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«Review»

A Bird's-Eye Overview of Leptin and Female Reproduction —with Mammalian Comparisons

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Leptin, a key regulator of reproductive physiology, influences various processes in vertebrates, including oocyte proliferation, embryogenesis, the onset of puberty, ovarian function, and follicle development. In mammals, leptin affects steroidogenesis, folliculogenesis, and hormonal regulation through the hypothalamic-pituitary-gonadal axis. Instead, in avian species, leptin-controlled mechanisms are poorly understood, because birds do not produce leptin in adipocytes. In birds, leptin is expressed in the brain, pituitary glands, and gonads, where it enhances ovarian function and egg-laying performance, particularly during feed deprivation. In this review, we discuss and summarize the recently discovered role of leptin in regulating ovarian function during different life stages in birds and compare it with its function in mammals.

Key words: birds, leptin, mammals, ovary, reproduction

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Introduction

Reproductive physiology is a complex and tightly regulated process in vertebrates, which involves interactions between internal and external factors. Hypothalamic-pituitary-gonadal (HPG) axis hormones and nutritional intake or available energy are the most important determinants of reproductive function. In females, gametogenesis, sexual maturation, mating, gestation, parturition, milking, and parental care rely heavily on the availability of energy and adequate nutrition to support successful reproduction[1,2]. Both insufficient and excessive nutritional intake negatively influence reproductive processes in vertebrates[3–5]. Feed intake is controlled by available nutrients, the gastrointestinal tract, and the central nervous system, which regulates orexigenic (appetite–suppressing) and anorexigenic (hunger-inducing) peptides[6–8]. Leptin, an anorexigenic peptide hormone, regulates not only food intake but also ovarian development and reproduction in mammals[9,10]. Discovered initially in humans in 1994, this hormone is synthesized predominantly in adipocytes and circulates in the blood, giving an estimate of total fat mass[11–13]. Studies in rodents and humans have revealed that leptin is also expressed in the hypothalamus, pituitary gland, endometrium, stomach, testes, placenta, mammary glands, and ovary[14–20]. In contrast to mammals, the physiological roles and mechanisms of action of leptin in avian species remain poorly understood. The discovery of an avian leptin gene occurred two decades after its mammalian homologue had been identified; the delay was due primarily to the gene's elevated guanine-cytosine content (~70%). In 2014, it was characterized in zebra finches[21], ducks[22], and rock doves[23], followed by Japanese quails[24] and chickens[25]. Interestingly, leptin is not produced in bird adipocytes and is not detected in circulating blood[26,27]. Instead, leptin and its receptors are co-expressed in the brain (cerebellum and hypothalamus), pituitary gland, adrenal glands, and gonads[21,23,25,27–29], suggesting an autocrine/paracrine action mechanism. In birds, the leptin receptor is expressed in exceptional amounts in the pituitary gland compared to other tissues, which may enhance the response to pituitary leptin[25,27]. In mammals and birds, leptin binds to its receptor, the product of the *Lepr* gene, to activate the Janus kinase (JAK) and signal transducer and activator of transcription (STAT)3 and STAT5[30–32]. Mitogen-activated protein kinases (MAPKs), phosphatidylinositol 3 kinase/serine-threonine kinase and protein kinase C are also activated by leptin[30,33,34]. The leptin feedback mechanism, which decreases leptin sensitivity by activating the suppressor

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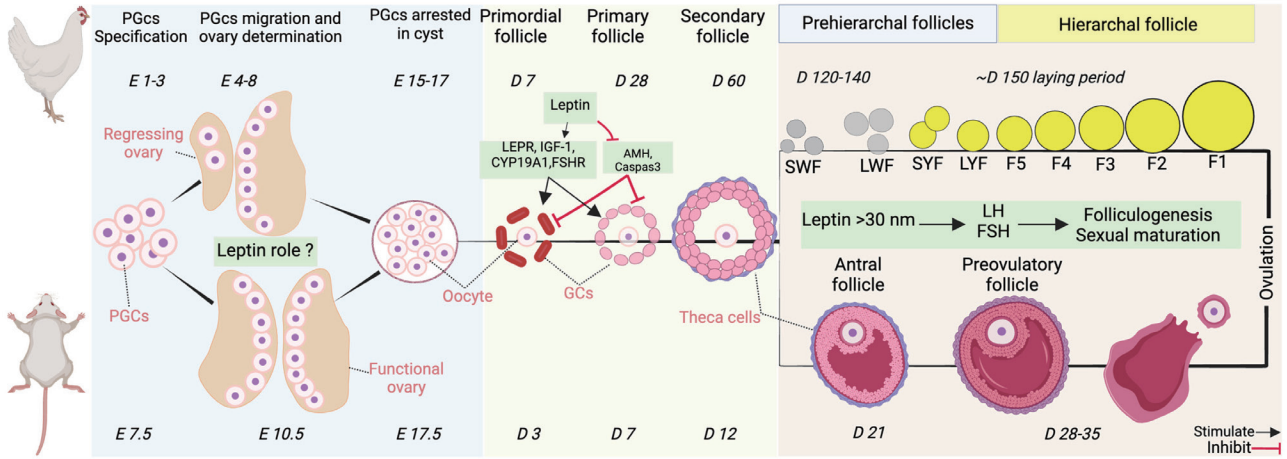

