [34] and luteinisation of these cells [35]. This abnormal evolution of the follicular cells into luteal cells may be reinforced by the poor quality of the granulosa cells at male introduction, as reflected by poor oestradiol secretion compared to P4-treated ewes (Cognie Y and Oldham CM personal communication).

All experiments done after the male effect measured plasma P4 concentrations in the jugular vein, but it is known in various species that it is much lower than that of the uterine and ovarian arteries (2.35 times lower in humans [36], sows [37, 38], re-

view [39]). Thus it is very probable that the small difference at day 4 between females which will experience a short cycle and females which will experience a normal one are dramatically amplified in the blood supplying the uterus and the ovary itself. This may have profound consequences on the chain leading to prostaglandin and oxytocin liberations (see below).

During the early luteal phase of the cycle, between days 3 and 9 of the goat oestrous cycle, LH is liberated in a pulsatile manner with a frequency that is strongly associated with plasma P4 concentration of luteal origin ($r = -0.97$ [40]). Thus, the low P4 plasma levels observed here may be responsible for an insufficient negative feed-back on the central nervous system controlling the frequency of LH pulses. Unfortunately, to our knowledge, only one experiment has been done in this area, reporting that the observed difference in P4 plasma concentrations between short-lifespan and normal CL at around D4, does not provoke a significant difference in LH pulsatility [11]. This is probably due to the difficulty of measuring differences in this parameter which imposes using a quite large number of ewes sampled during sufficient durations.

As stated earlier, it is possible to manipulate on a long-term basis (months) the frequency of short cycles induced by the male [11, 15]. This has been done quite extensively in Barbarine ewes and it was demonstrated that this long-term regulation of body condition not only changes this frequency, but also changes the ability of the short-lifespan CL to synthesise and secrete P4 after introduction of rams: amongst ewes experiencing short cycles, underfed females had lower P4 plasma concentrations on Days 5–6 compared to well-fed ewes [11]. This suggests that these underfed Barbarine ewes had their CL constituted of a lower large/small luteal cell ratio than those of wellfed-ewe CL. More recently, it was demonstrated in Rasa

Aragonesa ewes that previous treatment with a sub-cutaneous melatonin implant modifies the frequency of short cycles after introduction of rams. A majority of the treated ewes exhibited a cycle of normal duration (80%), whereas 52% of the untreated ewes exhibited a short cycle after the introduction of rams [41]. However, in more strongly seasonal breeds, such as Alpine and Saanen goats, under conditions when most of the animals develop short cycles after the male effect, melatonin treatments do not modify the percentage of goats experiencing a short luteal phase [42] or the distribution of parturitions [43].

4. IMPORTANCE OF THE UTERUS AND PROSTAGLANDINS, AND OF THE OVARIAN FOLLICLES AND E2

Classically, at the end of a normal cycle, prostaglandin (PGF) secretion from the endometrial cells of the uterus induces luteolysis which provokes the triggering of a new cycle. This secretion is controlled by the ovarian secretion of E2 coming from the new wave of follicles. The same phenomenon acts to control early luteolysis after male-induced ovulation.

Hysterectomy completely prevents the appearance of short cycles after introduction of males in ewes and leads to the maintenance of CL over a long period of time. In Prealpes and Barbarine ewes, hysterectomy does not modify the percentage of ewes ovulating after the introduction of rams, and completely prevented luteolysis of ram-induced CL compared to control ewes: 0 vs. 50% in Prealpes and 78% in Barbarine ewes, respectively [19, 44].

The involvement of PGF in early regression of corpora lutea induced by the ram effect was extensively studied in Barbarine ewes. Intra-uterine injection of indometacin, a specific inhibitor of PGF synthesis, on days 2, 3 and 4 after in-

troduction of rams, significantly increased P4 plasma concentrations on Days 4–5, and significantly reduced the frequency of short cycles compared to control ewes but not completely suppressed them (71 vs. 43%, respectively [45]). The i.m. injection of a more potent PGF2 alpha synthetase inhibitor (finadyne) every 12 h from D3 to D6, significantly decreased 13-14-dihydro-15-keto-PGF2 α (PGFM) pulses (1.3 vs. 0.4 pulses), and reduced the frequency of short cycles (50 vs. 14% [44]). Thus, as early as D3, that is when CL are just sensitive to PGF [46], a part of the females have their male-induced CL which is luteolysed by uterine prostaglandins.

It was, consequently, interesting to explore if PGF secretion is, as it is during a normal cycle, under the control of E2 secretion by the ovarian follicles. In Barbarine ewes, surgical destruction by cauterisation of the largest follicles visible at the surface of the ovary at D3, in spite of an absence of effect on PGFM secretion and on LH pulsatility at D4, completely suppresses short-lifespan CL, while E2 injection in females with cauterised follicles induces a complete restoration of short cycles, compared to control females (0, 100 and 50% of short cycles, respectively [11]).

