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Clinical Use of Progesterone and Its Relation to Oxidative Stress in Ruminants

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Abstract

Studies to determine the physiological effects and functions of progesterone started in the twentieth century. Progesterone is a steroid-structured hormone with 21 carbon atoms originating from cholesterol. The corpus luteum, formed after ovulation in ruminants, secretes progesterone, which plays a role in the continuity of the pregnancy. Progestagens can be used for estrus synchronization in cows and heifers. Similarly, they are used for estrus synchronization during the breeding season or outside the breeding season by taking advantage of the negative feedback effect of progesterone in small ruminants. It is applied for the treatment of embryonic deaths due to luteal insufficiency in cows with high milk yield. In anovulatory anestrus, exogenous progesterone applications can be very useful. Progesterone treatment contributes to the resolution of the anestrus by rearranging hypothalamic functions in cattle with follicular cysts. The oxidative stress index in the luteal phase, when progesterone is high in ruminants, is higher than in the follicular phase. In the critical period of pregnancy, a high index of oxidative stress-induced progesterone causes embryonic death. Factors that cause stress in high milk-yielding cows can affect the amount of progesterone synthesis by inhibiting luteal cell function due to excessive free radical production.

Keywords: progesterone, ruminants, oxidative stress, estrus synchronization, embryonic death

1. Introduction

Many methods have been developed for controlling reproduction in farm animals. Among these methods, synchronization protocols to increase reproductive efficiency have an important

place. The desired level of pregnancy rates is often not obtained because of the difficulty of following the estrus cycle in each animal on large farms. For this reason, estrus synchronization use in large farms becomes inevitable. Thus, progesterone-assisted estrus synchronizations are implemented intensively in farm animals. In addition, progesterone can also be used for the treatment of reproductive problems such as anestrus, cystic ovarian disease, and luteal insufficiency [1, 2].

This section provides information on the structure of progesterone, its role in physiological events in ruminants, its use in clinical practice, and its relation to oxidative stress.

2. The structure and biochemical synthesis of progesterone

Steroid hormones are lipophilic organic compounds with a low-molecular weight derived from cholesterol (**Figure 1**). Steroid hormones are synthesized in the mitochondria and smooth endoplasmic reticulum in gonads, such as the ovary and testis, and then released into the bloodstream. The steroid hormones are broadly classified into three categories based on their physiological functions: glucocorticoids, mineralocorticoids, and sex steroids [3]. Cholesterol is an obligate intermediate used for steroid hormone synthesis by the adrenal gland, ovary, testis, and placenta that can be obtained from three principal sources: de novo synthesis of cholesterol from acetate, cholesterol from circulating high-density lipoproteins, and cholesterol
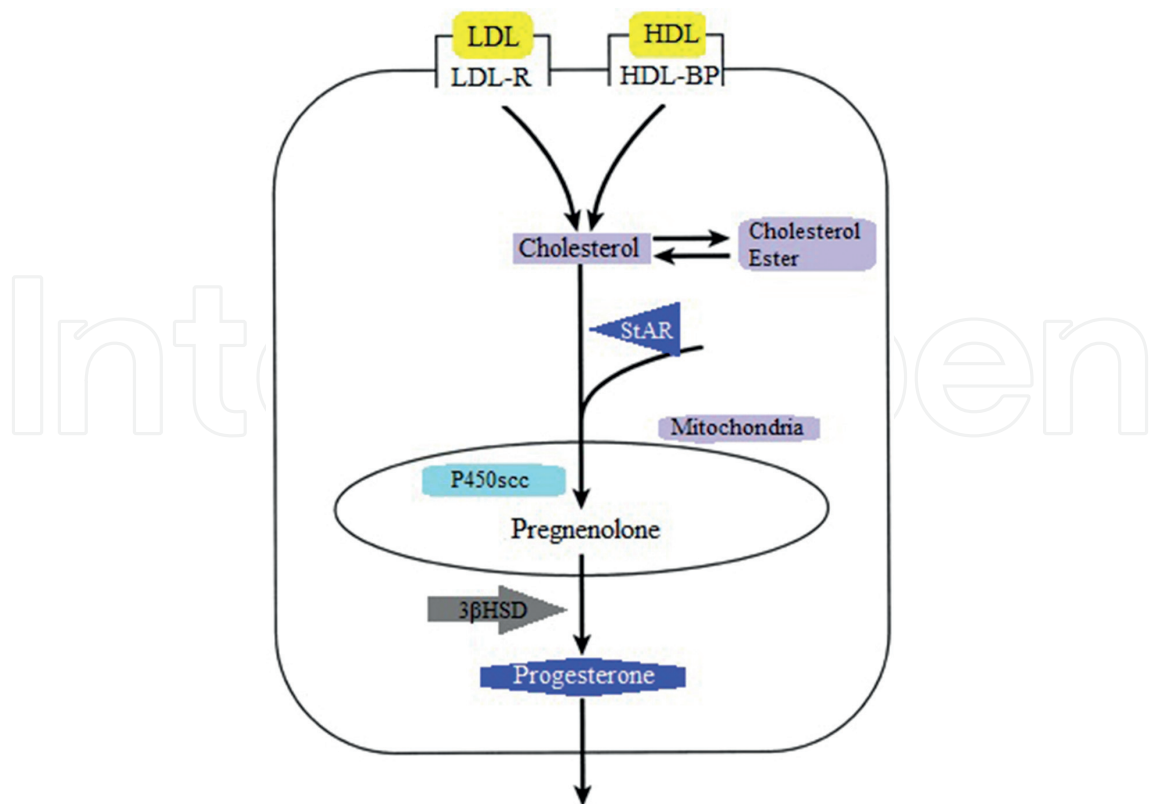

Figure 1. Sources of cholesterol for progesterone biosynthesis.

stored in plasma membranes. The major source of cholesterol for luteal cells in ruminants is circulating high-density lipoproteins [3, 4].

Cholesterol is primarily a hydrophobic molecule, and this makes it difficult for cholesterol to diffuse freely through hydrophilic environments such as the cytoplasm. In addition, cholesterol has a hydroxyl group at the 3 position that produces a discrete hydrophilic region making it difficult for the "flip-flop" of cholesterol between membrane surfaces within the lipid bilayer of cellular membranes. Therefore, movement of cholesterol in the circulatory system (lipoproteins) or within the cell is dependent upon transport proteins. Addition of another hydroxyl group at the other end of the cholesterol molecule alleviates the need for transport proteins [5].

Progesterone is a steroid hormone primarily secreted by the corpus luteum and placenta. Production of progesterone in luteal cells is dependent more on transport of cholesterol within the cell than to changes in the activity of steroidogenic enzymes. The P450 cholesterol side chain cleavage enzyme (P450scc) is located on the inner mitochondrial membrane and catalyzes the conversion of cholesterol to pregnenolone [6]. This enzyme catalyzes three oxidation steps: hydroxylations at the 20 and 22 positions and then cleavage between these two carbons. Pregnenolone has two hydrophilic residues that increase mobility through cellular membranes. Pregnenolone diffuses from the mitochondria to the smooth endoplasmic reticulum where it is converted to progesterone by the enzyme 3-β hydroxysteroid dehydrogenase (3β-HSD). This final reaction produces a double bond between the 4 and 5 carbon of the molecule and is the basis for the abbreviation of pregnenolone as progesterone (**Figures 1** and **2**). Progesterone then diffuses from the luteal cells to the bloodstream for transport to target tissues [7, 8].

Progesterone is synthesized from pregnenolone in the corpus luteum, the placenta during pregnancy, and the adrenals as a step in androgen and mineralocorticoid synthesis. Its actions are primarily mediated by an intracellular progesterone receptor, whose numbers increase in the presence of estrogen [9].

The products of hormone synthesis vary with the menstrual cycle; estradiol is the main product during follicular maturation, whereas progesterone is the main product in the luteal phase following ovulation. Progesterone is secreted by ovarian follicular cells prior to ovulation; it is also secreted in larger amounts by the corpus luteum, which forms from follicular granulosa cells following ovulation. The corpus luteum will grow for 10–12 days and then regress if fertilization does not occur; if fertilization does occur, the corpus luteum is maintained for the first 2–3 months of pregnancy. Progesterone plays several important actions in the normal female reproductive cycle. Progesterone prepares the uterus for pregnancy by shifting the endometrium from proliferation to secretion. Withdrawal of progesterone in the absence of pregnancy leads to organized shedding (menstruation) and it helps to mediate sexual response in the brain. After fertilization, progesterone organizes the vasculature of the endometrium to prepare for implantation. It promotes enzymatic digestion of the zona pellucida to allow the oocyte to implant into the uterine wall. In addition, it inhibits contractions of the uterine myometrium (smooth muscle layer) and counteracts the effects of oxytocin on contractility. Progesterone promotes lobuloalveolar growth in the breasts to prepare for lactation, but suppresses premature milk protein synthesis prior to parturition. Some of the effects of progesterone may be related to its ability to antagonize estrogen by decreasing expression of estrogen receptors, e.g. the ability of progesterone to inhibit estrogen-mediated endometrial proliferation. It also has a potent effect as a mineralocorticoid
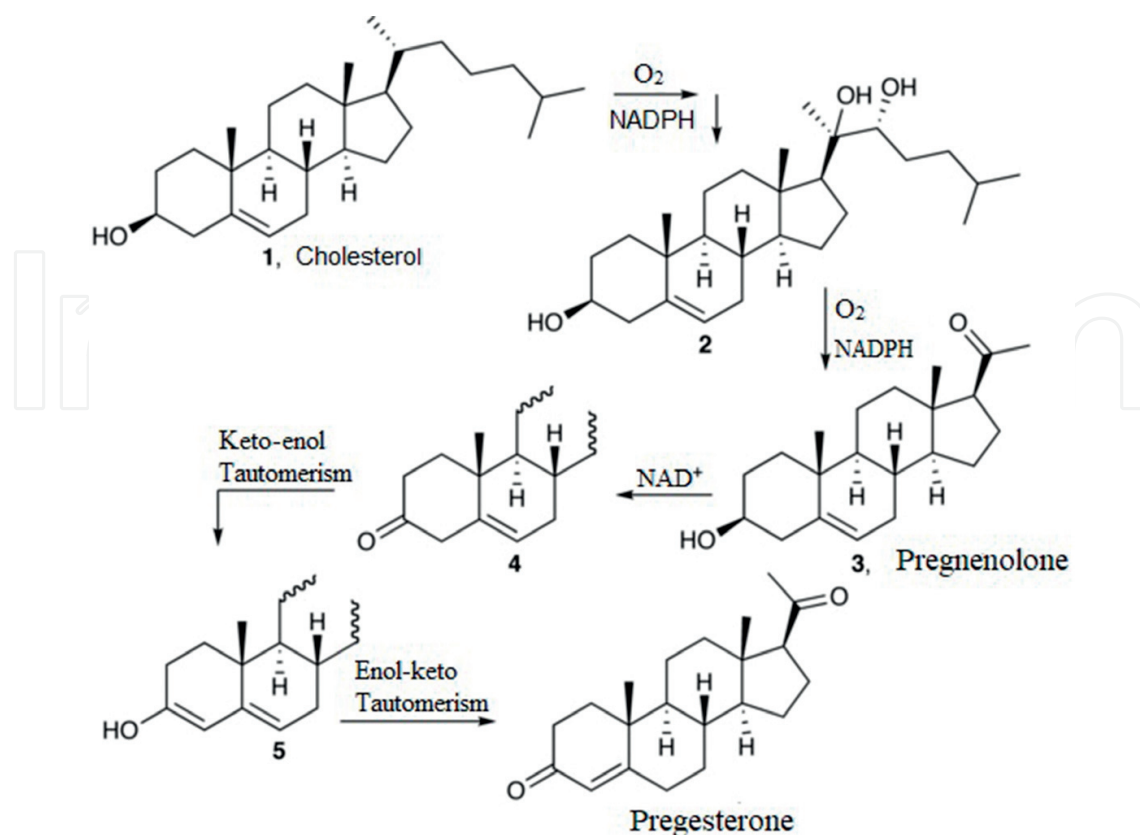
Figure 2. Pathway synthesis of progesterone from cholesterol.