Fig. 1. **Schematic representation of ovarian development and folliculogenesis in birds (chickens) and mammals (mice).** After specification, primordial germ cells (PGCs) migrate to the gonads on embryonic days (E) 1–3 in chickens and E7.5 in mice. The gonads then differentiate into testes or ovaries on E4–8 in chickens and E10.5 in mice, followed by the differentiation of PGCs into oocytes. The oocytes are then arrested in cysts until hatching or birth. Up to this age, the role of leptin has not been well-defined in either mammals or birds. In chickens and mice, the initial wave of primordial follicles appears around day (D) 7, followed by a similar process that produces primary and secondary follicles with different time frame intervals. At this point, leptin alters several genes essential for follicle activation in chickens. Late folliculogenesis differs significantly between birds and mammals. In chickens, the secondary follicles develop into small white follicles (SWF), large white follicles (LWF), small yellow follicles (SYF), large yellow follicles (LYF), hierarchical follicles (F5–F1), and finally, ovulate. In mice, late folliculogenesis progresses through antral follicles, preovulatory follicles, and ultimately mature follicles ready for ovulation. During puberty in mammals and birds, leptin acts via the luteinizing hormone (LH) and follicle-stimulating hormone (FSH), affecting folliculogenesis. GCs, granulosa cells; IGF-1, insulin-like growth factor 1; CYP19A1, aromatase; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; FSHR, follicle-stimulating hormone receptor. Created with BioRender.com, accessed on 18 October 2024.

of cytokine signaling 3, is conserved between mammals and birds[35].

Besides regulating body weight in response to fat accumulation, leptin conveys also metabolic signals to the brain and activates the HPG axis genes, thus influencing reproductive functions in adult mammals[9,36]. In contrast, its roles in avian reproduction and early folliculogenesis in mammals remain unclear. This review summarizes current knowledge on the role of leptin in female reproduction in birds, focusing on its effects on early folliculogenesis and corresponding ovarian development. Understanding the function of leptin in poultry, especially in layer and broiler parent stock chickens, is critical for optimizing global meat and sustainable egg production.

Ovarian follicle development in birds

Ovarian development involves the transformation and growth of primordial germ cells (PGCs) into primordial, primary, secondary, antral, and preovulatory follicles, as well as subsequent ovulation. This process has been well studied in mammalian species and is reviewed extensively elsewhere[10,37,38]. Bird ovarian development will be briefly explained to understand the role of leptin in the specific timing of folliculogenesis. Except for birds of prey, most bird species exhibit asymmetric gonadal development, in which only the left female gonad develops into a functional ovary; whereas the right gonad regresses owing to apoptosis (Fig. 1)[39,40]. Gonadal development is initiated at an early stage of embryogenesis. In chicken gonads, PGCs are located mainly in the central region of the embryo during intrauterine embryonic development and move passively toward the anterior region during morphogenesis. PGCs then enter blood vessels and circulate in the blood from embryonic day (E)2. During E3–E3.5, circulating PGCs enter the genital ridge and ultimately form and colonize the cortical and medullar cords[41,42]. In chicken gonads, PGCs proliferate and differentiate into oogonia (at about E8.0), followed by sex determination and oogonia growth until the first meiotic arrest[43,44]. Cells are arrested in meiotic prophase I as primary oocytes starting at E15.5. The number of germ cells derived to the ovary via blood circulation gradually increases and peaks at approximately 680,000 by E17. At this time, chicken ovaries exhibit a mixture of oocytes at various stages of meiotic prophase I, with the highest number of pachytene-stage oocytes observed around hatching. Although not fully understood, oocytes arrested in meiosis and accumulated in germ cell cysts have been reported at least one day and up to four weeks post-hatch. The number of oocysts gradually decreases until hatching because of apoptosis[45–48]. Within the first week of

