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The rabbit estrous cycle: A comprehensive review

Merve Sena Kumcu[1]*, Buket Boğa Kuru[2], Mushap Kuru[1]

[1]Kafkas University, Faculty of Veterinary Medicine, Department of Obstetrics and Gynecology, Kars, Türkiye
[2]Kafkas University, Faculty of Veterinary Medicine, Department of Animal Breeding and Husbandry, Kars, Türkiye
*Corresponding: mervesenakumcu@gmail.com

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Abstract
The reproductive system of the female rabbit is a complex and specialized structure. Its proper functioning is crucial for the success of rabbit breeding. This study provides a detailed examination of the anatomy, physiology, and estrous cycle of the female rabbit reproductive system. The female rabbit reproductive system consists of the vulva, vagina, cervix, uterus, fallopian tubes, and ovaries. Each of these organs has a specific structure and function that are essential for reproduction. Female rabbits reach puberty at an average age of 3.5 months. They become capable of pregnancy at 4-4.5 months. The recommended age for first breeding is between 4 and 9 months. Female rabbits do not have a regular estrous cycle. They have a characteristically induced ovulation. The estrous cycle averages 16-18 days in length, and the female rabbit is receptive to mating for 12-14 days. Follicle-stimulating hormone (FSH) promotes the growth and development of follicles. Luteinizing hormone (LH) triggers ovulation and initiates progesterone production. Progesterone is essential for pregnancy and allows the uterus to prepare a suitable environment for embryonic development. Ovulation occurs 10-13 hours after mating. After ovulation, granulosa cells form a structure called the corpus luteum (CL). The CL secretes progesterone and regresses through a process called luteolysis if pregnancy does not occur. The estrous cycle is divided into four phases: diestrus, proestrus, estrus, and metestrus. Vaginal cytology and behavioral observation are common methods used for estrus detection. Behavioral signs include swelling and redness of the vulva, lordosis position, interest in the male rabbit, and nest building. In conclusion, the female rabbit reproductive system and estrous cycle are highly complex and specialized. Academic research and detailed studies will contribute to a better understanding of the reproductive system and the development of more effective methods in rabbit breeding.
Keywords: *Estrous cycle, estrus, female rabbit, hormones, reproduction*

1. Introduction

The European rabbit (*Oryctolagus cuniculus*) serves as the foundation for domestic rabbit breeds. However, not all domestic rabbits belong solely to this species. Hybridization between the European rabbit and the wild rabbit (*Lepus europaeus*) has resulted in the diversification of domestic rabbit breeds observed today.[1,2] While initially viewed primarily as charming and manageable companion animals, domestic rabbits possess the potential to become one of the world's most crucial livestock species. This significance is attributed to their multifaceted contributions, including serving as a reliable food source, playing a pioneering role in medical research, and generating economic value through meat, fur, and manure production. A key characteristic of domestic rabbits is their remarkable reproductive capacity. Their ability to reproduce throughout the year positions them as ideal candidates for continuous meat production. Even with a limited breeding stock, rabbits can become a significant source of meat due to their ability to deliver multiple litters annually.[1–4]

Domestic rabbits (*Oryctolagus cuniculus*) exhibit a reproductive physiology and endocrinology distinct from many other mammalian species. This distinctiveness is characterized by a remarkably short gestation period, rapid offspring growth, and the ability to reproduce shortly after parturition (giving birth). These unique features have made rabbits a subject of considerable research interest.[1–3] The average lifespan of domestic rabbits is approximately 5-6 years, with a reproductive lifespan ranging from 1 to 3 years. Body weight varies depending on breed, with medium-sized breeds typically weighing between 1.8 and 7.3 kg, and smaller breeds weighing between 0.9 and 1.8 kg. Puberty is attained at around 3.5 months of age, and females can become pregnant as early as 4.5-5 months old. A key anatomical distinction of the female rabbit reproductive tract is the presence of a duplicate cervix, a characteristic not shared by most mammals. Additionally, rabbits exhibit induced ovulation, similar to felines and mustelids (e.g., cats and ferrets). This means ovulation is not spontaneous but triggered by copulation or hormonal stimulation. The efficient management of modern rabbit production systems hinges on the accurate detection of estrus (heat) in females and the subsequent implementation of timely mating practices. These factors significantly impact reproductive success and overall production output.[3,5,6]