receptor antagonist that reduces sodium retention when present and increases sodium retention when progesterone is withdrawn [8, 9].

The role of progesterone in males is less clear, but it is believed to play a role in activating sperm in the female reproductive tract. It has also been implicated as a modulator of male sexual response and behavior [7].

3. Progesterone synthesis and secretion during the sexual cycle and pregnancy in ruminants

The corpus luteum formed after ovulation in ruminants is a functional structure formed by membrane granulosa in the wall of Graaf follicles. Hypertrophy and luteinization of the theca interna cells play a role in the continuity of the pregnancy, secrete progesterone for a temporary period, and have endocrine activity. In particular, there is a close correlation between corpus luteum development and blood progesterone levels [10, 11].

Progesterone levels in the proestrus and estrus stages of the estrous cycle in cattle are very low. Newly developing corpus luteum cannot produce sufficient progesterone after ovulation (in the period of metaestrus). Therefore, a significant increase in blood progesterone levels cannot be detected. In the diestrus period, the corpus luteum acquires a functional structure and

synthesizes >2 ng/mL progesterone. The progesterone level is highest during days 8–10 of the estrous cycle in cows. If pregnancy does not occur, prostaglandin F2 alpha (PGF2α), which is synthesized in the uterus, passes to the ovarian arteries from the uterine vein inducing corpus luteum degeneration. As a result, the blood progesterone level decreases rapidly to less than 0.5 ng/mL [11]. If pregnancy occurs, blood progesterone levels in the cows can be 6–8 ng/mL on day 21 of pregnancy [12, 13].

In sheep, the corpus luteum following ovulation begins to secrete progesterone after the third day of the estrous cycle. Because the corpus luteum formation is rapid, the blood progesterone level rises rapidly and reaches measurable levels [13]. The progesterone level is the highest (4 ng/mL) between days 9 and 13 of the cycle. If there is no pregnancy, the corpus luteum starts to shrink and the amount of PGF2α in the blood starts to increase on the 12th day of the cycle. On the 14th day of the cycle, the progesterone level is 10 ng/mL but is <0.2 ng/mL on the 16th day of the cycle [14]. Pregnancy in sheep is maintained by the corpus luteum until the 50th day and later by placenta-derived progesterone. Progesterone levels are highest between 60 and 130 days of gestation. As long as pregnancy continues, the concentration of progesterone never falls below 1 ng/mL [12].

The corpus luteum forms after ovulation and progesterone levels begin to increase in goats. Maximum levels of progesterone (6–10 ng/mL) are found in the middle of the cycle. This level starts to decrease on the 15th day of the cycle and descends to basal levels on the 19th day [15, 16].

4. Clinical use of progesterone in ruminants

4.1. Use of progesterone for estrus synchronization in cattle

Progestagens (ear implants and intravaginal devices [progesterone-releasing intravaginal device (PRID) and controlled internal drug release (CIDR)]) can be administered for 5–20 days for the purpose of estrus synchronization in cows and heifers without uterine infection. Progesterone applications can stimulate puberty in some heifers and initiate normal cyclic activities in anestrus cows. In addition, following the first ovulation after progesterone treatment, normal length sexual activities may continue [2, 17–24].

After the end of progesterone application, synchronized estrus is observed within 3 days [2, 17]. However, when progesterone is used for a prolonged period, the fertility rates decrease due to the persistence of the follicle. In addition, when melengestrol acetate (MGA) is used for estrus synchronization, subfertile estrus occurs initially because of the persistent follicles and artificial insemination is not recommended [24]. Long-term use negatively affects the intrauterine environment and spermatozoon transport. For this reason, estrus synchronization with progesterone for 5–9 days is more suitable for increasing fertility [25, 26].

According to studies conducted in recent years, the pregnancy rate may be 10–15% higher in short-term progesterone use protocols than long-term protocols. However, other researchers argue that there is no difference between pregnancy rates [2, 26–28].

4.1.1. Estrus synchronization with progestagens + prostaglandins

Progesterone administration allows the synchronization of estrus in ruminants in different stages of the cycle. PGF2α may be injected on the last day of progesterone administration (5–10 days) or 1–2 days before the end of progesterone. After the application of progesterone, estrus occurs and artificial insemination is done [21, 29–31]. Some researchers obtained 54% pregnancy rates in the first estrus in dairy cows (n = 102) given progesterone for 7 days (CIDR) with PGF2α administered on day 6. In addition, 49% pregnancy rates were obtained when a similar protocol was applied to non-cyclic and cyclic heifers [29]. In a similar study, the pregnancy rate was 47% in beef heifers (n = 247) and 59% in dairy heifers (n = 129) [32].

In some studies, artificial insemination was performed according to PGF2α injection and estrus follow-up (4–6 days) 17–19 days after 14 days of MGA application [25, 28]. In this protocol, the purpose of PGF2α injection is to lyse the corpus luteum that can be formed at the end of 14 days of MGA application [33].

4.1.2. Ovulation synchronization protocols + progesterone

Progesterone is administered as an ear implant or an intravaginal device between days 0 and 7 in order for the Ovsynch (GnRH/PGF2α/GnRH) protocol to be successful and the pregnancy rate to increase [27]. In a study performed on heifers (n = 383), a 47% pregnancy rate was obtained [34]. In another study, progesterone administration in Ovsynch did not increase the pregnancy rate in cows with corpus luteum [35]. Others reported that premature estrus was not observed due to progesterone used between 0 and 7 days for ovulation synchronization protocols and full synchronization was achieved [36, 37].

Progesterone administration is also performed in the Cosynch protocol. On day 0, the progesterone device is inserted and gonadotropin-releasing hormone (GnRH) is injected. Progesterone devices are removed during PGF2α injection (day 7). Fixed-time artificial insemination is performed in 48, 56, or 60 hours after GnRH is injected [38–40]. Such protocols may be applied for 12–14 days with progesterone [41, 42].

4.1.3. Five-day Cosynch + progesterone protocols in the heifer

Ovulation synchronization methods have a high pregnancy rate, especially in cows, although this rate is lower in heifers [2]. Synchronization protocols have been developed to stimulate ovulation, which do not require heat detection. Progesterone administration occurs for 5 days. During progesterone removal, PGF2α is administered. GnRH is administered 72 hours later and fixed-time artificial insemination is performed [19, 21, 22, 26, 27]. A 10.5% higher pregnancy rate can be obtained with this protocol [43]. The pregnancy rate improves between 45.9 and 54.2% in the 5-day Cosynch + PRID protocol and fixed-time artificial insemination with sexed semen in cyclic heifers [26].

It was determined that vaginitis and mucopurulent discharge were observed after use of intravaginal progesterone devices in heifers. The incidence of vaginitis in the heifers may be around 70% or more [22, 23, 26, 44].

4.2. Use of progesterone in estrus synchronization in small ruminants

In small ruminants, progesterone suppresses GnRH and luteinizing hormone (LH) release by negative feedback [45]. There may be up to 30-fold increases in LH concentration with a decrease in the plasma level of progesterone. In addition, the dominant follicular LH receptors are sensitive and thus ovulation occurs. As a general principle, these effects of progesterone can be used in estrus synchronization protocols [46–48]. Medroxyprogesterone acetate (MAP), fluorogestone acetate (intravaginal sponge), melengestrol acetate, levonorgestrel, and intravaginal progesterone-releasing devices (CIDR and DICO) are used for estrus synchronization in sheep and goats [48–55].

In sheep, progestagens are used effectively in the control and synchronization of estrus. Equine chorionic gonadotropin (eCG) injection is performed in addition to progestagen administration for 12–14 days in order to obtain high estrus rates and ovulation, especially during anestrus. Nevertheless, these types of manipulations may also vary depending on nutrition, body condition score, lactation, age, temperature, light, and breed [56–60].

In sheep synchronized with MAP during the breeding season, follicle size and LH pulse increase after ram introduction [61, 62]. Intravaginal CIDR or chronolone intravaginal sponge and 500 IU eCG did not affect the LH wave and peak in Tuj sheep outside the breeding season [63].