hatching, a sharp increase in follicle-stimulating hormone receptors (FSHR) triggers the development of primordial follicles. By one week of age, the chick ovary exhibits a well-defined germinal epithelium, cortex, and medulla[49]. Folliculogenesis is initiated by the breakdown of germ cell cysts and the enclosure of oocytes by a single layer of flattened pregranulosa cells called primordial follicles[50]. Primordial follicles, approximately 0.05 mm in diameter, are located mainly in the cortex, organized in clusters, and most remain dormant until sexual maturation. Up to four weeks of age, primordial follicles transition to primary follicles while flat and elongated granulosa cells (GCs) differentiate into cuboidal GCs and enclose the oocytes. Afterward, the secondary follicles differentiate, with oocytes surrounded by both granulosa and theca cells[51,52]. At this stage, follicles lack an antrum or follicular fluid, protrude from the ovarian surface, and are classified by developmental stage and size into pre-hierarchical follicles (small white: 1–4 mm, large white: 4–6 mm, small yellow: 6–8 mm) or preovulatory hierarchical follicles (large yellow: 9–40 mm)[46,53,54]. An oocyte that has matured from the largest yolk-filled hierarchical follicle is expelled into the infundibulum of the chicken oviduct. The released egg is surrounded only by the perivitelline layer, which is similar to the mammalian zona pellucida[55]. Oocytes are constantly arrested during meiotic prophase I of follicular development, but resume oogenesis a few hours before ovulation, when oocytes become fully grown. Then, they are arrested again in the metaphase of meiosis II until ovulation, akin to mammalian oocyte maturation[55–57].

Role of leptin during embryonic ovarian development in mammals and birds

Leptin plays a crucial role in the embryonic development. It also influences early oocyte maturation and supports nutrient transport and embryonic growth. Herein, we discuss the effects of leptin on these processes in mammals and birds.

Mammalian embryos and leptin

In mammals, the placenta is another significant source of leptin during pregnancy[58]. Leptin synthesis and circulation during pregnancy are influenced by genetic factors, hormones, and nutrition. Leptin produced by the placenta facilitates the transport of nutrients, particularly neutral amino acids and free fatty acids, from the mother to the fetus, thereby supporting growth and development[59,60]. *In vitro* studies have indicated that this adipokine improves oocyte maturation and overall embryonic development by reducing apoptosis and degradation of oocytes and cumulus cells, enhancing ovarian angiogenesis, and promoting fatty acid oxidation[61]. Addition of leptin to the embryo culture medium promotes transition from the 2-cell stage to hatched blastocysts in both mice and humans. The same process is significantly inhibited by blocking the leptin receptor. Leptin also increases the number of cells within blastocysts, especially in the trophectoderm, suggesting a paracrine effect that may influence ovarian development[62–64]. However, exposure to higher doses of leptin, such as those found in obese individuals, can negatively affect embryo development, reduce hatching rates, and increase apoptosis in a dose- and stage-dependent manner[65,66]. A study on obese women undergoing *in vitro* fertilization revealed that higher circulating leptin levels were associated with increased follicular fluid leptin, which resulted in low-quality embryos and a low pregnancy rate. The same study revealed that a higher leptin dose inhibited the proliferation of GCs, which is essential for oocyte maturation, and promotes apoptosis[67]. Consequently, higher leptin levels in obese mothers adversely affect reproductive outcomes. In pigs, *Lepr* polymorphisms are associated with lower oocyte quality, decreased ovulation rates, and early embryo loss due to failed implantation[68]. In bovine studies, leptin treatment during oocyte maturation enhanced developmental potential, resulting in increased blastocyst formation and fewer apoptotic cells, suggesting that leptin may have long-term effects on genes crucial for early embryonic development[69]. Changes in leptin levels at any critical time point during embryonic development may affect future reproductive outcomes[70]. Mouse models indicate that leptin influences the development and function of fetal hypothalamic networks and alters the regulation of appetite and metabolism in adulthood[71,72]. Overfeeding in pregnant ewes affected the plasma leptin concentration in the offspring at birth and was suggested to have a prolonged impact on growth and metabolism[73]. A maternal high-fat diet also impairs leptin signaling in the offspring and negatively affects ovarian development[74,75]. The direct effect of leptin on embryonic ovarian development and its prolonged impact on puberty are yet to be clarified in most mammalian species, including humans. Therefore, further studies are needed to elucidate the direct and long-term effects of maternal leptin or high-fat diet-induced hyperleptinemia on the ovaries of adult individuals. Overfeeding alters plasma leptin levels and the mRNAs of genes related to the growth of follicles in the fetus, including growth differentiation factor-9, alpha-1-antitrypsin, alpha-fetoprotein, and apoptotic markers[75]. Hence, leptin plays a vital role in embryonic ovarian development in mammals by influencing oocyte maturation, blastocyst formation, and gene expression, with potential long-term reproductive consequences.

