



HDL cholesterol and female infertility: lessons from animal models

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Abstract

Cholesterol metabolism, particularly the role of high density lipoprotein (HDL), plays a critical role in female fertility. This review examines the implications of HDL metabolism on various aspects of female reproduction using animal models, including ABCA1 KO mice, SCARB1 KO mice, a restricted ovulator chicken mutant model, and liver X receptor KO mice. The paper highlights the importance of HDL in oocyte development, embryo quality, and overall reproductive outcomes. By summarizing the findings from these models, significant insights into the mechanisms behind dysfunctional HDL metabolism and its impact on female infertility are revealed. The methodology employed in this review includes a systematic analysis of literature and data from studies on animal models, providing a comprehensive understanding of the complex relationship between HDL cholesterol and female reproductive health.

Keywords: HDL, Female Fertility, Animal Model

Introduction

Cholesterol, a fundamental component of cellular membranes, serves as a precursor to bile acids, aids in steroid and vitamin synthesis, and plays a crucial role in maintaining cellular health by regulating cholesterol balance through various pathways (Craig et al., 2023). Lipoproteins (LP) transport cholesterol in the bloodstream, with high density lipoprotein (HDL) crucial for reverse cholesterol transport (RCT), where cholesterol is transported from peripheral tissues back to the liver for excretion (Feingold, 2014). HDL metabolism, facilitated by proteins like Apolipoprotein A-I (ApoA-I), ABCA1, ABCG1, and Scavenger Receptor Class B Type 1 (SCARB1), is closely intertwined with female reproductive physiology, particularly in the context of oocyte and early embryo development.

Research has highlighted the significance of HDL in female reproduction, with studies indicating the presence of HDL in follicular fluid (FF) and its potential role in providing essential nutrients for oocytes and embryos (Ji et al., 2012). Studies have shown that disturbances in HDL metabolism, such as observed in SCARB1 knockout (KO) mice, can lead to female infertility despite normal ovulation, with implications on oocyte quality and embryo development (Bacchetti et al., 2019).

The aim of this review is to delve deeper into the implications of irregular HDL metabolism, focusing on the specific connection between HDL cholesterol levels and oocyte quality in female infertility. By examining findings from animal models like SCARB1 KO mice, this review seeks to elucidate the mechanisms underlying

Significance | This review describes HDL metabolism's role in oocyte quality and female fertility offers insights for targeted interventions and personalized treatments in reproductive medicine.

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cholesterol surplus in oocytes and its impact on reproductive outcomes. Through a systematic analysis of these animal models, this review aims to provide insights into the intricate relationship between HDL metabolism and female fertility, offering a platform for future research endeavors in the field of reproductive medicine (Figure 1).

The role of LP Cholesterol in Ovarian Steroid Synthesis

Various studies across species have underscored the significance of cholesterol in female fertility. Within the ovarian follicle of mammals, cholesterol plays a pivotal role in the biosynthesis of steroids. The follicle comprises two distinct chambers separated by a basal lamina: the outer chamber housing vascularized theca cells and the inner chamber enveloping the oocyte, surrounded by granulosa cells, cumulus cells, and antrum brimming with follicular fluid (Futamata et al., 2023). During steroidogenesis, follicle cells rely on cholesterol from various sources, including synthesis *in situ* and uptake from lipoproteins present in the follicular fluid. This orchestrated process is vital for optimal steroid production and involves the expression of receptors for different lipoprotein types in a cyclic manner. The complex milieu of the follicular fluid nurtures a microenvironment rich in hormones, metabolites, growth factors, and nutrients that support oogenesis throughout follicular development (Miller and Auchus, 2011).