During the breeding season, estrus start and end times were different in sheep treated with MAP or CIDR for 12 days [64]. High estrus rates and similar fertility rates were determined in sheep that applied short-term (6 days) CIDR-G or fluorogestone acetate (FGA, intravaginal sponge) [52].

Short-term (5 day) FGA and eCG administration produce higher estrus rate than long-term FGA and eCG treatments in sheep during the breeding season [50]. Injections of eCG at different doses (300, 400, and 500 IU) to Awassi sheep in estrus synchronization with progesterone similarly affect fertility parameters [65]. The testosterone antibody, β-carotene, and vitamin E administration did not change the estrus and pregnancy rates 7 days before intravaginal 40 mg FGA administration in Tuj ewes during the non-breeding season [66].

Vaginal sponges with progesterone for 11–14 days were applied to Pirlak ewes during the non-breeding season and 92–100% entered estrus. The pregnancy rate was 37.7–44%. In the study, the fertility parameters did not change for 11 or 14 day vaginal sponge application. Progesterone administration at different day lengths may be effective for the onset of estrus [48].

Short or long-term progesterone treatment for estrus synchronization in goats can be done depending on the breeding season. At the end of progesterone treatment, the protocol is terminated by eCG administration [54, 58, 67–69].

Intravaginal levonorgestrel for 10 days and intramuscular PGF2α administration were used in goats causing high estrus rates (95%) during the breeding season [70]. In a study conducted on Abaza goats during the breeding season, the first estrus pregnancy rate was 73.3% and the pregnancy rate was 93.3% after estrus synchronization using CIDR for 11 days. In addition, the same pregnancy rate was achieved in goats that did not receive any intervention in the study. However, progesterone treatment and estrus synchronization contribute positively to reproductive parameters and increase twinning rates [55].

In sheep and goats, short-term progesterone-impregnated sponge therapy changed the microbial flora of the vagina and formed vaginitis. Staphylococcus is usually detected in these cases of vaginitis [13, 71, 72].

4.3. Use of progesterone to prevent embryonic death

Progesterone is the most important hormone for the continuity of pregnancy. Progesterone affects oocyte quality by affecting LH wave frequency and persistent follicle formation. Again, progesterone plays a vital role in influencing the endometrium and creating the appropriate environment for the survival of the embryo [73].

The rate of embryonic deaths in cows may range from 7 to 16% in the first week, 6–44% in the second week, 3–33% in the third week, and 19–42% after the fourth week. Embryonic deaths are caused by genetic and environmental factors. Most of the embryonic deaths, especially due to hormone insufficiency, are the result of luteal insufficiency. For this reason, progesterone or its analogues are applied to reduce embryonic losses before or after artificial insemination [74–76].

In ovulation synchronization protocols, such as Ovsynch and Cosynch, progesterone administration for 7 days between the first GnRH and PGF2α injections reduces the embryonic loss rate due to luteal phase deficiency [13]. Gestational losses were 3.6–6.8% after the 5-day Cosynch + progesterone protocol [26].

Progesterone-assisted estrus synchronization protocols can prevent early embryonic losses and increase the pregnancy rate. In many studies, there are reports that progesterone-assisted applications increase the pregnancy rate and decrease the embryonic loss rate. However, some researchers disagree [2, 35, 77, 78].

One of the most important causes of embryonic deaths in high milk-yielding cows is inadequate embryo development prior to implantation due to insufficient progesterone concentrations. Progesterone application performed between 3, 5, and 10 days after artificial insemination caused a statistically significant increase after CIDR administration compared with the control group. The pregnancy rate was 35% (22/63) in the control group and 48% (32/67) in the progesterone-treated group. The effect of exogenous progesterone is important for the development of pregnancy, especially in cows with first and second lactation [79].

Some researchers report an overall increase of 5% in pregnancy rates following progesterone administration. Progesterone administration time is critical to success. Progesterone treatment for 6 days after artificial insemination can increase pregnancy rates (10% more) [80].

Cows in the CIDR groups, which were administered progesterone for 6 or 12 days after the 5th and 7th days following artificial insemination, had higher pregnancy rates than the control group [81]. Intravaginal progesterone administration for 7 days starting 14 days after artificial insemination can reduce both embryonic deaths and fetal losses [77]. Similarly, post-mating treatment of FGA (intravaginal sponge) in sheep has been reported to reduce embryonic mortality [82].

4.4. Use of progesterone in anestrus or anovulatory anestrus

Anestrus is a situation in which a sign of heat cannot be detected in beef or dairy herds. Many forms of functional infertility result in anestrus in cows. This leads to serious economic losses for large farms [73].

Four different types of anovulatory anestrus may be encountered in the postpartum period. The first (type I) is characterized by follicle development remaining "emergent" (~ 4 mm) and not progressing to the "deviation" (~ 9 mm) phase. This type of anestrus is classically referred to as "inactive ovary." In type II, the "deviation" phase is passed, and after the "growth" phase, the follicle undergoes atresia. In type III, the follicle develops to the preovulatory stage but does not ovulate, thus becoming permanent follicles or follicular/luteal cysts. In type IV, the follicles develop and ovulate and the corpus luteum is formed, but the corpora lutea cannot regress and become permanent [13, 83].

In anovulatory anestrus, exogenous progesterone applications can be very useful [84]. The use of intravaginal progesterone devices, such as PRID or CIDR, may induce the restart of cyclic activity in the ovary [13]. Especially at the end of this application, the use of PGF2α and analogues may increase the pregnancy rate [73]. At the end of 10 days of progesterone therapy, injection of eCG, estradiol, or PGF2α is beneficial [83]. In this context, successful results were obtained after 9 days of PRID and intramuscular cloprostenol injection 1 day before PRID removal. Higher pregnancy rates can be achieved by adding progesterone to ovulation synchronization protocols in acyclic cows [13, 85].

4.5. Use of progesterone in cystic ovarian disease

Cystic ovarian follicles are non-ovulated preovulatory follicles that maintain long-lasting persistence without any luteal structure on the ovary. With progesterone administration, the number of LH pulses, and thus the LH level, is reduced and maintained at a luteal phase level throughout the cycle [73].

PRID or CIDR can be administered intravaginally for 7–14 days in cows with cystic ovarian disease [86]. In addition, progesterone is frequently used in the treatment of follicular cysts that cannot be mitigated with GnRH or human chorionic gonadotropin (hCG) injections. Progesterone therapy in cows with follicular cysts restarts hypothalamic functions and contributes to the resolution of the problem [83, 87].

Combination of progesterone administration for 9 days with GnRH and PGF2α may improve outcomes in cows with cystic ovarian disease. GnRH is injected and a progesterone-releasing device is applied intravaginally for 9 days. On day 7, PGF2α is administered intramuscularly, and 2 days later, the vaginal progesterone-releasing device is removed. Artificial insemination is done when the cows are in heat [88].

4.6. Use of progesterone to induction of lactation

The induction of lactation is a procedure that is applied to infertile heifers and non-lactating cows. The main purpose is to generate profit by initiating milk production. In particular, the combination of progesterone and estradiol in this type of cattle helps to develop the lobule alveolar system. Lactation can be successfully induced in 60% of cows treated with a combination of estrogen and progesterone for 7 or 10 days [89, 90].

When 50 mg progesterone and 20 mg 17β-estradiol are injected subcutaneously twice a day for 7 days in repeat breeders or aborted heifers, milk synthesis starts 10–21 days after the treatment [91]. In another study, lactation started 11–21 days after the first 17β-estradiol and

progesterone injection. The highest milk yield was reached 30–35 days after the start of lactation [92].

Lactation can be induced in non-pregnant ewes using progesterone and estrogen treatment. Progesterone and 240 mg estradiol benzoate injection once every 3 days for 60 days increased udder size. At the same time, the development of the udder is stimulated daily by injecting 10 mg dexamethasone trimethylacetate or injecting 5 mg estradiol benzoate and 12.5 mg progesterone for 6 days. After this protocol, milk synthesis starts from the udder with physiological size [93].

5. Relationship between progesterone and oxidative stress in ruminants

Oxygen is necessary for metabolism in living organism, but oxygen can be damaging to the living organism when it generates reactive oxygen species [94]. Thus, living organism face an oxygen paradox. During vital biochemical reactions in living organisms, intermediate metabolic products called reactive oxygen species (ROS) are generated that cause oxidative damage in many tissues by reducing oxygen. Oxygen is a potentially toxic molecule that is necessary for aerobic organisms to survive. Oxygen species are called "oxidants" or "free radicals" because of the oxidative destruction they provoke. Free radicals occur in all living organisms that metabolize molecular oxygen [95]. Free radicals carry a single number of unshared electrons in their outer orbitals [96]. They are very short-lived reagents, which disrupt the structure of other electrons in the environment of highly energetic electrons. Therefore, free radicals are dangerous to the organism [97]. Free radicals can occur as a by-product in all parts of aerobic cells, during metabolism, or in pathological conditions and they can cause various changes in the cells. As a result, serious cell, tissue, and/or organ damage can occur [98].

Free radicals are highly reactive molecules. Electrons interact with other molecules in the cell generating oxidative damage. They also damage many biological materials such as proteins, lipids, DNA, and nucleotide coenzymes [99]. There are many defensive mechanisms in place to prevent the formation of ROS and damage to the organism. These mechanisms are generally referred to as "antioxidant defense systems" or "antioxidants" [100]. Antioxidants control the metabolism and free radical levels that occur in normal metabolic or pathological conditions and prevent or repair damage that may be caused by these radicals [101–103].