2. Anatomy of reproductive organs

The female rabbit reproductive organs follow a craniocaudal sequence, consisting of the vulva, vagina, cervix, uterus, uterine tubes, and ovaries (Figure 1).[6–8]

The paired ovaries, situated in the abdominal cavity near the kidneys, are ovoid structures critical for female

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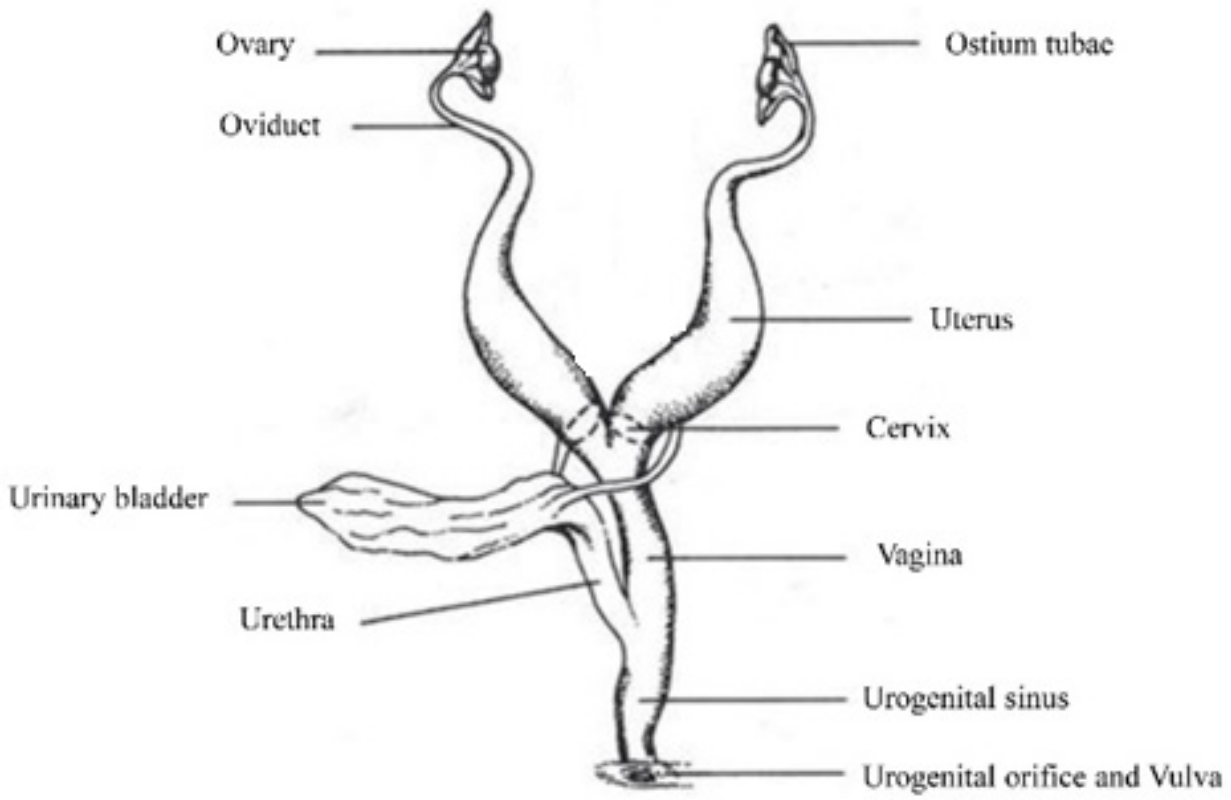