In mammalian species, including humans, high-density lipoprotein (HDL) takes center stage as the primary lipoprotein found in follicular fluid, with larger lipoprotein particles being scarce in antral follicles. Research suggests that follicular fluid HDLs predominantly originate from plasma sources (Nagy et al., 2019). Studies by Le Goff and colleagues endorsed this hypothesis, showcasing smaller HDL variants in follicular fluid with higher cholesterol esters compared to unesterified cholesterol and an abundance of cholesterol relative to phospholipids, distinguishing them from circulating HDLs. It is postulated that the smaller size of follicular fluid HDLs enables their penetration through the basal lamina's narrow pores into the follicular antrum, facilitating metabolic transformations crucial for reverse cholesterol transport (RCT) (Le Goff et al., 2004). Notably, human follicular fluid HDLs exhibit a distinct composition compared to plasma HDLs, characterized by smaller size, elevated phospholipids, a higher ApoA-IV/ApoA-I ratio, and greater cholesterol esterification, hinting at unique genesis or transformation within the follicular antrum (Liu et al., 2022).

Experimental evidence supporting the transport of plasma HDLs to the follicular antrum was gleaned from an ovarian cross-transplantation murine study involving ApoA-I knockout (KO) ovaries transplanted into wild-type mice. Immunodetection revealed the presence of ApoA-I on granulosa cells' surfaces facing the antrum and within the antrum of ApoA-I KO ovaries (Cedó et

al., 2020). In contrast, transplantation of wild-type ovaries into ApoA-I KO mice showed the absence of ApoA-I immunodetection in ovarian granulosa cells or the antrum. These observations support the theory that murine follicular fluid HDLs derive from plasma. However, limited follicular fluid available in murine models posed challenges in conducting the necessary biochemical analyses to determine precise murine follicular fluid HDL properties. Intriguingly, human and chicken ovarian granulosa cells containing protein and ApoA-I mRNA suggest that some follicular fluid HDLs might originate intrafollicularly, synthesizing within the ovaries [20-22] (Schomberg et al., 1999; Burchall et al., 2019; Yuan et al., 2021).

Follicular fluid HDLs, rich in cholesterol esters, are inefficient substrates for steroid hormone synthesis. Thus, theca cells assimilate cholesterol from plasma HDL during the follicular phase to produce testosterone and androstenedione, supporting estrogen production by granulosa cells within the maturing follicle (Bisgaier et al., 1985). The surge of luteinizing hormone increases the permeability of the basal lamina, facilitating the import of cholesterol for heightened steroid production during ovulation. Notably, increasing follicle size correlates positively with follicular fluid cholesterol levels, while the percentage of low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL) in follicles gradually increases before ovulation. Luteinizing hormone stimulation triggers the SREBP/SCAP pathway, promoting cholesterol synthesis in murine granulosa cells (Miranda-Jiménez and Murphy, 2007). Post-ovulation and follicular vascularization, follicular cells mobilize stored cholesterol esters and upregulate lipoprotein receptors (such as SCARB1, LRP8, VLDLR, and LDLR). In the corpus luteum, luteal cells utilize freshly synthesized cholesterol alongside cholesterol from blood LDL and HDL to expedite progesterone synthesis, with thecal and corpus luteum cells primarily expressing SCARB1 to provide essential cholesterol for steroid hormone synthesis (Chang et al., 2017). As luteal phase progresses, the downregulation of LDLR in granulosa cells is accompanied by the modulation and enhanced expression of SCARB1, ensuring adequate cholesterol acquisition critical for luteal cell steroidogenesis while evading strict cholesterol homeostasis regulation compared to LDLR, as evidenced in rat experiments employing primary cultures of ovarian granulosa cells (Shen et al., 2018).

Research led by A. Rodriguez and colleagues posits the pivotal role of SCARB1 in steroid biosynthesis in human granulosa cells during the follicular phase (Rodriguez, 2021). Increased SCARB1 expression in granulosa cells harvested from mature follicles during *in vitro* fertilization procedures positively correlated with estrogen levels, oocyte retrieval count, and fertilization outcomes. Further supportive evidence from *in vitro* studies demonstrated that inhibiting SCARB1 with siRNA compromised progesterone

expression in granulosa cells, despite forskolin administration (Amin et al., 2014). Additionally, single nucleotide polymorphisms (SNPs) in the SCARB1 gene associated with SCARB1 were linked to follicular fluid progesterone levels and successful pregnancy outcomes in patients undergoing in vitro fertilization. In essence, the research findings underline the significant role of lipoprotein-mediated cholesterol flux in steroid synthesis across granulosa, theca, and luteal cells (Zeng et al., 2017).