In the organism, the formation rate of free radicals and the rate of their removal are in balance. This condition, called "oxidative balance," prevents the organism from being affected by free radicals. An imbalance between free radical formation and the antioxidant defense mechanism in favor of free radicals is termed "oxidative stress," which in turn leads to tissue damage [104]. Antioxidants are known to have protective effects on lipids, proteins, nucleic acids, and other macromolecules. Antioxidants affect ROS in four ways: scavenger, quencher, restorative, and chain breaker [103]. All biomolecules are exposed to free radicals. However, lipids are most easily affected [105]. The membranes surrounding the cells and organelles contain a large amount of unsaturated fatty acids. The oxygen molecule has a high affinity for lipids in these unsaturated fatty acids in the cell membrane. The binding of oxygen to the double bonds in the unsaturated fatty acids found in tissues is the result of lipid peroxidation. Lipid peroxidation is

the reaction of unsaturated fatty acids in the structure of phospholipids, glycolipids, glycerides, and steroids in the membrane by free oxygen radicals to various products such as peroxides, alcohols, aldehydes, hydroxy fatty acids, ethane, and pentane [106]. The major intracellular antioxidants found in organisms include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione S transferase, glucose 6 phosphate dehydrogenase, and paraoxonase enzymes. Vitamin E, ferritin, transferrin, haptoglobin, uric acid, ceruloplasmin, glutathione, albumin, bilirubin, and β-carotene are antioxidant defenses in the extracellular environment [107].

Every month, the oocyte grows and begins to develop in the ovary. However, meiosis-I continues only in the dominant oocyte. This process is inhibited by antioxidants causing an increase in ROS. Thus, antioxidants promote meiosis-II [108]. The ROS produced by the preovulatory follicle is considered an important inducer of ovulation [109]. Thus, ROS do not always cause adverse effects [110]. Recently, ROS have been reported to regulate cell function by controlling the production or activation of substances with biological activity [111]. Oxygen deprivation stimulates follicular angiogenesis, which is important for the growth and development of the follicle in the ovary. While follicular ROS increases apoptosis, glutathione (GSH) and follicle stimulating hormone (FSH) act as a balance in the growing follicle. FSH increases in response to estrogen, which triggers catalase production in the dominant follicle, thereby preventing apoptosis [108].

After ovulation, the corpus luteum synthesizes progesterone. Likewise, ROS, which has a key role in reproduction, is also produced in the corpus luteum [108, 112], and antioxidants play an important role in corpus luteum physiology during the cycle [112–114]. When pregnancy does not occur, the corpus luteum shrinks. During pregnancy, progesterone is continuously synthesized [112].

In mammalian species, the main function of the corpus luteum (CL) is the synthesis of progesterone, which is required for the establishment of a uterine environment suitable for the development of the peri-implantation conceptus and the successful progression and maintenance of pregnancy. Progesterone acts on the endometrium to regulate the synthesis of growth factors, cytokines, transport and adhesion proteins, protease inhibitors, hormones, and enzymes, which are primary regulators of conceptus implantation, survival, and development. Thus, compromised CL progesterone production is a potential risk factor for prenatal development and pregnancy outcomes [114].

There should be a rapid decline in the progesterone level for good follicular growth. During the middle luteal phase, superoxide dismutase 1 (SOD1, cofactor Cu or Zn) increases in the CL and decreases during regression [108]. PGF2α is defined as luteolysin because it increases in the CL during regression [115] and inhibits progesterone production by luteal cells. The inhibitory effect of PGF2α on progesterone production by the CL is due in part to increased ROS. In addition, progesterone levels decrease due to the destructive effects of oxidative stressors on luteal cell steroidogenesis [116–118]. ROS can also inhibit progesterone synthesis through inhibition of cytochrome P450, mitochondrial intracellular transport of cholesterol, and degradation of LH receptors [112].

Although the mechanisms of CL rescue from cell death and maintenance of progesterone production are very complex and vary among mammalian species, substantial evidence

suggests ROS are key factors in determining the CL lifespan and antioxidants play significant roles in CL physiology during the estrous/menstrual cycle. Luteal ROS production and propagation depend upon several regulating factors, including luteal antioxidants, steroid hormones and cytokines, and their crosstalk. However, it is unknown which of these factors have the greatest contribution to CL function. In addition, the sequence of events leading to the functional and structural luteal regression at the end of the estrous/menstrual cycle is still not clear. The scarce in-vivo reports studying the CL of rats and sheep have shown the importance of antioxidant enzymes in the control of CL function during the peri-implantation period. As a luteal phase defect can impact fertility by preventing implantation and early conceptus development in livestock and humans, this review attempts to address the importance of ROS-scavenging antioxidant enzymes in the control of mammalian CL function and integrity [119].

The production of ATP is derived from the mitochondrial respiratory chain oxidative phosphorylation, which is the main source of oxygen-free radicals and non-radical ROS. The ROS include superoxide anion ($-O_2-$), hydroxyl radical ($-OH$), nitric oxide (NO), hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO-$). ROS are also produced via enzymatic pathways, including the activity of membrane-bound NADH and NADPH oxidases, the activity of xanthine oxidase, the metabolism of arachidonic acid by lipoxygenases and cyclooxygenases (COX), and the mitochondrial cytochrome P450 [119].

The cause of the ROS concentration increase in the regression phase may be a decrease in the SOD1 concentration. A decrease in SOD1 concentration may be due to an increase in PGF2α or macrophages, or a decrease in blood flow to the ovaries [108]. In the CL, luteal cells and phagocytic leukocytes stimulate the production of a superoxide anion. With decreased blood flow to the ovaries, ROS production increases and causes tissue damage. Concentrations of superoxide dismutase 2 (SOD2, cofactor Mn) in the CL increase to clear the ROS produced in the mitochondria during regression. Along with the complete lysis of the CL, the regressor decreases significantly in the SOD2 cells [110]. The SOD1 enzyme is closely related to progesterone production. SOD2 protects luteal cells from oxidative stress induced inflammation [108].

Aerobic cells are equipped with antioxidant enzymes that control ROS production and prevent their propagation to toxic ROS. The conversion of $-O_2-$ to H_2O_2 by superoxide dismutase (SOD) is the first enzymatic antioxidative pathway. Two different SOD enzymes were identified: copper-zinc-containing SOD (SOD1) is predominantly localized in the cytosol and can be found in mitochondria, and manganese-containing SOD (SOD2) localizes in the mitochondrial matrix. Glutathione peroxidase (GPX) is a group of selenium-containing enzymes that belong to the first antioxidant mechanism preventing the propagation of highly reactive ROS by catalyzing the conversion of H_2O_2 to H_2O and O_2. NADH and NADPH are key elements in the control of ROS production and maintenance of the cellular redox state. The mitochondrial NADP+-dependent isocitrate dehydrogenase generates NADPH via oxidative decarboxylation of isocitrate [119].

Like any aerobic cells, those of the CL produce ATP through the respiration of O_2 with the consequence of luteal ROS production. The rate-limiting step in steroidogenesis in all steroidogenic organs, including the CL, is the transfer of cholesterol from the outer to the inner mitochondrial membrane where it is converted into pregnenolone by the enzyme cytochrome

P450scc. Luteal ROS are generated via enzymatic pathways of the mitochondrial cytochrome P450. In the CL, macrophages and luteal cells produce ROS where they can affect progesterone production. Indeed, there is substantial evidence to indicate that ROS regulate steroid hormone biosynthesis in the CL. The induction of ovarian SOD by LH, which in turn could lead to the production of H_2O_2, suggests that this action is involved in the LH stimulation of progesterone secretion in the CL. Thus, ROS can function beneficially to control the production of progesterone by luteal cells over the course of the reproductive cycle and inhibit progesterone synthesis at the end of the cycle. The O_2— radical is reported to be involved in the mechanism by which LH stimulates progesterone secretion [94, 119].

Oxidative stress may affect various physiological functions, such as folliculogenesis and steroidogenesis, in the female reproductive system. High ROS levels may also cause adverse pregnancy outcomes or embryonic/fetal losses [120–122] and are implicated in the etiopathogenesis of cystic ovarian disease [123]. ROS and the oxidative stress index in cows may be higher in the luteal phase than follicular phase, especially when progesterone is high. Again, in the luteal phase, the antioxidant status can be high or low. Imbalances, especially in oxidant and antioxidant capacity, can cause cystic ovarian disease by disturbing physiological events necessary for ovulation [124].

High free radical and low progesterone concentrations were detected in cows identified as repeat breeders. Infertility problems such as repeat breeder are encountered due to a low progesterone level in the critical period of pregnancy and the short life of the CL. All kinds of stress factors cause excessive radical production in high milk-yielding cows. This may be a determining factor for the amount of progesterone synthesized by inhibiting luteal cell function [125, 126]. In another study, the complex arrangement of antioxidant enzymes and compounds in the bovine CL was discussed. In particular, the correlation between antioxidant capacity and progesterone concentration was determined in the luteal phase of the estrous cycle. Findings show that antioxidative mechanisms are activated to cope with oxidative stress, which has a negative effect on steroid hormone synthesis [127]. In support of the previous study, it has been suggested that an antioxidant substance (astaxanthin) promotes progesterone synthesis in bovine luteal cell culture. However, attention has been drawn to the fact that the use of antioxidant material at low doses is beneficial [128].

Anestrus is a problem of infertility in which cyclic activity is absent and therefore estrogen-progesterone hormones are not expressed. Non-cyclic Murrah buffaloes were found to have low concentrations of antioxidants such as β-carotene and vitamin E [129]. Oxidative stress biomarkers change in cow milk during the anovulatory and ovulatory estrous cycles. In particular, the SOD levels in cyclic cows are significantly higher than levels in the anovulatory cycle, while the concentrations of lipoperoxides, GSH-Px, and GSH are lower. A low level of lipoperoxides, GSH-Px, and GSH is assumed to be an important event prior to the ovulation response, with high levels of milk SOD concentration in the ovulatory cycle cows [130].