Figure 1. Female rabbit genital tract organs.[8]

reproduction. Their size and weight (approximately 20 x 10 mm and 0.5-0.75 g, respectively) fluctuate with ovarian activity. These organs serve two primary functions: producing oocytes (female reproductive cells) and synthesizing essential hormones like estrogen and progesterone. The ovaries consist of two distinct layers: the outer cortex and the inner medulla. The medulla primarily comprises connective tissue, housing a network of nerves and blood vessels. In contrast, the cortex harbors a more diverse array of tissues, including blood vessels, nerves, and muscle fibers. Interestingly, at birth, the germinal epithelium layer within the cortex of female rabbits contains thousands of immature oocytes. These oocytes undergo development throughout the female's reproductive lifespan, from puberty until their eventual expulsion or degeneration. Fertilization, the union of sperm and egg, occurs within the fallopian tubes. These tubes also play a vital role in sperm capacitation, the process by which sperm mature and gain the ability to fertilize an egg. The upper end of each fallopian tube opens into the ostium tubae, which partially encircles the ovary. Notably, the fimbriae, numerous finger-like projections lining the fallopian tubes, generate wave-like movements. These movements facilitate the capture of the oocyte and its transport towards the fallopian tube during ovulation.[3,4,6]

The rabbit uterus consists of two separate horns that do not fuse to form a single organ. Each horn connects to a distinct cervical canal that opens into the common vagina. Consequently, rabbits possess a structure known as a duplex cervix (Figure 2).[7,9] The uterus serves as the site where the majority of embryonic development takes place. It also facilitates the expulsion of fetuses during parturition through powerful contractions. The cervixes, on the other hand, keep the uterus closed and protected except during mating and delivery.[3,4,6]

The vagina serves a dual purpose in the rabbit reproductive system. During copulation, it acts as a depository for sperm. Subsequently, it functions as a birth canal during parturition, allowing for the passage of offspring. The female rabbit's vulva encompasses the vaginal opening and also houses the urogenital sinus. This chamber serves as the endpoint for the urethra, allowing for urine elimination. The external labia of the urogenital sinus forms the visible vulva, which can be a valuable indicator of sexual receptivity. A female rabbit with a moist, red, or pink vulva is significantly more likely to be receptive to mating compared to a female with a pale and dry vulva. Notably, the clitoris resides within the urogenital sinus. Its sensitive glans clitoridis protrudes towards the urogenital opening.[3,4,6]

3. Puberty

Rabbits reach puberty at approximately 3.5 months of age, with variation observed based on breed, body size, and nutritional status. Reproductive competence is achieved at 4-4.5 months old.[6] The recommended age for initial breeding differs between sexes: 6-10 months for males and 4-9 months for females.[3] A rabbit's reproductive capacity exhibits a characteristic trajectory.[10] Following the onset of puberty, there is a rapid increase in fertility for a limited period. Subsequently, a decline in reproductive capacity occurs with age. This decline likely results from a decrease in the oocyte population,[11] an increased frequency of defective oocytes, and a diminished ability of the uterus to sustain pregnancy.[12] Additionally, the ovaries of aging rabbits may exhibit a