As previously highlighted, follicular fluid exhibits low levels of LDL and larger lipoprotein particles. Oxidation of LDL can lead to the production of oxidized LDL (oxLDL) molecules, capable of inducing oxidative stress (OS) that may compromise cellular function and metabolism, as evidenced in various disease contexts (Poznyak et al., 2021). Notably, human granulosa cells expressing apoB-containing lipoprotein particles demonstrated an association with improved fertility outcomes post in vitro fertilization. These insights suggest a potential local production and release of large lipoproteins into the follicular fluid (Da Broi et al., 2018). Recent research reports indicate that obese women, grappling with impaired fertility, may experience systemic chronic OS and elevated oxLDL levels. This heightened OS and the presence of oxLDL could potentially impact oocyte quality, posing a contributing factor to infertility in obese females (Wang et al., 2022). Further multidimensional research efforts are imperative to unravel the intricate mechanisms through which aberrant cholesterol metabolism might influence fertility in obese women (Dağ and Dilbaz, 2015).

Evidence from animal models

The discoveries related to ABCA1, a cholesterol efflux regulatory protein, and the SCARB1 HDL receptor have unveiled critical insights into HDL metabolism. Gene knockout models for these proteins have provided significant revelations regarding the indispensable role of HDL in reproduction, as evidenced by experiments utilizing animal models with disrupted genes (KO) (Figure 2). This section delineates the reproductive dysfunctions observed in female murine models lacking SCARB1 and ABCA1 (Yvan-Charvet et al., 2010). It is noteworthy to mention that mice deficient in LCAT maintain fertility and exhibit elevated levels of pre- β -HDL particles. Furthermore, even ApoAI knockout female mice appear to be fertile, potentially attributable to the participation of various apolipoproteins in HDL-dependent reverse cholesterol transport. Several models featuring mutated or knocked-out genes crucial to lipoprotein (LP) metabolism have been described, illustrating irregular lipid levels, atypical LP particles—predominantly HDL—and compromised or absent fertility in females (Sorci-Thomas et al., 2012).

SCARB1 KO mouse model

The development of a mouse model with a knocked-out SCARB1 gene facilitated a deeper understanding of SCARB1's role in regulating cholesterol levels. Studies involving SCARB1 knockout (KO) mice have provided compelling evidence supporting the significance of HDL in mammalian oocyte growth and function. SCARB1 is instrumental in lipoprotein (LP) metabolism, serving as a crucial mediator for the uptake of cholesteryl esters (CE) from LPs, including HDL, through selective lipid uptake (Contreras-Duarte et al., 2018).

Research on murine SCARB1 KO models has revealed distinctive features of plasma HDL particles, characterized by their unusually large size, enriched ApoE content, and elevated unesterified cholesterol to total cholesterol (UC:TC) ratio. Female SCARB1 KO mice, when crossed with wild-type males, exhibited infertility due to consistent embryo arrest at the zygote or 2-cell stages. Notably, no significant morphological abnormalities were observed in their ovaries. The female SCARB1 KO mice displayed: (i) reduced ovarian cholesteryl ester (CE) content without a decrease in progesterone production; (ii) normal estrous cycles and a typical number of ovulated oocytes; and (iii) irregular morphology in embryos and unfertilized oocytes (Zanoni et al., 2016). Additionally, Trigatti et al. reported similar structural alterations in the oocytes of wild-type mice exposed to cholesterol-binding agents like filipin and nystatin (Trigatti et al., 1999).

In subsequent investigations, Miettinen et al. explored infertility in SCARB1 KO mice using surgical, pharmaceutical, and genetic interventions (Miettinen et al., 2001). Fertility was restored through various approaches: (i) transplantation of SCARB1 KO ovaries into wild-type mice, implicating that infertility was not solely attributed to the SCARB1-deficient ovaries themselves; (ii) administration of probucol, a cholesterol-lowering medication, which regulated cholesterol levels and the UC:TC ratio; and (iii) simultaneous suppression of the ApoAI gene by crossing ApoAI 2/2 with SR-BI 2/2, leading to a reduction in total cholesterol in plasma without altering the unusually large size of HDL particles (Quiroz et al., 2020).