Nitric oxide is synergistic with progesterone and may reduce relaxation by relieving uterine contraction during the paracrine-style secretion phase. In sheep, the regulation of reproductive physiology is related to the effects of oxidative stress [117]. Increased levels of progesterone during pregnancy in sheep and goats as well as increased levels of malondialdehyde (MDA) in

placentomas have been reported [131]. Significant reductions in antioxidant substances may occur in placentomas during early gestation in sheep. These changes in the antioxidant enzymatic defenses of the placenta are thought to be an adaptation to the oxidative stress caused by ROS in early pregnancy [132]. According to the results obtained, pregnancy may be a stressor and it may be beneficial to support progesterone production with antioxidants in order to mitigate oxidative stress effects [131, 132]. The application of antioxidant vitamins in estrus synchronization during the breeding season reduces free radical levels, increases pregnancy performance, and increases the litter size in Tuj sheep [133]. However, β-carotene and vitamin E applications before estrus synchronization did not cause significant changes in plasma MDA levels in sheep during the breeding season [66]. Serum progesterone concentration increases after administration of intravaginal progesterone-releasing devices for estrus synchronization in goats increases oxidants such as eNOS activity, NO, MDA, and total oxidation status total oxidation status decreased [68, 69]. Short-term PRID treatments increase serum progesterone levels but decrease total antioxidant capacity in dairy heifers [23].

6. Conclusion

Progesterone is synthesized in the luteal phase and is an important hormone required for the continuity of pregnancy in ruminants. It is widely used in cattle for the purpose of estrus synchronization. In addition, this hormone, which has many uses in clinical practice, continues to be explored in ruminants. As time progresses, more detailed facts about the complex effects of progesterone in the organism, its use in clinical practice in ruminants, and the relationship of progesterone to oxidative stress in ruminants will be revealed.

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References

[1] Helbling IM, Luna JA. Progesterone administration in planned reproduction of cattle. In: Rivera C, editor. Progesterone: Functions, Uses and Research Insights. USA: Nova Science Publishers; 2017. pp. 69-125

[2] Kuru M. Holstein ırkı düvelerde progesteron ile kombine edilen Cosynch protokolünde ovulasyonun uyarılması amacıyla hCG veya GnRH hormonu kullanılmasının gebelik oranları üzerine etkisi [thesis in Turkish]. Kars: Kafkas University; 2015

[3] Salmon AB, Richardson A, Pérez VI. Update on the oxidative stress theory of aging: Does oxidative stress play a role in aging or healthy aging? Free Radical Biology and Medicine. 2010;**48**:642-655. DOI: 10.1016/j.freeradbiomed.2009.12.015

[4] Brewer GJ: Epigenetic oxidative redox shift (EORS) theory of aging unifies the free radical and insulin signaling theories. Experimental Gerontology. 2010;**45**:173-179. DOI: 10.1016/j.exger.2009.11.007

[5] Descamps A, Cespuglio R. Influence of aging on the sleep rebound induced by immobilization stress in the rat. Brain Research. 2010;**1335**:14-23. DOI: 10.1016/j.brainres.2010.03.087

[6] Garrido P, de Blas M, Del Arco A, Segovia G, Mora F. Aging increases basal but not stress-induced levels of corticosterone in the brain of the awakened rat. Neurobiology of Aging. 2010;**33**:375-382. DOI: 10.1016/j.neurobiolaging.2010.02.015

[7] Durieux J, Wolff S, Dillin A. The cell-non-autonomous nature of electron transport chain-mediated longevity. Cell. 2011;**144**:79-91. DOI: 10.1016/j.cell.2010.12.016

[8] Woo DK, Shadel GS. Mitochondrial stress signals revised an old aging theory. Cell. 2011;**144**:11-12. DOI: 10.1016/j.cell.2010.12.023

[9] Huang N, Pandey AV, Agrawal V, Reardon W, Lapunzina PD, Mowat D, Jabs EW, Van Vliet G, Sack J, Flück CE, Miller WL. Diversity and function of mutations in P450 oxidoreductase in patients with Antley-Bixler syndrome and disordered steroidogenesis. American Journal of Human Genetics. 2005;**76**:729-749. DOI: 10.1086/429417

[10] Miyamoto A, Shirasuna K: Luteolysis in the cow: A novel concept of vasoactive molecules. Animal Reproduction. 2009;**6**:47-59

[11] Kuru M, Oral H, Kulaksiz R. Mechanism of luteolysis and vasoactive agents in cows. Atatürk Üniversitesi Veteriner Bilimleri Dergisi. 2014;**9**:141-148. DOI: 10.17094/avbd.01918

[12] Alaçam E, Saban E, Ay SS. The evaluation of various radioimmunoassay progesterone kits for different stage of reproductive period in the cow, sheep and bitch. Ankara Üniversitesi Veteriner Fakültesi Dergisi. 2009;**56**:37-41. DOI: 10.1501/Vetfak_0000002183

[13] Öcal H, Doğan H, Saat N, Aydin M. Progesterone, progestins and antiprogestins. Turkiye Klinikleri Journal of Veterinary Sciences – Obstetrics and Gynecology – Special Topics. 2015;**1**:60-86

[14] Alaçam E. Koyun ve keçilerde döl verimi. In: Aytuğ CN, Alaçam E, Özkoç Ü, Yalçın BC, Gökçen H, Türker H, editors. Koyun-Keçi Hastalıkları ve Yetiştiriciliği. İstanbul: TÜM VET Hayvancılık Hizmetleri Yayını, Teknografik Matbaası; 1990. pp. 355-366 (Book in Turkish)

[15] Kalkan C, Horoz H. Pubertas ve seksüel sikluslar. In: Alaçam E, editor. Evcil Hayvanlarda Doğum ve İnfertilite. Ankara: Medisan, 2015. pp. 23-40 (Book in Turkish)

[16] Canooğlu E, Sarıbay K. Koyun keçilerde üreme kanalının morfolojisi ve fizyolojisi. In: Semacan A, Kaymaz M, Fındık M, Rişvanlı A, Köker A, editors. Çiftlik Hayvanlarında Doğum ve Jinekoloji. Malatya: Medipres; 2012. pp. 467-490 (Book in Turkish)

[17] Hanlon DW, Williamson NB, Wichtel JJ, Steffert IJ, Craigie AL, Pfeiffer DU. The effect of estradiol benzoate administration on estrous response and synchronized pregnancy rate in dairy heifers after treatment with exogenous progesterone. Theriogenology. 1996;**45**: 775-785. DOI: 10.1016/0093-691X(96)00007-6

[18] Patterson DJ, Wood SL, Kojima FN, Smith MF. Current and emerging methods to synchronize estrus with melengestrol acetate (MGA). In: Fields MJ, Sand RS, Yelich JV, editors. Factors Effecting Calf Crop Biotechnology of Reproduction. London: CRC Press; 2002. pp. 57-86

[19] Kuru M, Merhan O, Kaya S, Oral H, Kükürt A. The effect of short time PRID application on acute phase proteins for Holstein heifers. Turkish Journal of Chemistry. 2015;**40** (Suppl 1):63-64

[20] Kuru M, Oral H, Çolak A, Gürbulak K, Bekyürek T. The effect of hCG or GnRH administration for induction of ovulation as part of a 5-day Cosynch + Progesterone protocol on the pregnancy rates of heifers. In: VI. National Congress of Turkish Society of Veterinary Gynaecology; October 15–18, 2015; Muğla, Turkey: Plaza Event Kongre; pp. 86-87

[21] Kuru M, Merhan O, Kaya S, Oral H, Kukurt A. The effect of short term progesterone-releasing intravaginal device treatment on acute inflammation markers for Holstein heifers. Revue de Medecine Veterinaire. 2015;**166**:336-340

[22] Kuru M, Kükürt A, Oral H, Karapehlivan M. Relationship between pregnancy rate and serum sialic acid levels and paraoxonase activity after synchronization with progesterone releasing intravaginal device protocol in heifers. Journal of Cellular Neuroscience and Oxidative Stress. 2016;**8**:556-557

[23] Oral H, Ögün M, Kuru M, Kaya S. Evaluation of certain oxidative stress parameters in heifers that were administered short term PRID. Kafkas Universitesi Veteriner Fakultesi Dergisi. 2015;**21**:569-573. DOI: 10.9775/kvfd.2015.12969

[24] Day ML, Geary TW: Handbook of Estrous Synchronization. Western Association of Agricultural Experiment Station Directors (WAAESD). California: Western Region Publication No. 014; 2005

[25] Dorsey BR, Kasimanickam R, Whittier WD, Nebel RL, Wahlberg ML, Hall JB. Effect of time from estrus to AI on pregnancy rates in estrous synchronized beef heifers. Animal Reproduction Science. 2011;**127**:1-6. DOI: 10.1016/j.anireprosci.2011.07.014

[26] Kuru M, Oral H, Çolak A, Gürbulak K, Bekyürek T. The effect of hCG or GnRH administration on pregnancy rates in Holstein heifers when used to induce ovulation as part of a 5-day Co-Synch + Progesterone-Releasing Intravaginal Device protocol. Revue de Medecine Veterinaire. 2017;**168**:38-45

[27] Semacan A, Pancarcı ŞM. Üremenin denetlenmesi. In: Semacan A, Kaymaz M, Fındık M, Rişvanlı A, Köker A, editors. Çiftlik Hayvanlarında Doğum ve Jinekoloji. Malatya: Medipres; 2012. pp. 99-124 (Book in Turkish)

[28] Funston RN, Ansotegui RP, Lipsey RJ, Geary TW. Synchronization of estrus in beef heifers using either melengestrol acetate (MGA)/prostaglandin or MGA/Select Synch. Theriogenology. 2002;**57**:1485-1491. DOI: 10.1016/S0093-691X(02)00654-4

[29] Lucy MC, Billings HJ, Butler WR, Ehnis LR, Fields MJ, Kesler DJ, Kinder JE, Mattos RC, Short RE, Thatcher WW, Wettemann RP, Yelich JV, Hafs HD. Efficacy of an intravaginal progesterone insert and an injection of PGF2alpha for synchronizing estrus and shortening the interval to pregnancy in postpartum beef cows, peripubertal beef heifers, and dairy heifers. Journal of Animal Science. 2001;**79**:982-995. DOI: 10.2527/2001.794982x

[30] Lamb GC, Larson JE, Geary TW, Stevenson JS, Johnson SK, Day ML, Ansotegui RP, Kesler DJ, DeJarnette JM, Landblom DG. Synchronization of estrus and artificial insemination in replacement beef heifers using gonadotropin-releasing hormone, prostaglandin F2α, and progesterone. Journal of Animal Science. 2006;**84**:3000-3009. DOI: 10.2527/jas.2006-220