Avian embryos and leptin

Leptin and its receptor are expressed during early embryonic development in bird gonads, suggesting a potential role for leptin signaling at that stage[25,40]. As in mammals, leptin boosts embryonic growth in birds with long-term consequences. *In vitro* leptin stimulation enhances embryonic muscle cell proliferation in a dose- and age-dependent manner[76]. Administration of leptin to fertile eggs affects thyroid hormones and enhances embryonic and post-hatch growth in Japanese quail[77], possibly because of the improved utilization of nutrients, gas exchange, and angiogenesis during embryogenesis. Leptin treatment of chicken embryo chorioallantoic membranes enhanced endothelial cell proliferation and capillary network formation in a dose-dependent manner by increasing the expression of angiogenic markers, including vascular endothelial growth factor 165 and matrix metalloproteinase 2[78]. Furthermore, *in ovo* leptin injection enhances total and free triiodothyronine serum levels, which

boost post-hatching body weight in a sex-specific manner in broiler chicks[79]. A recent study from our group demonstrated that the administration of leptin on the third day of incubation in broiler eggs increased pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH) mRNA expression in 7-day-old chicks. This increase in LH and FSH may trigger primary follicle activation, as observed in post-hatching birds fed a low-protein diet until day 28. However, the same study revealed no changes in follicle numbers in birds injected with leptin *in ovo* and fed a higher-protein diet[80], suggesting that nutritional intake might counteract the stimulatory effects of leptin and ovarian growth in birds. Our unpublished observations showed that *in ovo* leptin injection induced aromatase mRNA expression in female gonads of 7-day-old chick embryos. Further studies will determine whether follicular growth induced by *in ovo* leptin injection advances sexual maturation and egg productivity in chickens. Additionally, egg whites contain several bioactive polypeptides that are highly resistant to thermal denaturation[81]. Leptin is also a polypeptide, but it is unknown whether it is naturally produced in egg whites by laying hens. The leptin receptor, for example, is expressed in the oviducts of laying hens[82]. Establishing a leptin protein detection method for birds would answer several questions. At present, evidence emphasizes the pivotal role of leptin in avian embryogenesis via its influence on nutrient utilization, angiogenesis, and ovarian development as well as its long-term effects on post-hatching growth and follicular development. Additional studies are required to better understand the role of embryonic leptin in sexual maturation and egg production across various bird species, particularly commercial chicken breeds.

Role of leptin in ovarian development of juvenile mammals and birds

Leptin in early mammalian ovaries

In the mammalian ovaries, follicle formation begins immediately before or shortly after birth. These primordial follicles progress through several differentiation stages into primary follicles, preantral (secondary) follicles, antral (tertiary) follicles, and finally maturation into preovulatory Graafian follicles (Fig. 1). These transitions are regulated by the coordinated actions of hormones and intraovarian factors, including leptin[83,84]. In mammals, leptin is essential for reproduction because leptin-knockout mice are sterile, and leptin injection restores reproductive development[85,86]. After birth, plasma leptin levels increase in mice and are thought to promote the growth and development of several organs, including the ovaries, because the leptin receptor is expressed in neonatal mammalian ovaries and ovarian germ cells[87–89]. Leptin surges are pivotal for the overall growth and development of neonatal mammals. The peak of the postnatal leptin surge depends on maternal nutrient status and is not associated with increased fat mass, appetite control or feed regulation[90]. This surge has lifelong effects on the metabolism of the offspring because leptin can restore maturation and development in mice only when administered during the neonatal period[91–93]. The postnatal leptin peak on day 7 was associated with increased expression of the gonadotropin-releasing hormone receptor, FSH, and activin in mice[94–97]. A recent study in mice demonstrated that the female offspring of mothers subjected to 20% caloric restriction anticipated the postnatal leptin peak from day 11 to day 8 and delayed the onset of puberty, which was indicated by a later vaginal opening compared to the control group[98]. Accordingly, maternal caloric restriction negatively influenced embryonic and neonatal development, caused a shift in leptin levels, and reduced body weight in adulthood. Nonetheless, it remains unclear whether delayed puberty is caused by maternal caloric restriction or a change in the leptin surge, and the exact factors controlling the latter remain unidentified. Leptin administration stimulates oogonia and oocyte growth, and increases the number of primary follicles in piglets with intrauterine growth restriction, a disorder marked by developmental delays and an increased risk of adverse neonatal outcomes[88]. Leptin receptors have also been identified within ovarian germ cells, indicating that leptin may directly influence these cells and support ovarian development. Neonatal overfeeding in rats elevated plasma leptin levels and induced weight gain, which led to increased ovarian leptin, leptin receptor, and FSHR transcripts, but downregulation of anti-Müllerian hormone (AMH) mRNA, resulting in early sexual maturation and fewer primordial follicle pools in adulthood[99]. According to these findings, an early leptin surge may affect postnatal ovarian development and the effect may persist throughout adulthood. Further studies will shed light on the regulation of leptin in normal neonates and, hence, the transition of early growing follicles, as well as on how leptin mediates its effects and interacts with pathways essential for mammalian folliculogenesis[100].