Furthermore, Yesilaltay et al. induced SCARB1 expression in the liver of SCARB1 2/2 mice through stable transgenic expression and transient adenovirus-mediated expression of both wild-type SCARB1 and the SCARB1 double point mutation (SR-BI RR), which has affinity for LDLs and abnormally large HDLs but not typical HDLs (Yesilaltay et al., 2014). The transgenic expression of SCARB1 in the liver of female SCARB1 2/2 mice resulted in decreased total cholesterol levels in plasma, increased cholesterol secretion in bile, and restored fertility. Similarly, overexpression of SR-BI RR reinstated fertility in female SCARB1 2/2 mice. In both experiments, the size of HDL particles and the UC:TC ratio returned to normal levels. Overall, the research suggests that embryo arrest in SCARB1 KO mice before implantation is

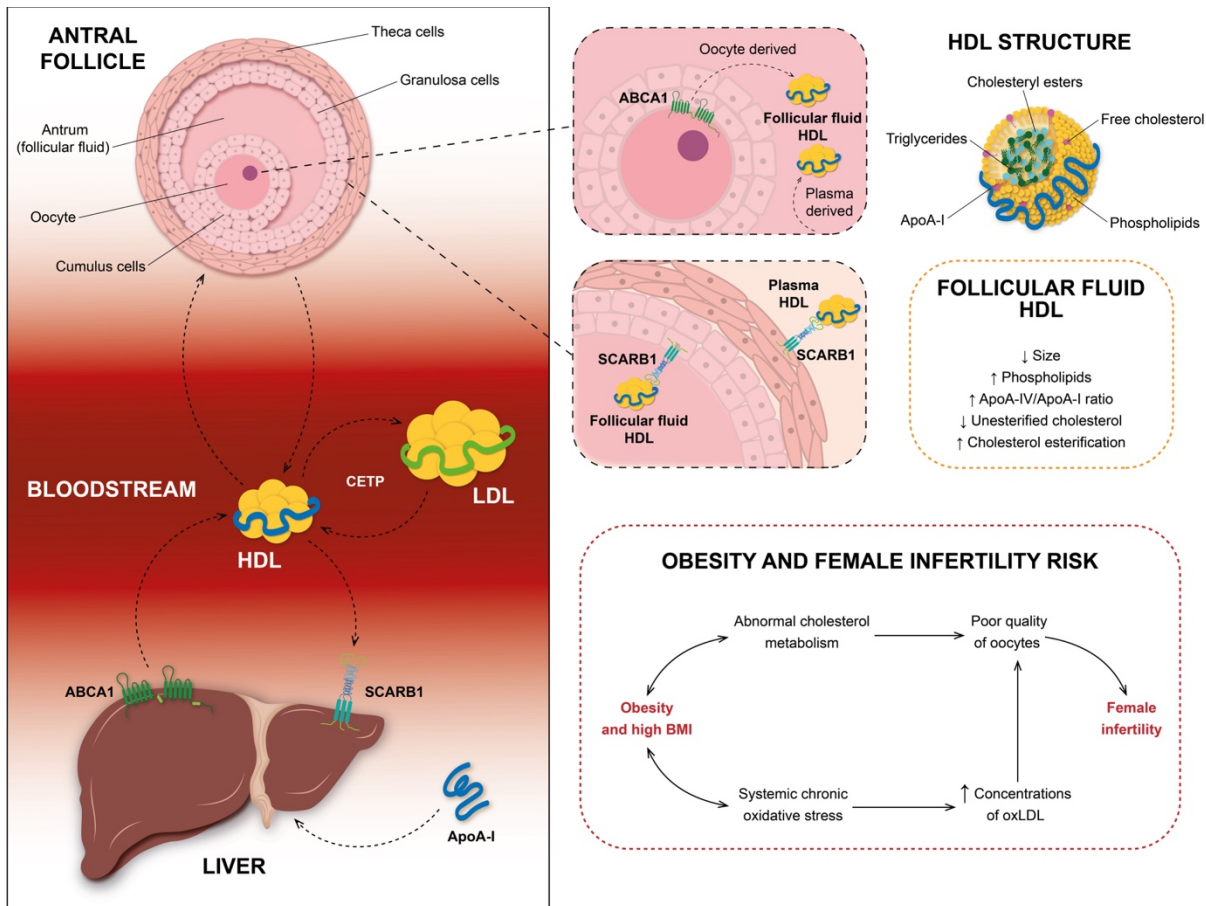


Figure 1. Structure, metabolism and main functions of HDL: relationship with female infertility.

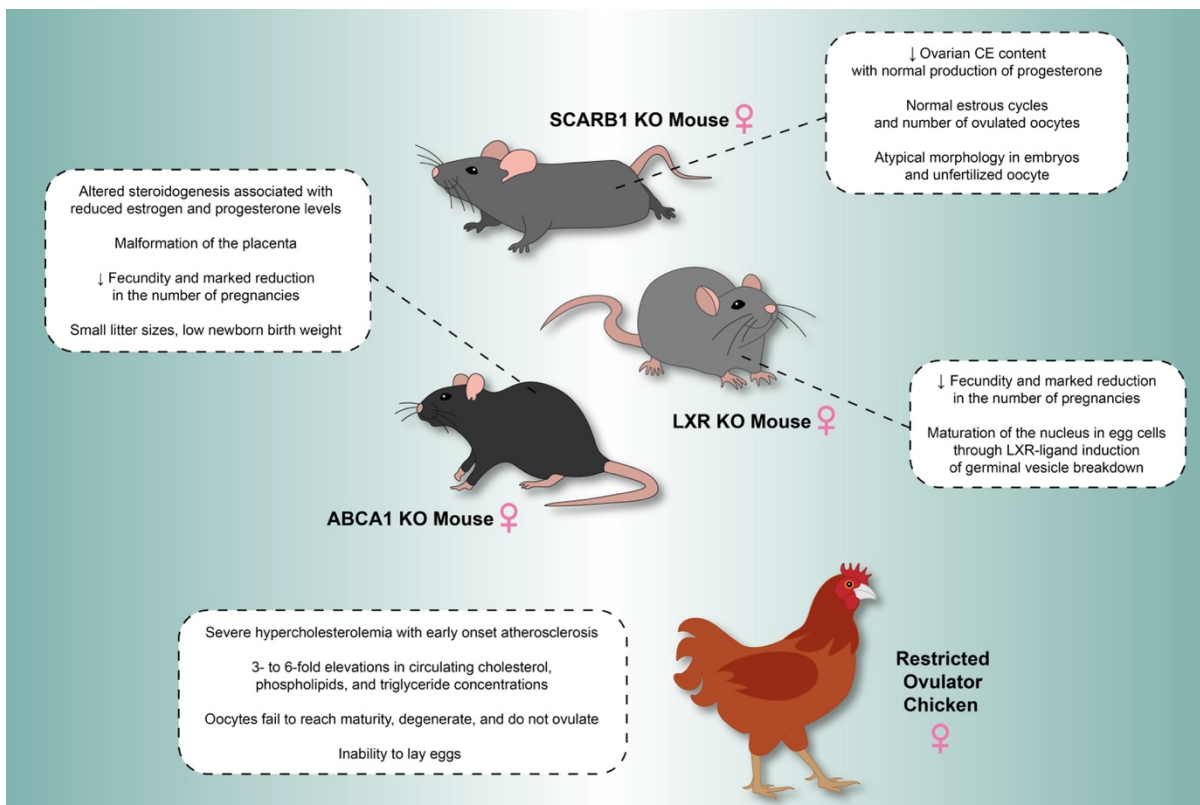


Figure 2. Animal models of lipid metabolism disorders: implications for reproductive function

attributed to the atypical regulation of HDL metabolism in the liver and plasma, leading to an unusual lipid profile, including the UC:TC ratio, and an increase in HDL particle size, rather than a deficiency in ovarian expression of the receptor (Vaisman et al., 2015).