[31] Richardson AM, Hensley BA, Marple TJ, Johnson SK, Stevenson JS. Characteristics of estrus before and after first insemination and fertility of heifers after synchronized estrus using GnRH, PGF2α and progesterone. Journal of Animal Science. 2002;**80**:2792-2800. DOI: 10.2527/2002.80112792x

[32] Chenault JR, Boucher JF, Hafs HD. Synchronization of estrus in beef cows and beef and dairy heifers with intravaginal progesterone inserts and prostaglandin F2α with or without gonadotropin-releasing hormone. The Professional Animal Scientists. 2003;**19**: 116-123. DOI: 10.15232/S1080-7446(15)31390-5

[33] Bridges GA, Portillo GE, de Araujo JW, Thatcher WW, Yelich JW. Efficacy of either a single or split treatment of PGF2α after a 14 day melengestrol acetate treatment to synchronize estrus and induce luteolysis in *Bos indicus* x *Bos taurus* heifers. Theriogenology. 2005;**64**:344-362. DOI: 10.1016/j.theriogenology.2004.12.003

[34] McDougall S, Rhodes FM, Compton CWR. Evaluation of three synchrony programs for pasture-based dairy heifers. Theriogenology. 2013;**79**:882-889. DOI: 10.1016/j.theriogenology.2012.12.013

[35] Bisinotto RS, Pansani MB, Castro LO, Narciso CD, Sinedino LD, Martinez N, Carneiro PE, Thatcher WW, Santos JE. Effect of progesterone supplementation on fertility responses of lactating dairy cows with corpus luteum at the initiation of the Ovsynch protocol. Theriogenology. 2015;**83**:257-265. DOI: 10.3168/jds.2014-9058

[36] Kim IH, Suh GH, Son DS. A progesterone – based timed AI protocol more effectively prevents premature estrus and incomplete luteal regression than Ovsynch protocol in lactating Holstein cows. Theriogenology. 2003;**60**:809-817. DOI: 10.1016/S0093-691X(03)00136-5

[37] Wheaton JE, Lamb GC. Induction of cyclicity in postpartum anestrous beef cows using progesterone, GnRH and estradiol cypionate (ECP). Animal Reproduction Science. 2007;**102**:208-216. DOI: 10.1016/j.anireprosci.2006.11.006

[38] Stevenson JL, Dalton JC, Santos JEP, Sartori R, Ahmadzadeh A, Chebel RC. Effect of synchronization protocols on follicular development and estradiol and progesterone concentrations of dairy heifers. Journal of Dairy Science. 2008;**91**:3045-3056. DOI: 10.3168/jds.2007-0625

[39] Howard JM, Falk DG, Carnahan KG, Dalton JC, Chebel RC, Ahmadzadeh A. The use of gonadotropin-releasing hormone in a progesterone-based timed artificial insemination protocol in replacement beef heifers. The Professional Animal Scientists. 2009;**25**:757-761. DOI: 10.15232/S1080-7446(15)30785-3

[40] Colazo MG, Ambrose DJ. Neither duration of progesterone insert nor initial GnRH treatment affected pregnancy per timed-insemination in dairy heifers subjected to a Co-synch protocol. Theriogenology. 2011;**76**:578-588. DOI: 10.1016/j.theriogenology.2011.03.013

[41] Busch DC, Wilson DJ, Schafer DJ, Leitman NR, Haden JK, Ellersieck MR, Smith MF, Patterson DJ. Comparison of progestin-based estrus synchronization protocols before fixed-time artificial insemination on pregnancy rate in beef heifers. Journal of Animal Science. 2007;**85**:1933, 1939. DOI: 10.2527/jas.2006-845

[42] Hyland A, Seidel GE Jr, Enns RM, Peel RK, Whittier JC. Intervals of five or seven days between controlled internal drug-release insertion, gonadotropin-releasing hormone, and prostaglandin F2α injections: Effects on pregnancy rate and follicular size. The Professional Animal Scientists. 2009;**25**:150-154. DOI: 10.15232/S1080-7446(15)30697-5

[43] Kasimanickam R, Day ML, Rudolph JS, Hall JB, Whittier WD. Two doses of prostaglandin improve pregnancy rates to timed-AI in a 5-day progesterone-based synchronization protocol in beef cows. Theriogenology. 2009;**71**:762-767. DOI: 10.1016/j.theriogenology.2008.09.049

[44] Bartolome JA, Silvestre FT, Kamimura S, Arteche ACM, Melendez P, Kelbert D, Mchale J, Swift K, Archbald LF, Thatcher WW. Resynchronization of ovulation and timed insemination in lactating dairy cows I: Use of the Ovsynch and Heatsynch protocols after non-pregnancy diagnosis by ultrasonography. Theriogenology. 2005;**63**:1617-1627. DOI: 10.1016/j.theriogenology.2004.07.016

[45] Goodman RL. Neuroendocrine control of the ovine estrous cycle. In: Knobil E, Neil JD, editors. The Physiology of Reproduction. New York: Raven Press; 1988. pp. 1929-1969

[46] Kaneko H, Nakanishi Y, Taya K, Kishi H, Watanabe G, Sasemoto S, Hasegawa Y. Evidence that inhibin is an important factor in the regulation of FSH secretion during the mid-luteal phase in cows. The Journal of Endocrinology. 1993;**136**:35-41. DOI: 10.1677/joe.0.1360035

[47] Kaçar C, Kaya S, Kuru M, Zonturlu AK. Contemporary methods for the control of reproduction in sheep and goats. Turkiye Klinikleri Journal of Veterinary Sciences – Obstetrics and Gynecology – Special Topics. 2016;**2**:29-37

[48] Kuru M, Sogukpinar O, Makav M, Cetin N. Effect of barium selenate injections on fertility of Pirlak ewes subjected to estrus synchronization during non-breeding season. Medycyna Weterynaryjna. 2017;**73**:479-482

[49] Jackson CG, Neville TL, Mercadante VRG, Waters KM, Lamb GC, Dahlen CR, Redden RR. Efficacy of various five-day estrous synchronization protocols in sheep. Small Ruminant Research. 2014;**120**:100-107. DOI: 10.1016/j.smallrumres.2014.04.004

[50] Martemucci G, D'Alessandro AG. Synchronization of oestrus and ovulation by short time combined FGA, PGF2α, GnRH, eCG treatments for natural service or AI fixed-time. Animal Reproduction Science. 2011;**123**:32-39. DOI: 10.1016/j.anireprosci.2010.11.007

[51] Vilarino M, Rubianes E, van Lier E, Menchaca A. Serum progesterone concentrations, follicular development and time of ovulation using a new progesterone releasing device (DICO®) in sheep. Small Ruminant Research. 2010;**91**:219-224. DOI: 10.1016/j.smallrumres.2010.02.014

[52] Fleisch A, Werne S, Heckendorn F, Hartnack S, Piechotta M, Bollwein H, Thun R, Janett F. Comparison of 6-day progestagen treatment with Chronogest® CR and Eazi-breedTM CIDR® G intravaginal inserts for estrus synchronization in cyclic ewes. Small Ruminant Research. 2012;**107**:141-146. DOI: 10.1016/j.smallrumres.2012.05.014

[53] Kuru M, Kükürt A, Oral H, Kulaksiz R, Karapehlivan M. The effects of the use of controlled internal drug release CIDR for estrus synchronization on paraoxonase activities and total sialic acid levels in Georgian goats. In: 12th International Conference on Goats; September 25–30, 2016; Antalya, Turkey: International Goat Association; p. 192

[54] Kuru M, Kükürt A, Kulaksiz R, Oral H, Çetin N, Karapehlivan M. Controlled internal drug release use for synchronization on paraoxonase activities and total sialic acid levels in Abasian goats. Journal of Cellular Neuroscience and Oxidative Stress. 2016;**8**:544

[55] Kuru M, Boga Kuru B, Kulaksiz R, Ari UÇ, Oral H. Effects of the progesterone-based estrus synchronization on some reproductive parameters in Abaza goats. Kocatepe Veterinary Journal. 2017;**10**:156-163. DOI: 10.5578/kvj.57526

[56] Gordon I. Controlled Reproduction in Sheep and Goats. United Kingdom: CABI Publishing; 1997

[57] Kulaksız R, Daşkın A, Dalcı T. Some reproductive traits of ewes from different breeds following oestrus synchronisation by flugeston acetate-eCG during the breeding season. Atatürk Üniversitesi Veteriner Bilimleri Dergisi. 2011;**6**:9-15

[58] Abecia JA, Forcada F, Gonzalez-Bulnes A. Hormonal control of reproduction in small ruminants. Animal Reproduction Science. 2012;**130**:173-179. DOI: 10.1016/j.anireprosci.2012.01.011

[59] Kulaksız R, Uçar Ö, Daşkın A. Effects of FGA sponge and Ovsynch based protocols on reproductive performance of fat tailed ewes during the breeding season. Kafkas Universitesi Veteriner Fakultesi Dergisi. 2013;**19**:629-633. DOI: 10.9775/kvfd.2013.8568

[60] Fentoni LS, Shackell GH, Ramsay ML, Dodds KG, Reid PJ, Mcleodi BJ. Influence of year, age, and geographical location on induced oestrus in ewes early in the breeding season. New Zealand Journal of Agricultural Research. 1997;**40**:69-74. DOI: 10.1080/00288233. 1997.9513231

[61] Evans ACO, Duffy P, Crosby TF, Hawken PAR, Boland MP, Beard AP. Effect of ram exposure at the end of progestagen treatment on estrus synchronisation and fertility during the breeding season in ewes. Animal Reproduction Science. 2004;**84**:349-358. DOI: 10.1016/j.anireprosci.2003.12.013

[62] Ungerfeld R, Rubianes E. Estrous response to ram effect in Corriedale ewes primed with medroxyprogesterone during the breeding season. Small Ruminant Research. 1999;**32**: 89-91. DOI: 10.1016/S0921-4488(98)00164-3