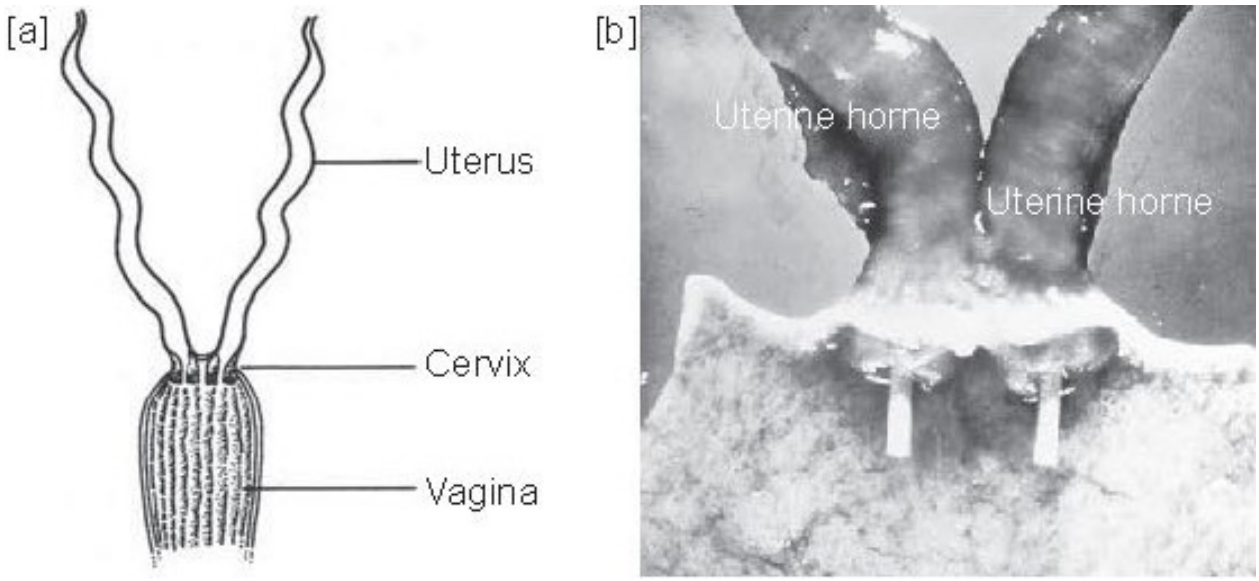

Figure 2. a) Illustration of the duplex cervix in rabbits. b) Anatomical view demonstrating the double cervix structure in rabbits.7

reduced capacity to produce steroid hormones, and the hypothalamic-pituitary-gonadal axis function within the reproductive system likely diminishes.[13,14]

4. Sexual cycle in female rabbits

Reproduction is a complex physiological process that necessitates coordinated interactions between males and females. The estrous cycle is intricately linked to the endocrine system, with reproductive hormones functioning as chemical messengers that orchestrate the coordinated activity of various systems and organs.[5]

4.1. Hormonal mechanism

Unlike many other species, rabbits exhibit a unique ovarian cycle, distinct from the classic estrous cycle.[3] Following puberty, follicle-stimulating hormone (FSH) secreted by the anterior pituitary gland stimulates the growth and development of follicles within the ovaries. Follicular development typically occurs in waves, with each ovary containing 5 to 10 follicles at any given time in a similar stage of development. These follicles continuously begin development, ensuring a constant presence of follicles in various stages of maturity. Upon reaching maturity, a dominant follicle actively produces estrogen for approximately 12-14 days, facilitating the female's receptivity to mating. If ovulation does not occur after this period, these mature follicles degenerate, leading to a decline in estrogen levels and a resulting decrease in receptivity to mating. Approximately 4 days later, a new wave of follicles begins producing estrogen, and the female rabbit becomes receptive to mating once again. Consequently, female rabbits exhibit a cycle of approximately 16 to 18 days, characterized by a receptive period of 12-14 days followed by a non-receptive period of 4 days. The timing of this cycle can be highly variable due to individual differences, sexual stimulation, nutritional status, light exposure, and ambient temperature.[5,15–17]

With ovulation, luteinizing hormone (LH) is released from the anterior pituitary. This hormone surge triggers ovulation of one or multiple dominant follicles in one or both ovaries, typically around 10 hours after the onset of mating stimulation. Once the oocytes are released from the ovaries, LH stimulates changes in the remaining follicular cells, which rapidly develop into the corpus luteum. The corpus luteum begins actively secreting hormones known as progestins within three days of ovulation. Progestins are essential throughout pregnancy for the development of the embryo into a fetus. Their primary function is to inhibit uterine contractions and support nutrient production for the developing embryo and fetus. The corpus luteum starts actively secreting progestins within three days after ovulation and continues throughout pregnancy. Hormone production increases until approximately day 15 of pregnancy and remains high until the last week when it starts to decline. Although follicular development continues and some estrogen is produced throughout pregnancy, progestins suppress the female's receptivity to mating during gestation.[5,16,17]

4.2. Molecular control

The molecular regulatory mechanism of the estrous cycle in mammals is highly complex, involving a multitude of key genes and signaling pathways. Bone Morphogenetic Protein Receptor Type 1B (BMPR1B) expression in granulosa and theca cells is most prominent during follicular development and can be influenced by FSH and LH hormones.[18] Aromatase (CYP19A1) can regulate the estrous cycle by mediating reproductive hormone synthesis and follicular development through positive or negative feedback.[19,20] CYP1A1 is the most highly expressed in the ovaries during ovulation. It has been reported that this plays an important role in increasing estrogen hydroxylation and eliminating the negative feedback effect of estrogen on LH secretion, which plays a direct or indirect role in ovulation.[5,21]