ABCA1 KO mouse model

Further evidence of the role of HDL in reproduction is evident in female ABCA1-KO mice with homozygous traits, displaying reduced fecundity, lower newborn birth weights, and decreased pregnancies attributed to lower HDL-C levels. As previously mentioned, the ABCA1 transporter is a critical enzyme in reverse cholesterol transport (RCT), essential for normal HDL metabolism. In the ABCA1-KO model, there is a significant decrease in HDL maturation, along with noticeable alterations in the morphology of phospholipids, including an 80% reduction in phosphatidylcholine content (DeAngelis et al., 2014).

Inherited HDL deficiency or absence, known as Tangier disease, is associated with premature atherogenesis. Women with homozygous ABCA1 mutations and markedly reduced HDL-C levels in plasma (1–2 mg/dl) have shown fertility across several familial cases of this condition. This suggests that while HDL-C may not be indispensable for female fertility, it could play a crucial role in oocyte quality and reproductive aging. It is now understood that other ABC transporters such as ABCG4 and ABCG1 might also contribute to RCT from cells, potentially mitigating the consequences of decreased or absent ABCA1. The direct impact of HDL-C on oocyte health through follicular regulatory processes involving cumulus granulosa cells remains to be fully elucidated (Pervaiz et al., 2012).

Restricted ovulator chicken mutant model

In chickens, the nourishing substances in the oocyte yolk are mainly obtained from plasma very-low-density lipoprotein and vitellogenin through receptor-mediated endocytosis (RME) utilizing the 95-kDa oocyte vitellogenesis receptor (OVR), analogous to the VLDL receptor in mammals. Hens from a mutant strain termed restricted-ovulator (R/O) harbor a naturally occurring single OVR mutation (Barber et al., 1991). R/O hens present severe hypercholesterolemia with early-onset atherosclerosis, evidenced by 3- to 6-fold elevations in circulating cholesterol, phospholipids, and triglyceride concentrations. The R/O mutation leads to a substantial reduction in OVR expression on the oocytes, with somatic cells exhibiting a differentially spliced variant absent in germ cells. Oocytes from R/O hens fail to attain maturity, degenerate, and consequently do not ovulate, culminating in sterility characterized by the inability to lay eggs. Roosters carrying the aberrant R/O gene exhibit normal reproductive

functions; however, the homozygous state has not been thoroughly investigated (Elkin et al., 2012).

Given the significant differences in lipoprotein (LP) metabolism and oogenesis between birds and mammals, the mechanisms underlying female infertility in chicken models may vary from those in SCARB1 KO mice. Nevertheless, it is noteworthy that chicken yolk, akin to mammalian follicular fluid (FF), primarily contains HDL sourced from plasma. Early research predating the discovery of SCARB1 did not elucidate the transportation of HDL components into the yolk (Klees et al., 2022). However, it was observed that the mechanism of HDL transportation differed from other yolk LPs and was governed by processes distinct from RME. Subsequently, with the discovery of SCARB1, which regulates selective lipid uptake from HDL, it was found to align with the previously hypothesized theory of HDL transport from plasma to yolk. Moreover, hepatic expression of SCARB1 in birds was demonstrated, further indicating SCARB1 as a probable mediator transporting HDL components into the yolk (Marques et al., 2018).

The liver X receptor KO model

The liver X receptor (LXR) plays a role in controlling cellular cholesterol homeostasis through the release of ABCA1 transporter proteins. LXRs are essential for balancing cholesterol, glucose, and fatty acids in cells. Within the adrenal glands, LXRA and LXR β regulate steroid hormone production by controlling genes involved in cholesterol efflux, storage, and steroidogenesis, thereby preventing the accumulation of unesterified cholesterol (UC) (Patel et al., 2008). LXRA regulates UC concentration within cells by activating genes linked to cholesterol efflux (ABCA1) and accumulation (ApoE and SREBP-1c), while reducing the expression of genes related to steroidogenesis. Deficiency in LXR leads to adrenal gland enlargement, cholesterol accumulation, and excessive synthesis of steroids in adrenal tissues (Beyea et al., 2007).