Leptin in avian hatchling ovaries

Figure 1 illustrates the growth of bird follicles after hatching. A few studies on juvenile chickens have demonstrated the effects of leptin on primordial growth and ovarian development. Leptin and its receptor are expressed in the ovaries of post-hatching chicks and are altered by exogenous leptin treatment. This supports the idea that leptin is a local mediator in bird ovaries[25,28,101]. Our studies on 7-day-old layer chicks demonstrated that 24-h intraperitoneal mouse leptin injection significantly augmented the mRNA levels of ovarian growth markers, including leptin receptor, FSHR, aromatase, and insulin-like growth factor 1 (IGF-1), which led to elevated serum estradiol levels[28,101]. In addition, leptin treatment downregulated the apoptotic marker caspase-3 while increasing the number of primordial follicles. We hypothesize that leptin may exert its effects on the ovary directly and/or by regulating local IGF genes, as it influences the expression of IGF-1 and that of its receptors insulin-like growth factor-binding protein (IGFBP) 2 and IGFBP5. Stimulation of IGF-1 by leptin is particularly significant in birds, where hepatic IGF-1 may not contribute as much to ovarian development as the locally expressed IGF-1. This is supported by our findings that leptin administration does not influence hepatic IGF-1 in chickens *in vivo* or *in vitro*[28], and that local IGF-1 regulates GC proliferation and ovarian development in an autocrine-paracrine man-

ner[102]. This hypothesis is further reinforced by the observation that sex-linked dwarf chickens remain fertile despite lacking the growth hormone receptor, because their ovaries produce more IGF-1 than their normal counterparts[103,104]. In layer chicks, follicular activation by leptin may also result from the direct suppression of AMH by leptin or via synergistic stimulation with IGF-1, both *in vivo* and *in vitro*[28]. Given that AMH is highly expressed in the ovary during early folliculogenesis, it inhibits GCs proliferation, aromatase activity, and follicle growth by decreasing FSHR sensitivity to FSH[105,106]. Direct stimulation with IGF-1 also inhibits AMH expression, which leads to GC proliferation and primordial follicle formation[107]. Although early follicular growth (preantral) in mammals is gonadotropin-independent, intraovarian growth factors, such as apoptotic markers AMH and IGF-1, play a role in its development[108]. In chickens, a sharp rise in serum gonadotropin levels and its receptor, FSHR, which is enhanced by leptin, is associated with ovarian development post-hatching[109]. We reported that leptin administration induced gonadotrophin expression, leading to elevated serum estradiol levels and subsequent formation of primordial follicles[28,80,101]. In conclusion, these studies highlight the known positive role of leptin in early follicle development in post-hatch layer chicks, either directly or synergistically with intraovarian growth factors (Fig. 2).