Thus, the same mechanisms regarding the PGF synthesis and liberation by the uterus under oestrogenic control of the ovary as in normal cycles are in place and seem to work, except that luteolysis occurs much earlier than in normal cycles. The fact that the new wave of follicles growing around D3–D4 after the first induced ovulation, at the time when the responsiveness to prostaglandins of the new-formed CL is initiated, seems to control this part of the system, may be a comprehensive explanation to the very constant duration of the short male-induced cycle. It is known that follicular waves in sheep and goats (as in cattle) are working on a very precise time-scale basis, emerging generally at 5–7 day intervals and being associated

to one E2 peak (review [47], goats [48–50], ewes [51–53]). Three E2 peaks occur in the plasma during the oestrus cycle [54]. The first E2 peak in ewes, at around 3–4 days of the cycle [55], could be the peak responsible for the early luteolysis of short-lifespan CL.

5. HOW EXOGENOUS P4 ACTS TO COMPLETELY SUPPRESS SHORT CYCLES? IS THIS WORKING FOR ENDOGENOUS P4 FROM THE EARLY CL?

Progesterone injections (or progestagen treatments) were described very early as being able to completely suppress short-lifespan CL and were demonstrated to achieve a better synchronisation of oestrous behaviour in one peak instead of two after introduction of males. These experiments were also interesting tools which provided arguments for the hypotheses raised to explain the existence of these short cycles.

Most experiments were done injecting the adequate doses of P4 (i.e. 20 mg per ewe) at exactly the same time as the introduction of males. This provokes an important delay in the post-introduction events: LH surge and subsequent ovulations are delayed from 24 to 72 h, depending on the experiments [5, 17, 56, 57]. This was also demonstrated in goats [58, 59]. The concomitant suppression of short-lifespan CL and of enlargement of the interval, introduction of male- LH preovulatory surge, led to the proposition that the existence of these short-lifespan CL is due to an insufficient follicle maturation before ovulation [57]. This hypothesis is reinforced by the fact that an early induction of premature ovulations using GnRH injections in P4 treated ewes, restores short-lifespan CL [11, 17]. The hypothesis of a longer duration of the follicular phase in females experiencing a normal lifespan CL duration

has also been proposed based on a difference in the timing of the LH surge after introduction of rams in a limited number of ewes [5, 17]. But very few experiments or observations have been done.

However, three groups of results do not favour this hypothesis. (a) In spite of a quite large number of experiments and measurements in untreated ewes, the association between the duration of the follicular phase and the duration of ram-induced CL was not demonstrated: ewes showing a long duration of the interval between the introduction of the males and ovulation were not those experiencing normal cycles (20.9 ± 11.2 vs. 14.2 ± 6.9 h, in 12 and 22 Barbarine ewes experiencing short vs. normal cycles, respectively [11]). (b) The injection of P4 (or progestagen treatment) performed some days (3–5) before introduction of rams had the same effect on suppression of short-lifespan CL, but did not delay the interval between male introduction and LH surge [5]. (c) A single injection of P4 in GnRH treated ewes without the ram effect, is able to restore CL of normal life span on the contrary to control ewes with no P4 treatment [30, 60]. Thus, the initial hypothesis of an enlargement of the duration of the follicular phase after P4 treatment is probably not adequate and suggests that other mechanisms are working at the ovarian and/or uterine levels.

More recently, experiments performed in Barbarine ewes to identify the sites of P4 action, the minimal efficient doses and duration of P4 treatments and the effects of P4 injection on uterine PGF synthesis and release and on oxytocin plasma concentrations [11] has provided interesting results on the doses of P4 and on the role of the uterus.

One single 2.5 mg injection of P4 intramuscularly (im) or in the uterine lumen (iu) at D0 did not modify the frequency of short cycles compared to control ewes (40, 57 vs. 71% in iu, im and control ewes, respectively) and did not restore normal luteal

function as 20 mg im did (1% of short cycles [11]). The efficiency of the minimal doses described previously (20 mg in one single injection) is due to the duration of the presence of P4 rather than to the P4 quantity: two subsequent intramuscular injections of 2.5 mg, at the introduction of rams and 6 h later, completely suppress short-lifespan CL compared to control ewes (0, 73%, respectively) and is as efficient as a single 20 mg im injection (0% [11]).

Measurement of PGF metabolite PGFM secretion and plasma oxytocin in ewes with cauterised follicles 48 h after ram-induced ovulation, receiving E2 injection 24 h after cauterisation, but treated or not with 20 mg P4 im at D0 (in comparison with control ewes C) revealed that P4 treatment (a) highly significantly impaired PGFM secretion from the uterus at D5: 21.9, 34.5 and 8.1 pg.mL⁻¹ of plasma and 3.6, 3.2 and 2.2 pulses in 14 h, in C, -P4 and +P4, respectively, (b) significantly reduced oxytocin secretion: 14.2 and 12.9 pg.mL⁻¹ of plasma in -P4 and +P4 ewes, respectively [11]. Thus, the classical P4 treatment dramatically acts upon the uterine secretion of PGF to reduce it and probably also reduces plasma oxytocin (which could be of ovarian origin). This reinforces the hypothesis of a local effect of P4 on the uterus and/or the ovary rather than a central effect to delay the LH surge.