4.3. Ovulation

Rabbits exhibit a unique reproductive feature known as induced ovulation, where ovulation in female rabbits does not occur before mating but only after copu-

lation or artificial stimulation. This phenomenon plays a significant role in rabbit breeding and can be utilized to enhance reproductive rates.[22] Unlike mammals with spontaneous ovulation, rabbits can be considered to be in continuous estrus as they display "stimulated" ovulation.[4] Therefore, it can also be stated that rabbits do not have a regular estrous cycle.[23] When a female rabbit is ready to mate, she perceives signals from the male rabbit through pheromones and hormones. These signals stimulate the pituitary gland, triggering the release of LH. Consequently, LH promotes the growth and ovulation of follicles ready for ovulation from the ovaries.[24,25] The mating stimulus initiates the ovulation process by causing an increase in LH via the elevation of Gonadotropin-releasing hormone (GnRH) due to physical stimulation of the genital tracts after copulation.[26] It has been reported that LH is particularly essential for initiating ovulation in rabbits.[24,25] Ovulation occurs 10-13 hours after mating, while 20-25% of cases experience ovulation failure,[26] which is a primary factor in rabbit infertility.[15,27,28]

4.4. Corpus luteum and luteolysis

The corpus luteum (CL) is a transient endocrine gland that supports pregnancy by secreting progesterone for a limited period. In rabbits, the CL has a prolonged lifespan during pregnancy. The CL is comprised of distinct cell types with varying morphologies and biochemical functions.[29–31] These cell types are primarily classified into two groups based on size: large and small luteal cells. Additionally, vascular cells are present, including endothelial cells, erythrocytes, leukocytes, and fibroblasts. The formation of the CL (lutealization) occurs from post-ovulatory follicles. This process involves angiogenesis and tissue remodeling under the influence of various angiogenic factors, including Vascular Endothelial Growth Factor (VEGF), Transforming Growth Factor Alpha (TGF-α), and Fibroblast Growth Factors (FGFs). The CL acts locally in a paracrine/autocrine manner with different luteotropic hormones such as LH, estradiol-17α, and PGE2. The age of the CL affects the balance between factors promoting its function (luteotropic) and those leading to its regression (luteolytic). In early pregnancy, luteotropic hormones are dominant, and the CL continues to produce progesterone. Later in pregnancy, luteolytic factors become dominant, leading to CL regression and breakdown.[29,30]

Luteolysis is a simplified process involving functional and structural alterations that culminate in the complete elimination of the CL via apoptosis. The luteolytic mechanism plays a pivotal role in reproductive physiology, as it dictates the length of the estrous cycle in species with spontaneous ovulation.[31,32] This mechanism is also significant in rabbits. If fertilization does not occur or implantation fails, luteal regression will ensue, leading to the cessation of CL and, consequently, progesterone secretion. In rabbits, luteolysis commences on day 14 of the luteal phase in cases where pregnancy is not established and is completed around day 18, when progesterone levels drop to baseline. Luteolysis encompasses a series of functional and structural changes culminating in the involution and elimination of the CL via apoptosis.[32]

Corpus luteum (CL) regression in rabbits, as in many other species, is primarily driven by the luteolytic factor PGF2α.[33] The response of rabbit CL to PGF2α has been studied extensively both in vivo and in vitro at different stages of the estrous cycle, demonstrating that the response to PGF2α varies depending on the day of the cycle. For example, CLs on day four of the luteal phase are resistant to PGF2α at this stage.[33,34] The down-regulation mechanisms activated after exogenous PGF2α administration in rabbits are still under investigation.[35–37] After binding to specific PGF2α binding sites (FP), PGF2α activates G protein-coupled PLC/PKC pathways, leading to the breakdown of phosphatidylinositol into DAG and IP3, an increase in intracellular Ca2+ stores, and phosphorylation of transcription factors. Consequently, depending on the luteal phase (early, mid, or late), several genes are either down- or up-regulated, modifying the responses of different luteal cell types, leading to either the maintenance of CL or the initiation of apoptosis. While exogenous PGF2α treatment has been used routinely for many years to control breeding in farm animals, its application in rabbits is much more limited. This is due to the different estrous stages of rabbits. Therefore, while PGF2α-induced CL regression can be used for estrus and ovulation synchronization in farm animals, in rabbits, this luteolytic mechanism only plays a role in pseudopregnancy or late pregnancy.[38]