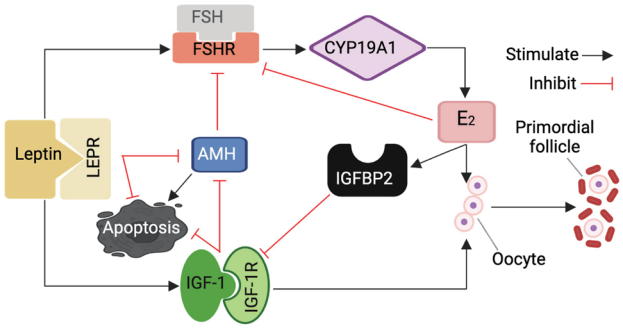

Fig. 2. **Direct effect of leptin on chicken primordial follicle activation. In early ovarian development (7-day-old chicks), leptin regulates ovarian function in birds through its receptor (LEPR), impacting key pathways involved in follicular development.** Leptin upregulates follicle-stimulating hormone receptor (FSHR) and aromatase (CYP19A1) mRNA, resulting in increased serum estradiol (E_2) and primordial follicle activation. Leptin upregulates also ovarian insulin-like growth factor 1 (IGF-1), which is necessary for granulosa cell growth and follicle development. Both leptin and IGF-1 downregulate anti-Müllerian hormone (AMH) and apoptosis, reducing atresia and promoting follicular survival. As a negative feedback mechanism (based on mammalian studies), E_2 directly inhibits FSHR expression and increases mRNA levels of IGF-1 binding protein (IGFBP) 2, which inhibits IGF-1 binding to its receptor (IGF-1R). Increased AMH inhibits primordial follicle activation by decreasing FSHR sensitivity to FSH, further preventing follicle activation and ovarian development in birds. Created with BioRender.com, accessed on 18 October 2024.

Role of leptin in the ovary during sexual maturation and adulthood

Leptin in ovarian maturation in mammals

Most studies on leptin have focused on its role during sexual maturation and adulthood[110], rather than during embryonic or neonatal stages. This bias is rooted mainly in the pathophysiological impact of leptin on human health and reproduction[10,111,112]. Ovaries from adult mammals express high levels of *Lepr* mRNA, suggesting a direct role of leptin in ovarian function[113–115]. Leptin levels rise at night during pubertal development in young female mice; during this stage, leptin injections also advance sexual maturation[116,117]. Leptin levels are increased also during the menstrual cycle, with a mid-cycle peak associated with higher LH and estradiol amounts, suggesting that leptin is involved in ovulation[118]. Leptin is produced by adipose tissue, targets the HPG axis, and stimulates the reproductive system through neurons in the ventral premammillary nucleus. These neurons, in turn, activate kisspeptin neurons, leading to gonadotropin-releasing hormone stimulation and subsequent regulation of LH and estradiol levels. This function of leptin is crucial for the onset of puberty, maintenance of estrous cycles, and fertility in females[119,120]. *In vivo* and *in vitro* studies have shown that leptin influences pituitary gonadotrophs, modulates LH and FSH secretion, and affects the reproductive hormone balance and ovarian function[121–124]. Given that increased leptin levels due to higher fat mass result in HPG axis activation and precocious puberty, leptin acts as a gatekeeper hormone for the onset of puberty[125,126]. Conversely, reduced leptin signaling during low-energy states or energy deprivation triggers suppression of the HPG axis and delays sexual maturation[126,127].

Furthermore, leptin plays a dual role in ovarian function, acting as a stimulator and an inhibitor depending on its concentration. Previous studies using high leptin levels (>30 ng/mL) in obese patients with polycystic ovarian syndrome (PCOS) led researchers to propose that leptin had an inhibitory effect on the ovaries[128,129]. Indeed, leptin concentrations associated with obesity suppress mammal steroidogenesis, follicular growth, and oocyte maturation *in vitro*[128,130]. Recent studies have challenged this view by demonstrating that the role of leptin in the ovary is dose-dependent[33,131,132]. Leptin enhances ovarian function at physiological levels (10–20 ng/mL), stimulates granulosa and theca cell proliferation, and acts synergistically with LH and FSH to promote follicular development, ovulation, and oocyte maturation[69,131]. A lower leptin concentration increases steroid hormone production, improves oocyte maturation rates, and stimulates germinal vesicle breakdown in mammalian ovaries[133,134]. Leptin affects cumulus cell mRNA expression and improves *in vitro* maturation of goat oocytes through the MAPK and JAK2/STAT3 pathways[135]. A recent study revealed that mice fed high-carbohydrate and high-protein diets

had elevated leptin, as well as increased FSH, LH, estradiol, and progesterone, serum levels. The intensified folliculogenesis may be attributed to upregulation of ovarian growth markers, including bone morphogenetic protein 15 and growth differentiation factor-9, along with an increase in the above hormones[136]. These findings emphasize the essential role of leptin in regulating folliculogenesis, oocyte maturation, and female reproductive hormones in both premature and adult animals. These effects are dose-dependent: physiological levels stimulate ovarian growth; whereas higher levels, which are common in obese individuals, hinder these processes.