However, these observations were done after exogenous injections of robust doses of P4 and it remains to demonstrate that natural progesterone of the early CL via counter-current mechanisms and/or general circulation, may be able to participate directly in the inhibition of PGF secretion and of oxytocin synthesis and liberation. This is suggested by the fact that more "physiological" doses of P4 (i.e. 2.5 mg in two injections) also provide the same results on duration of ram-induced cycles.

6. CONCLUSION

Taken together, these results allow building a working hypothesis to explain the reason(s) why short-lifespan CL are observed after introduction of rams and bucks (Fig. 5). The sequential mechanisms involved in the appearance of short-lifespan CL after introduction of rams during anoestrus could be the following:

(1) The follicles induced to ovulate are of poor quality because of the unsustained long-term gonadotropin activity during anoestrus. These follicles especially present a low granulosa cell quality compared to follicles developing during the breeding season.

(2) CL developed from these follicles have an abnormal development leading to an insufficient proportion of large luteal cells, and thus secrete lower quantities of progesterone conducting to lower concentrations in the blood of the ovarian vein and in the general circulation.

(3) The counter-current mechanisms acting locally amplifies the difference in P4 concentration in the uterine and ovarian arteries.

(4) Due to these insufficient P4 concentrations reaching the ovary and the uterus, the chain responsible for oxytocin and PGF liberations is more sensitive to estrogens.

(5) The plasma progesterone concentration of general circulation is insufficient to block the gonadotropin activity on days 3–5 after the LH surge.

(6) The new wave of follicles initiated on days 3–4 of the first male-induced cycle continues to grow and to secrete more oestrogens. The corpus luteum initiates its responsiveness to prostaglandins.

(7) These estrogens stimulate prostaglandin secretion by the uterus and oxytocin liberation from the CL, thus causing early luteolysis.

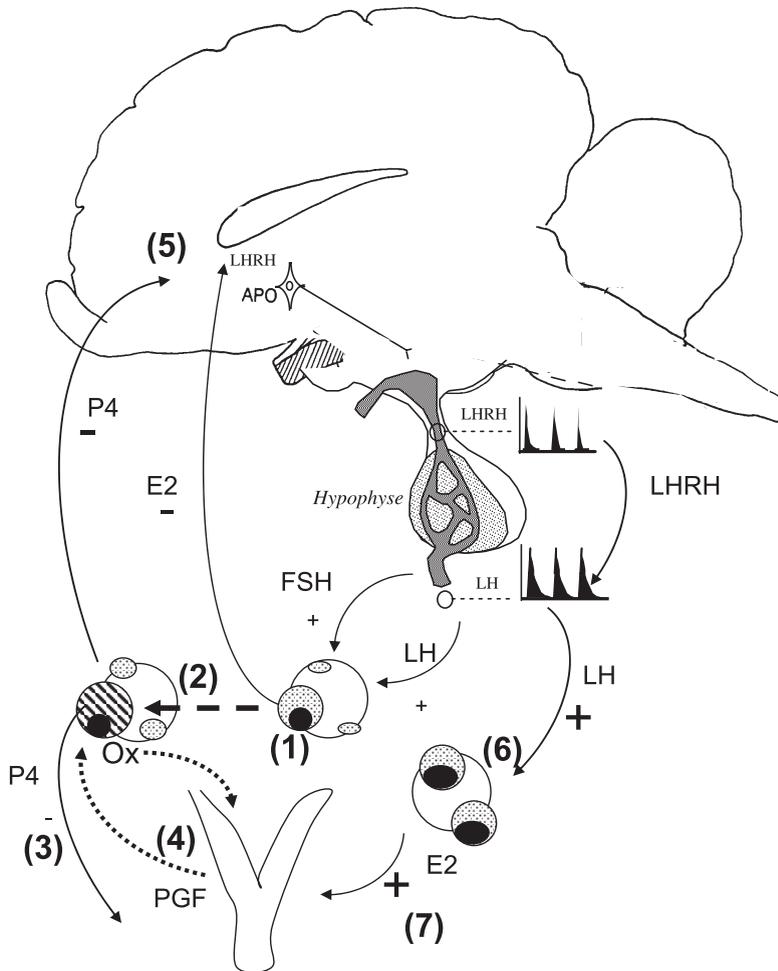


Figure 5. Working hypothesis for a global explanation of the underlying mechanisms controlling the lifespan of male-induced corpora lutea in sheep and goats: the 7 sequential events leading from low quality follicles of anestrus to early luteolysis at day 5 after introduction of males. (1) Low quality of granulosa cells in follicles during anestrus at D0, (2) low proportion of large/small luteal cells in induced CL at D5: low P4 concentration in the ovarian vein, (3) amplification of low P4 concentration in uterine and ovarian arteries by counter-current mechanisms, (4) high sensitivity of oxytocin and PGF chain to E2, (5) systemic plasma P4 insufficient to centrally block LH pulsatility, (6) high LH pulsatility stimulates the growth of the new follicular wave which started at D0, (7) E2 stimulates PGF and oxytocin which produce early luteolysis.

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