[63] Gungor O, Cenesiz M, Pancarci SM, Yildiz S, Kaya M, Kacar C, Ozyurlu N, Gurbulak K. Effects of different intravaginal progesterone releasing devices on estrous synchronization and LH surge in fat-tailed ewes during non-breeding season. Medycyna Weteryn aryjna. 2007;**63**:1316-1319

[64] Hashemi M, Safdarian M, Kafi M. Estrous response to synchronization of estrus using different progesterone treatments outside the natural breeding season in ewes. Small Ruminant Research. 2006;**65**:279-283. DOI: 10.1016/j.smallrumres.2005.07.051

[65] Zonturlu AK, Özyurtlu N, Kaçar C. Effect of different doses PMSG on estrus synchronization and fertility in Awassi ewes synchronized with progesterone during the transition period. Kafkas Universitesi Veteriner Fakultesi Dergisi. 2011;**17**:125-129. DOI: 10.9775/kvfd.2010.2572

[66] Kaçar C, Kamiloğlu NN, Gürbulak K, Pancarcı ŞM, Güngör Ö, Güvenç K, Gürbulak K, Şaban E. The effect of administration of testosterone antibody, β-carotene and vitamin E on multiple pregnancy and MDA (malondialdehyde) in Tuj breed sheep in non-breeding season. Kafkas Üniversitesi Veteriner Fakültesi Dergisi. 2008;**14**:51-56. DOI: 10.9775/ kvfd.2008.03-A

[67] Abecia JA, Forcada F, González-Bulnes A. Pharmaceutical control of reproduction in sheep and goats. The Veterinary Clinics of North America Food Animal Practice. 2011;**27**:67-79. DOI: 10.1016/j.cvfa.2010.10.001

[68] Kuru M, Ögün M, Oral H, Kükürt A, Makav M, Kulaksiz R. The use of controlled internal drug release for synchronization augmented oxidative and nitrosative stress and leptin levels in Georgian goats. Journal of Cellular Neuroscience and Oxidative Stress. 2016;**8**:541-542

[69] Kuru M, Ögün M, Oral H, Kükürt A, Erkiliç EE, Kulaksiz R. Synchronization with controlled internal drug release CIDR on exacerbate oxidative and nitrosative stress and leptin levels in Abasian goats. In: 12th International Conference on Goats; September 25–30, 2016; Antalya, Turkey: International Goat Association; p. 191

[70] Zhao Y, Zhang J, Wei H, Sun X, Mu B, Yu M, Wang L. Efficiency of methods applied for goat estrous synchronization in subtropical monsoonal climate zone of Southwest China. Tropical Animal Health and Production. 2010;**42**:1257-1262. DOI: 10.1007/s11250-010-9558-6

[71] Penna B, Libonati H, Director A, Sarzedas AC, Martins G, Brandão FZ, Fonseca J, Lilenbaum W. Progestin-impregnated intravaginal sponges for estrus induction and synchronization influences on goats vaginal flora and antimicrobial susceptibility. Animal Reproduction Science. 2013;**142**:71-74. DOI: 10.1016/j.anireprosci.2013.09.006

[72] Oliveira JK, Martins G, Esteves LV, Penna B, Hamond C, Fonseca JF, Rodrigues AL, Brandão FZ, Lilenbaum W. Changes in the vaginal flora of goats following a short-term protocol of oestrus induction and synchronisation with intravaginal sponges as well as their antimicrobial sensitivity. Small Ruminant Research. 2013;**113**:162-166. DOI: 10.1016/j.smallrumres.2013.02.011

[73] Şenünver A, Nak Y. İnfertilite. In: Semacan A, Kaymaz M, Fındık M, Rişvanlı A, Köker, editors. Çiftlik Hayvanlarında Doğum ve Jinekoloji. Malatya: Medipres; 2012. pp. 409-464 (Book in Turkish)

[74] Perry GA, Smith MF, Roberts AJ, MacNeil MD, Geary TW. Relationship between size of the ovulatory follicle and pregnancy success in beef heifers. Journal of Animal Science. 2007;**85**:684-689. DOI: 10.2527/jas.2006-519

[75] Diskin MG, Morris DG. Embryonic and early foetal losses in cattle and other ruminants. Reproduction in Domestic Animals. 2008;**43**(Suppl 2):260-267. DOI: 10.1111/j.1439-0531.2008.01171.x

[76] Diskin MG, Parr MH, Morris DG. Embryo death in cattle: An update. Reproduction, Fertility, and Development. 2011;**24**:244-251. DOI: 10.1071/RD11914

[77] Alnimer MA, Lubbadeh WF. Effect of progesterone (P4) intravaginal device (CIDR) to reduce embryonic loss and to synchronize return to oestrus of previously timed inseminated lactating dairy cows. Animal Reproduction Science. 2008;**107**:36-47. DOI: 10.1016/j.anireprosci.2007.06.018

[78] Mehni SB, Shabankareh HK, Kazemi-Bonchenari M, Eghbali M. The comparison of treating Holstein dairy cows with progesterone, CIDR and GnRH after insemination on serum progesterone and pregnancy rates. Reproduction in Domestic Animals. 2012;**47**:131-134. DOI: 10.1111/j.1439-0531.2011.01811.x

[79] Larson FS, Butler RW, Currie BW. Pregnancy rates in lactating dairy cattle following supplementation of progesterone after artificial insemination. Animal Reproduction Science. 2007;**102**:172-179. DOI: 10.1016/j.anireprosci.2007.02.023

[80] Mann GE, Lamming GE. The influence of progesterone during early pregnancy in cattle. Reproduction in Domestic Animals. 1999;**34**:269-274. DOI: 10.1111/j.1439-0531.1999.tb01250.x

[81] Macmillan KL, Taufa VK, Day AM, Peterson AJ. Effects of supplemental progesterone on pregnancy rates in cattle. Journal of Reproduction and Fertility. Supplement. 1991;**43**:304

[82] Ataman MB, Aköz M, Saribay MK, Erdem H, Bucak MN. Prevention of embryonic death using different hormonal treatments in ewes. Turkish Journal of Veterinary and Animal Sciences. 2013;**37**:6-8. DOI: 10.3906/vet-1102-795

[83] Peter AT, Vos PLAM, Ambrose DJ. Postpartum anestrus in dairy cattle. Theriogenology. 2009;**71**:1333-1342. DOI: 10.1016/j.theriogenology.2008.11.012

[84] Yániz J, Murugavel K, López-Gatius F. Recent developments in oestrous synchronization of postpartum dairy cows with and without ovarian disorders. Reproduction in Domestic Animals. 2004;**39**:86-93. DOI: 10.1111/j.1439-0531.2004.00483.x

[85] Stevenson JS, Tenhouse DE, Krisher RL, Lamb GC, Larson JE, Dahlen CR, Pursley JR, Bello NM, Fricke PM, Wiltbank MC, Brusveen DJ, Burkhart M, Youngquist RS, Garverick HA. Detection of anovulation by heatmount detectors and transrectal ultrasonography before treatment with progesterone in a timed insemination protocol. Journal of Dairy Science. 2008;**91**:2901-2915. DOI: 10.3168/jds.2007-0856

[86] Peter AT. An update on cystic ovarian degeneration in cattle. Reproduction in Domestic Animals. 2004;**39**:1-7. DOI: 10.1046/j.0936-6768.2003.00466.x

[87] Hatler TB, Hayes SH, Anderson LH, Silvia WJ. Effect of a single injection of progesterone on ovarian follicular cysts in lactating dairy cows. Veterinary Journal. 2006;**172**:329-333. DOI: 10.1016/j.tvjl.2005.04.020

[88] López-Gatius F, Santolaria P, Yániz J, Rutllant J, López-Béjar M. Persistent ovarian follicles in dairy cows: A therapeutic approach. Theriogenology. 2001;**56**:649-659. DOI: 10.1016/S0093-691X(01)00596-9

[89] Davis SR, Welch RAS, Pearce MG, Peterson AJ. Induction of lactation in nonpregnant cows by estradiol-17β and progesterone from an intravaginal sponge. Journal of Dairy Science. 1983;**66**:450-457. DOI: 10.3168/jds.S0022-0302(83)81813-X

[90] Mohan K, Shridhar NB, Jayakumar K, Honnappa TG, Madhusudhan HS. Lactation induction protocols and cost benefit analysis in repeat breeding cows. Indian Journal of Animal Research. 2010;**44**:44-47

[91] Öcal H, Apaydın AM, Timurkan H, Kalkan C, Deveci H, Çetin H, Kaygusuzoğlu E. Döl tutmayan ve yavru atan düvelerde laktasyonun uyarılması ve bunun gebe kalma üzerine etkisi. Fırat Üniversitesi Sağlık Bilimleri Veteriner Dergisi. 1994;**8**:76-82 (Article in Turkish)

[92] Larry Smith K, Schanbacher FL: Hormone induced lactation in the bovine. I. lactational performance following injections of 17β-estradiol and progesterone. Journal of Dairy Science. 1973;**56**:738-743. DOI: 10.3168/jds.S0022-0302(73)85243-9

[93] Fulkerson WJ, McDowell GH. Artificial induction of lactation in ewes. The Journal of Endocrinology. 1974;**63**:167-173. DOI: 10.1677/joe.0.0630167

[94] Takiguchi S, Sugino N. Esato Karube-Harada A, Sakata A, Nakamura Y, Ishikawa H, Kato H. Differential regulation of apoptosis in the corpus luteum of pregnancy and newly formed corpus luteum after parturition in rats. Biology of Reproduction. 2004;**70**:313-318. DOI: 10.1095/biolreprod.103.018853

[95] Stolon I, Oros A, Moldaveanu E. Mineral view, apoptosis and free radicals. Biochemical and Molecular Medicine. 1996;**59**:93-97. DOI: 10.1006/bmme.1996.0072

[96] Valko M, Izakovic M, Mazur M, Rhodes CJ, Telser J. Role of oxygen radicals in DNA damage and cancer incidence. Molecular and Cellular Biochemistry. 2004;**266**:37-56. DOI: 10.1023/B:MCBI.0000049134.69131.89