Leptin during ovarian maturation in birds

In birds, leptin has emerged as a significant regulator of ovarian function, influencing reproductive hormone levels, follicular growth, and sexual maturation, particularly in response to nutritional status and energy balance. Chronic leptin injection into prepubertal fasted pullets for 11 weeks decreased ovarian apoptosis and enhanced plasma LH, FSH, and steroid levels, thereby improving follicle growth and advancing sexual maturation[137]. The same study also detected leptin receptors in both granulosa and theca cells, indicating that leptin is an essential regulator of ovarian development. In newly hatched, prepubertal, and adult bird ovaries, the leptin receptor mRNA expression changes with nutritional status, thereby affecting follicle development[80,137–139]. In adult birds, leptin enhances ovarian development and egg laying. Leptin injections have been shown to restore ovarian function in ducks that experience regression due to fasting, by upregulating ovarian FSHR and LH receptor mRNA, increasing plasma estradiol levels, and improving follicle growth[140]. Similarly, leptin mitigates the adverse effects of fasting on ovarian function in laying hens by abolishing the effects of malnutrition on the ovaries, increasing estradiol levels, and improving ovulation[141]. These findings suggest that leptin plays a key role in regulating reproduction in response to nutritional status, helping maintain ovarian function during periods of energy deprivation in layer-type chickens[142]. In leptin receptor-immunized hens, the mRNA expression of ovarian LH receptor, FSHR, steroidogenic acute regulatory protein, IGF-1, and aromatase decreased; whereas leptin receptor and apoptotic markers, such as caspase-3 and Fas increased, resulting in follicle atresia and reduced egg production[143]. In addition, direct evidence of the role of leptin in the regulation of chicken ovarian function has been reported. In adult chicken GC cultures, leptin stimulation enhanced progesterone; whereas estradiol inhibited testosterone secretion into the medium, promoting the cells' proliferation[144]. This study also demonstrated that human leptin caused changes in MAPK/ERK1/2 accumulation in GCs. In another study using recombinant chicken leptin and goose GCs, leptin stimulation produced outcomes similar to those observed in chicken GCs, including increased progesterone, estradiol, and testosterone secretion, and enhanced proliferation[145]. This author further explored whether the effect of leptin in GCs was mediated by phosphoinositide 3-kinase, serine/threonine-kinase, and mammalian target of rapamycin pathways[146]. It is important to note that most studies on birds have used mammalian leptin, which influences leptin receptor expression and ovarian function across different life stages (Table 1) and shows effects on ovarian functions similar to those observed in mammals. Few studies have utilized the recombinant chicken leptin (Table 1), while the genuine chicken leptin gene was discovered later[25]. Although the effects of leptin have been comparatively well studied in layers, demonstrating regular follicular hierarchies, further research is required in broiler breeders that display an irregular follicle hierarchy and lower egg production. In conclusion, current studies using heterologous leptin, particularly in layer birds, indicate a significant role of leptin in reducing ovarian apoptosis, enhancing reproductive hormone levels, promoting folliculogenesis, advancing sexual maturation, and egg production. Except for appetite regulation, the effects of leptin on ovarian development in birds are consistent with those in mammals. Future studies should seek to develop and utilize endogenous chicken leptin, assessing how it affects bird reproduction across various life stages and species.

Conclusions and perspectives

Leptin is important for the regulation of ovarian function, follicle growth, and sexual maturation in vertebrates, particularly in response to nutritional changes. Typically, it acts as a gatekeeper for puberty and enhances the secretion of reproductive hormones, such as LH, FSH, and estradiol, while reducing follicle apoptosis. In mammals, the effects of leptin are dose-dependent, with physiological levels promoting ovarian function and higher levels potentially inhibiting it. However, studies on leptin levels in birds are limited. Research on layer-type birds has indicated that leptin enhances ovarian development, steroid hormone production, and egg laying, especially during periods of nutrient deprivation, which coincide with upregulation of apoptotic markers in the ovary. Therefore, leptin can be used as a potential biomarker for egg production. Leptin administration in broiler breeders may not offer the same benefits observed in layer birds because it accelerates early folliculogenesis, which may lead to follicle pool depletion before sexual maturation. Additionally, the feeding strategies used by broiler breeders could further affect the effectiveness of leptin. The function of leptin in the early life stages of broiler breeders and other bird species is poorly understood. The ontogenic expression of leptin from the embryonic phase to adulthood is vital for understanding its role in avian reproduction. It is also unclear whether the effects of post-hatching leptin administration in birds persist and influence the primordial follicle pool into adulthood, as observed in neonatal mammals. Blocking leptin signaling in boiler breeding hens will indicate whether leptin inhibition improves irregular follicle hierarchy. This condition is exacerbated in women with PCOS and obesity, whose elevated leptin levels may thus serve as a potential molecular marker for PCOS[111,147]. Although much is known about the role of leptin in adult mammals, its mechanism of action in birds remains obscure, particularly with respect to endogenous chicken leptin. Further research is essen-