Luteolysis, the process of CL regression, involves the stimulation of various vasoactive agents alongside PGF2α. These agents include nitric oxide (NO), apelin-apelin receptor, angiotensin II (Ang II), endothelin-I (EDN-I), oxytocin, and tumor necrosis factor alpha (TNF-α).[29,39] NO, synthesized in the ovaries via NO synthase, enters the luteal circulation. It is released from the CL during spontaneous luteolysis or PGF2α injection, leading to increased luteal blood flow. Apelin-apelin receptor expression increases during the luteal phase, promoting NO synthesis and augmenting peripheral blood flow in the CL. EDN-I exerts a vasoconstrictive effect, causing a decrease in CL volume and a significant drop in P4 levels. Oxytocin, synthesized by large luteal cells in the CL, induces a vasoconstrictive effect. TNF-α is released from the CL during the late luteal phase and plays a role in apoptosis.[40–42]

4.5. Season

The estrous cycle in female rabbits is a hormonally regulated cycle that encompasses proestrus, estrus, metestrus, and diestrus. This cycle can be influenced by environmental factors, such as light and temperature, and internal factors, such as the rabbit's age and breed.[4,43] A study investigating seasonal variation in estrous behavior in female rabbits observed significant changes. The study reported that only 15% of female rabbits exhibited estrous behavior in October, while this percentage increased to 80% between April and July.[4]

4.6. Stages of the estrous cycle and estrus detection

The estrous cycle in rabbits can be divided into four distinct phases: diestrus, proestrus, estrus, and metestrus. The differentiation of these stages relies on several parameters, including the condition of the vulvar mucosa, changes in the vaginal epithelium, and behavioral alte-