[97] Ozcan A, Ogun M. Biochemistry of reactive oxygen and nitrogen species. In: Gowder SJT, editor. Basic Principles and Clinical Significance of Oxidative Stress. Croatia: InTech; 2015. DOI: 10.5772/61193

[98] Koch OR, Pani G, Borrello S, Colavitti R, Cravero A, Farre S, Galeotti T. Oxidative stress and antioxidant defenses in ethanol-induced cell injury. Molecular Aspects of Medicine. 2004;**25**:191-198. DOI: 10.1016/j.mam.2004.02.019

[99] Kopani M, Celec P, Danisovic L, Michalka P, Biro C. Oxidative stress and electron spin resonance. Clinica Chimica Acta. 2006;**364**:61-66. DOI: 10.1016/j.cca.2005.05.016

[100] Gutteridge JMC, Halliwell B. Antioxidants in Nutrition, Health and Disease. New York: Oxford University Press; 1994

[101] Gitto E, Pellegroni S, Gitto P, Barberi I, Reiter RJ. Oxidative stress of the newborn in the pre- and postnatal period and the clinical utility of melatonin. Journal of Pineal Research. 2009;**46**:128-139. DOI: 10.1111/j.1600-079X.2008.00649.x

[102] Naito Y, Lee MC, Kato Y, Nagai R, Yonei Y. Oxidative stress markers. Anti-Aging. Medicine. 2010;**7**:33-44. DOI: 10.3793/jaam.7.36

[103] Cherubini A, Ruggiero C, Polidori MC, Mecocci P. Potential markers of oxidative stress in stroke. Free Radical Biology & Medicine. 2005;**39**:841-852. DOI: 10.1016/j.freeradbio med.2005.06.025

[104] Clarkson PM, Thompson HS. Antioxidants: What role do they play in physical activity and health? The American Journal of Clinical Nutrition. 2000;**72**:637-646

[105] Cheeseman KH, Slater TF. An introduction to free radical biochemistry. British Medical Bulletin. 1994;**49**:481-493. DOI: 10.1093/oxfordjournals.bmb.a072625

[106] Serarslan G, Altuğ E, Kontas T, Atik E, Avci G. Caffeic acid phenetyl ester accelerates cutaneous wound healing in a rat model and decreases oxidative stress. Clinical and Experimental Dermatology. 2007;**32**:709-715. DOI: 10.1111/j.1365-2230.2007. 02470.x

[107] Lichtenthaler R, Marx F, Kind OM. Determination of antioxidative capacities using an enhanced total oxidant scavenging capacity (TOSC) assay. European Food Research and Technology. 2003;**216**:166-173. DOI: 10.1007/s00217-002-0635-6

[108] Behrman HR, Kodaman PH, Preston SL, Gao S. Oxidative stress and the ovary. Journal of the Society for Gynecologic Investigation. 2001;**8**:S40-S42. DOI: 10.1177/107155760 1008001S13

[109] Ruder EH, Hartman TJ, Goldman MB. Impact of oxidative stress on female fertility. Current Opinion in Obstetrics & Gynecology. 2009;**21**:219-222

[110] Shkolnik K, Tadmor A, Ben-Dor S, Nevo N, Galiani D, Dekel N. Reactive oxygen species are indispensable in ovulation. Proceedings of the National Academy of Sciences of the United States of America. 2011;**108**:1462-1467. DOI: 10.1073/pnas.1017213108

[111] Ciani F, Cocchia N, d'Angelo D, Tafuri S. Influence of ROS on ovarian functions. In: Wu B, editor. New Discoveries in Embryology. Croatia: InTech; 2015. DOI: 10.5772/61003

[112] Sugino N. Roles of reactive oxygen species in the corpus luteum. Animal Science Journal. 2006;**77**:556-565. DOI: 10.1111/j.1740-0929.2006.00386.x

[113] Al-Gubory KH, Camous S, Germain G, Bolifraud P, Nicole A, Ceballos-Picot I. Reconsideration of the proposed luteotropic and luteoprotective actions of ovine placental lactogen in sheep: In vivo and in vitro studies. The Journal of Endocrinology. 2006;**188**: 559-568. DOI: 10.1677/joe.1.06550

[114] Brannstrom M. Potential role of cytokines in ovarian physiology: The case for interleukin-1. In: Leung PCK, Adashi EY, editors. The Ovary. New York: Elsevier Academic Press; 2004. pp. 261-265

[115] Olofsson J, Norjavaara E, Selstam G. In vivo levels of prostaglandin F2α, E2 and prostacyclin in the corpus luteum of pregnant and pseudopregnant rats. Biology of Reproduction. 1990;**42**:792-800. DOI: 10.1095/biolreprod42.5.792

[116] Tanaka M, Miyazaki T, Tanigaki S, Kasai K, Minegishi K, Miyakoshi K, Ishimoto H, Yoshimura Y. Participation of reactive oxygen species in PGF2α-induced apoptosis in rat luteal cells. Journal of Reproduction and Fertility. 2000;**120**:239-245. DOI: 10.1530/jrf.0.1200239

[117] Celi P. The role of oxidative stress in small ruminants' health and production. Revista Brasileira de Zootecnia. 2010;**39**(Suppl. spe):348-363. DOI: 10.1590/S1516-35982010001300038

[118] Hayashi K, Miyamoto A, Konari A, Ohtani M, Fukui Y. Effect of local interaction of reactive oxygen species with prostaglandin F2α on the release of progesterone in ovine corpora lutea in vivo. Theriogenology. 2003;**59**:1335-1344. DOI: 10.1016/S0093-691X(02)01173-1

[119] Sugino N, Karube-Harada A, Taketani T, Sakata A, Nakamura Y. Withdrawal of ovarian steroids stimulates prostaglandin F2α production through nuclear factor-κB activation via oxygen radicals in human endometrial stromal cells: Potential relevance to menstruation. The Journal of Reproduction and Development. 2004;**50**:215-225. DOI: 10.1262/jrd.50.215

[120] Agarwal A, Gupta S, Sharma R. Role of oxidative stress in female reproduction. Reproductive Biology and Endocrinology. 2005;**3**:1-21. DOI: 10.1186/1477-7827-3-28

[121] Celi P, Merlo M, Da Dalt L, Stefani A, Barbato O, Gabai G. Relationship between late embryonic mortality and the increase in plasma advanced oxidised protein products (AOPP) in dairy cows. Reproduction, Fertility, and Development. 2011;**23**:527-533. DOI: 10.1071/RD10268

[122] Celi P, Merlo M, Barbato O, Gabai G. Relationship between oxidative stress and the success of artificial insemination in dairy cows in a pasture-based system. Veterinary Journal. 2012;**193**:498-502. DOI: 10.1016/j.tvjl.2012.02.002

[123] Rizzo A, Minoia G, Trisolini C, Mutinati M, Spedicato M, Jirillo F, Sciorsci RL. Reactive oxygen species (ROS): Involvement in bovine follicular cysts etiopathogenesis. Immunopharmacology and Immunotoxicology. 2009;**31**:631-635. DOI: 10.3109/08923970902932962

[124] Talukder S, Ingenhoff L, Kerrisk KL, Celi P. Plasma oxidative stress biomarkers and progesterone profiles in a dairy cow diagnosed with an ovarian follicular cyst. The Veterinary Quarterly. 2014;**34**:113-117. DOI: 10.1080/01652176.2014.953264

[125] Rizzo A, Minoia G, Trisolini C, Manca R, Sciorsci RL. Concentrations of free radicals and beta-endorphins in repeat breeder cows. Animal Reproduction Science. 2007;**100**:257-263. DOI: 10.1016/j.anireprosci.2006.08.013

[126] Rizzo A, Roscino MT, Binetti F, Sciorsci RL. Roles of reactive oxygen species in female reproduction. Reproduction in Domestic Animals. 2012;**47**:344-352. DOI: 10.1111/j.1439-0531.2011.01891.x

[127] Rapoport R, Sklan D, Wolfenson D, Shaham-Albalancy A, Hanukoglu I. Antioxidant capacity is correlated with steroidogenic status of the corpus luteum during the bovine estrous cycle. Biochimica et Biophysica Acta. 1998;**1380**:133-140. DOI: 10.1016/S0304-4165(97)00136-0

[128] Kamada H, Akagi S, Watanabe S. Astaxanthin increases progesterone production in cultured bovine luteal cells. The Journal of Veterinary Medical Science. 2017;**79**:1103-1109. DOI: 10.1292/jvms.17-0044

[129] Ghosh M, Gupta M, Kumar R, Kumar S, Balhara AK, Singh I. Relation between antioxidant status and postpartum anestrous condition in Murrah buffalo. Veterinary World. 2015;**8**:1163-1166. DOI: 10.14202/vetworld.2015.1163-1166

[130] Talukder S, Kerrisk KL, Gabai G, Fukutomi A, Celi P. Changes in milk oxidative stress biomarkers in lactating dairy cows with ovulatory and an-ovulatory oestrous cycles. Animal Reproduction Science. 2015;**158**:86-95. DOI: 10.1016/j.anireprosci.2015.05.004

[131] Nawito MF, Hameed AR, Sosa AS, Mahmoud KG. Impact of pregnancy and nutrition on oxidant/antioxidant balance in sheep and goats reared in South Sinai, Egypt. Veterinary World. 2016;**9**:801-805. DOI: 10.14202/vetworld.2016.801-805

[132] Garrel C, Fowler PA, Al-Gubory KH. Developmental changes in antioxidant enzymatic defences against oxidative stress in sheep placentomes. The Journal of Endocrinology. 2010;**205**:107-116. DOI: 10.1677/JOE-09-0362

[133] Kamiloğlu NN, Kaçar C, Güven A, Yıldız B, Kuru M, Kaya S, Eroğlu HA, Koç E. Changes in lipid peroxidation, glutathione and fertility in Tuj sheep after combined administration of vitamin A and E and passive immunization with testosterone antibodies. Kafkas Universitesi Veteriner Fakultesi Dergisi. 2017;**23**:459-465. DOI: 10.9775/kvfd.2016.17053