Table 1. **Effect of leptin on reproduction and ovarian development in birds.**

Bird	Age (week)	Leptin type	Dose (kg/BW)	Mode of administration and time	Effects	Mechanism	Reference
Quail	E5,	Mouse	0.1-0.1 µg	*In ovo*	↑ Embryonic growth, T3, T4.	ns	77
Chicken	Before egg incubation	Murine	5 µg	*In ovo*	↑ Post-hatch growth, T3.	ns	79
Chicken	E3	Mouse	5 µg	*In ovo*	Post-hatch mRNA of pituitary; (↑ LH, FSH) ovarian; (↑ LEPR, IGFBP2, Wnt5b), ↑ folliculogenesis.	ns	80
Chicken	1	Mouse	25 µg	I.p. 24, 48 h	↑ LH, FSH, IGF-1, IGF-1R, LEPR, FSHR, CYP19A1, E_2, ↓ caspase-3, AMH, ↑ folliculogenesis.	ns	28,101
Chicken	1	Mouse	10 ng/mL	Ovary culture, 24, 48 h	↑ IGF-1, LEPR, ↓ AMH, FSHR, CYP19A1; ↑ folliculogenesis;	ns	28
Chicken	11	Chicken	256 µg	I.p. daily until 1st ovipo-sition	↑ sexual maturation, ↓ apoptosis.	ns	137
Duck	25	Mouse	250 µg	I.p. daily 3–5 days	↑FSHR, LHR, E_2, folliculogenesis, ovary weight.	ns	140
Chicken	25	Chicken	250 µg	I.p. twice a day from day 1–5 or 10	↑ LEPR, steroids, folliculogenesis, egg laying, ↓ apoptosis.	ns	142
Chicken	25	Human	1-100 ng/ml	*in vitro* culture of GCs, 48 h	↓ Apoptosis (Bax, ASK-1 and p53), ↑ Bcl2, PCNA, P, E_2	MAPK/ ERK1,2	144
Chicken	30	Human	25 µg	I.m. for 3 days	↑ E_2, ovulation.	ns	141
Goose	35	Chicken	1-100 ng/ml	*In vitro* culture of GCs, 24 h	↑ LEPR, Srebp1, Cyp51, StAR, CYP19A1, E_2, ↓ apoptosis.	PI3K/Akt/ mTOR	145,146

↑, stimulation; ↓, inhibition; ns, not studied; E, embryonic day; I.p., intraperitoneal; I.m., intramuscular; GCs, granulosa cells; T3, triiodothyronine; T4, thyroxine; E_2, estradiol; LEPR, leptin receptor; IGF-1, insulin-like growth factor 1; IGF-1R, IGF-1 receptor; CYP19A1, aromatase; AMH, anti-Müllerian hormone; LH, luteinizing hormone; LHR, LH receptor; FSH, follicle-stimulating hormone; FSHR, FSH receptor; Wnt5b, wingless-type MMTV integration site family member 5b; Bcl2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; ASK-1, apoptosis signal-regulating kinase 1; p53, tumor protein p53; PCNA, proliferating cell nuclear antigen; P, progesterone; Srebp1, sterol regulatory element-binding protein 1; Cyp51, cytochrome P450 family 51; StAR, steroidogenic acute regulatory protein; MAPKs, mitogen-activated protein kinases; PI3K/Akt, phosphatidylinositol 3 kinase/serine-threonine kinase; mTOR, mammalian target of rapamycin.

tial to investigate the specific roles of leptin throughout life and among different bird categories, such as laying hens and broiler breeding stocks.

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Author Contributions

Sadequllah Ahmadi and Takeshi Ohkubo wrote the paper.

Conflict of Interest

The authors declare no conflicts of interest.

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