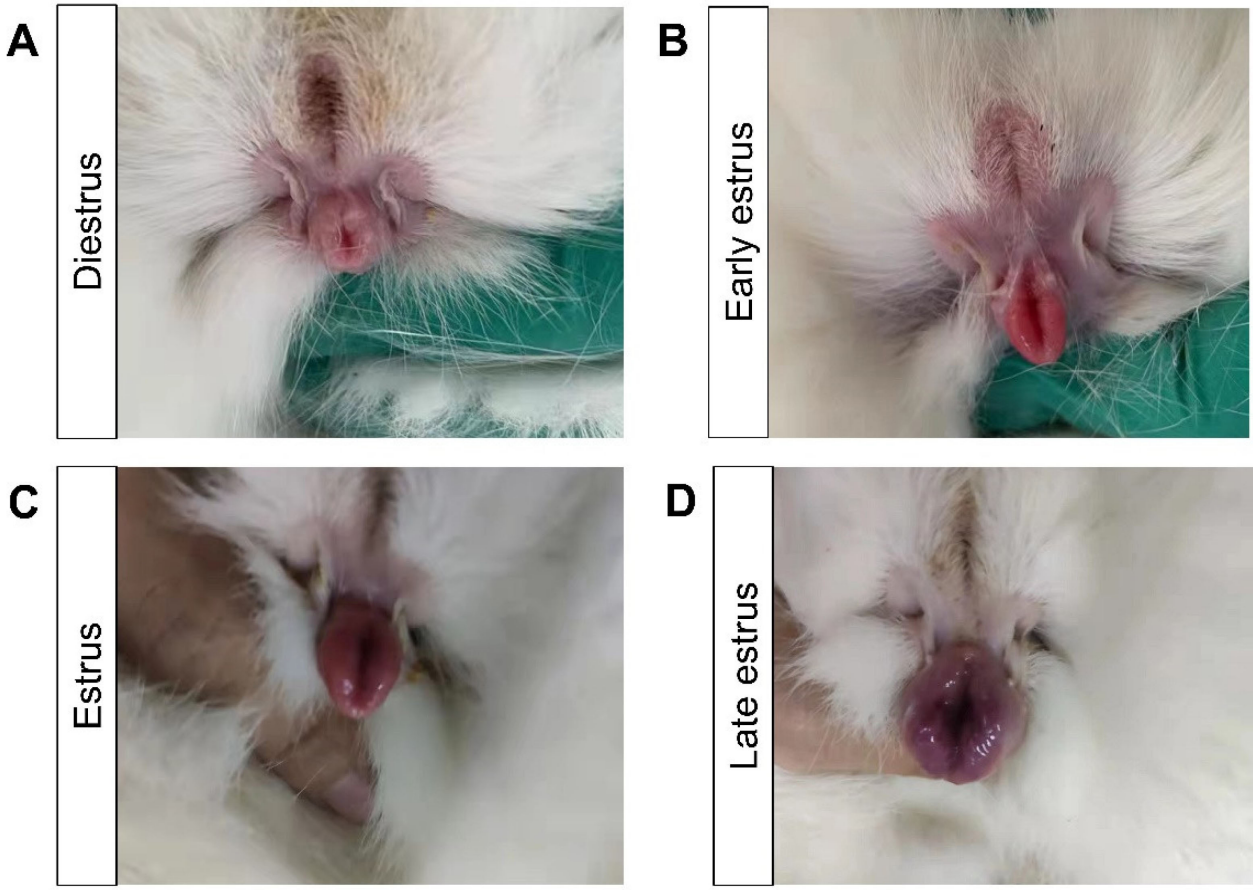

Figure 3. Vulvar mucosa appearance in different stages of the estrous cycle in rabbits. A) Diöstrus: Vulva is pale and dry, with a tightly closed ostium. B) Early Estrus: Vulva is slightly swollen and pink, with a slightly opened ostium. C) Mid-Estrus: Vulva is red, swollen, and moist, with a widely opened ostium. D) Late Estrus: Vulva is beginning to regress, with a decreasingly swollen and moist appearance.[5]

rations.[44] The state of the vulvar mucosa provides valuable insights into the specific phase of the estrous cycle. For instance, a rabbit with a moist, red or pink vulva is significantly more receptive to mating compared to a rabbit with a pale, dry vulva (Figure 3).[5]

During the estrous cycle of mammals, the vaginal epithelium undergoes characteristic changes that can be detected by vaginal cytology and used to indicate the stage of the cycle. However, some authors argue that these changes do not occur in rabbits and that vaginal cytology is unreliable for determining the physiological status of the estrous cycle.[45] Other authors, however, have reported that estrous cycle staging can be performed in rabbits using vaginal cytology, similar to other species.[46]

In rabbits, vaginal cytology, similar to other species, serves as a valuable tool for monitoring the estrous cycle stage. Analysis of epithelial cell types within vaginal smears reveals cyclical variations. These cell types include: parabasal cells (round or oval with a large nucleus-to-cytoplasm ratio), intermediate cells (round, oval, or polygonal with a normal nucleus), superficial cells (polygonal with a pyknotic nucleus), and anucleate cells (cornified epithelial cells lacking a nucleus and exhibiting clear cytoplasm). During estrus, the period of receptivity to mating, superficial cells dominate the vaginal cytology. Conversely, diestrus, characterized by sexual inactivity, is reflected by a predominance of parabasal cells with a minor presence of intermediate cells. Additionally, other cell types, such as leukocytes, erythrocytes, and bacteria, may be observed in vaginal smears.[46,47]

The estrous cycle of female mammals is characterized by distinct behavioral changes that provide insight into the underlying hormonal fluctuations.[48] During estrus, a female rabbit exhibits lordosis, a characteristic posture where the back is arched downward, and the hindquarters are elevated (Figure 4).[49] In contrast, a female rabbit in diestrus may exhibit behaviors such as crouching in a corner of the cage or displaying aggression towards the male. It is generally accepted that receptivity to mating occurs during estrus and is rejected during diestrus.[1]

Transferring the female rabbit to the male's cage instead of introducing the male into the female's cage can lead to more successful mating. When a male rabbit is introduced to the female's cage, she often displays aggression and rejects mating attempts.[1,28] Additionally, a doe in estrus experiences decreased appetite, restlessness, and engages in various activities such as sniffing around, nest building, grooming, and biting. A typical behavior observed in female rabbits is the active deposition of scent marks by touching the buck and rubbing objects with their chin. The mechanism and function behind this behavior have been studied by ethologists and biologists for a long time. During this process, the female approaches the male and rubs her nose against his nose or genital region. She also deposits scent marks by

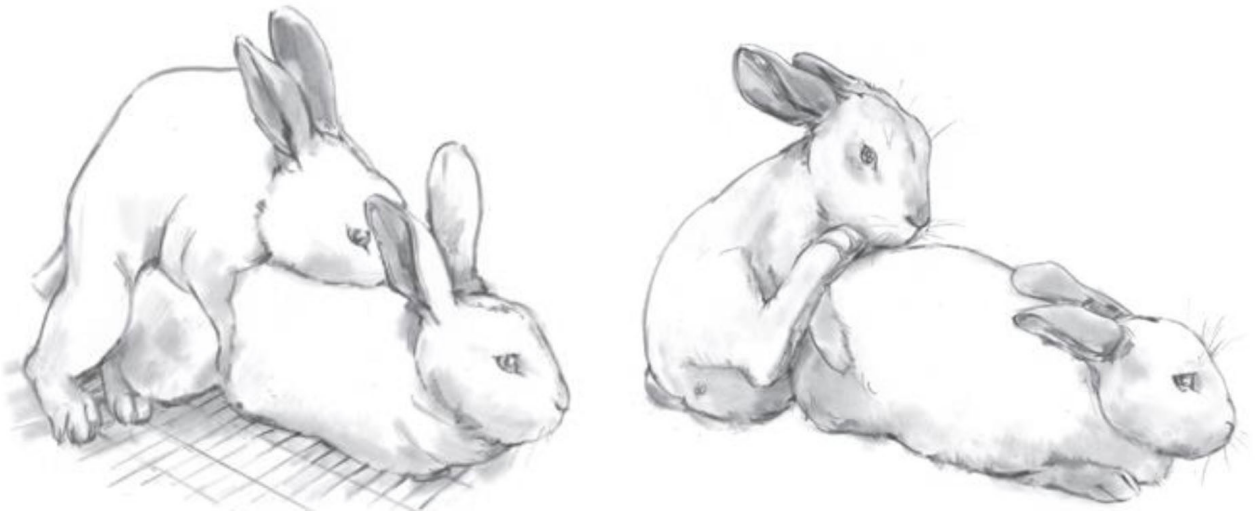

Figure 4. Mating behavior in rabbits.[49]

rubbing her chin on the ground, walls, or other objects. These secretions contain chemicals called pheromones, which transmit various messages to other rabbits.[48,50,51]

5. Conclusion

In conclusion, the reproductive system of rabbits exhibits distinct characteristics compared to other mammals, rendering their reproductive biology, breeding practices, and management strategies unique. Rabbits stand out due to specific features such as irregular estrous cycles, ovulation dependent on stimuli, and an extended estrus phase, emphasizing the uniqueness of their reproductive biology. Recognizing these characteristics, breeders should meticulously plan their breeding programs and diligently monitor the reproductive cycles of female rabbits. In-depth research and detailed investigations will significantly contribute to a more profound understanding of the rabbit reproductive system and the development of more effective methods in rabbit breeding.

Ethical approval

This study does not require approval from the Ethics Committee for Animal Experiments.

Authors contribution

MSK, BBK, and MK: Research, planning, article scanning, wri-ting-original draft & review. All authors contributed to the article and gave final approval of the version to be submitted.

Conflict of interest

There are no conflicts of interest associated with this re-search publication, according to the authors.

Data availability

The data that support the findings of this study are ava-ilable from the corresponding author upon reasonable request.

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