In the process of steroidogenesis, follicular granulosa and theca cells in the ovary accumulate significant amounts of cholesterol esters, which are subsequently converted into UC. During the follicular phase, luteinizing and follicle-stimulating hormones stimulate granulosa cells to produce progesterone, which inhibits the esterification of cholesterol. Elevated levels of UC within cells must be cleared to prevent accumulation on the cell membrane, which could impair cellular function (Bergh et al., 1993).

Compared to other tissues, granulosa cells release substantial amounts of liver X receptors, particularly LXR β . Stimulation of luteinizing granulosa cells with an LXR agonist enhances the production of ApoE, ABCG1, ABCA1, and PLTP, facilitating cholesterol clearance in the cells. Although theca interna cells express mRNA for the ABCA1 transporter, evidence of LXR expression in these cells is currently lacking (Ben Aissa et al., 2021).

Murine oocytes express LXR, and LXR knockout (LXR2/2) mice exhibit reduced pregnancy frequency and fewer offspring compared to wild-type (WT) mice. Administration of GW3965, an LXR agonist, in WT mice triggers germinal vesicle breakdown in naked oocytes without affecting cumulus-enclosed oocytes. Conversely, LXR knockout mice show germinal vesicle breakdown only upon zymosterol administration, impacting meiosis (Gao and Liu, 2013).

These findings suggest that decreased fertility in female LXR knockout mice may be partially explained by nuclear maturation in egg cells induced by LXR ligands during germinal vesicle breakdown. Moreover, the effects of LXR on ABCA1 release in WT oocyte-granulosa complexes raise questions about changes in cholesterol metabolism in WT mice. In addition to reduced fertility in females, LXR knockout mice also exhibit significant infertility in males, linked to testicular damage from cholesterol accumulation, severe perturbation in cellular composition, and disorders in spermatogenesis (Robker et al., 2018).

Hypothesized role of HDL-dependent cholesterol efflux in reproduction

The study conducted by Krieger et al. indicates that atypical HDL particles are responsible for pregnancy disruption due to embryo arrest in the SCARB1 KO mouse model, an issue not observed in other HDL metabolism mutant models (Krieger and Kozarsky, 1999). All of the animal models mentioned above exhibit impairments that hinder normal HDL metabolism within the follicle, impeding the efflux of cholesterol to HDL. The infertility observed in these models (LXR KO, ABCA1 KO, SCARB1 KO, and R/O chicken) may arise from the absence of a cholesterol efflux mechanism, such as a cholesterol acceptor, transporter, or transporter-mediator. Consequently, defects in cholesterol efflux could disrupt cholesterol metabolism within the follicle, potentially impairing normal oogenesis (Adorni et al., 2021).

A functional regulator of HDL may be crucial for maintaining cholesterol homeostasis through an efflux mechanism, as evidenced by the presence of ABCA1 and LXR in cumulus-oocyte complexes and the infertility observed in their absence. Effective cholesterol efflux is primarily supported by HDL particles interacting with the ABCA1 transporter, with minimal contribution from reciprocal interactions between HDL and SCARB1 (Nandi et al., 2009). ABCA1 is most efficient with small prebeta HDL particles with low cholesterol content, and the reduction of prebeta HDL by chymase hinders ABCA1-dependent efflux. Large HDL particles containing ApoAI in the SCARB1 KO mouse model fail to efficiently uptake cholesterol. These atypical HDL particles provide an insufficient foundation for LCAT, negatively affecting the ApoAI structure and reducing its ability to trigger LCAT (Favari et al., 2009).

While ABCA1 KO mice are expected to be completely sterile as they lack the ABCA1 transporter, recently discovered ABCG1 and ABCG4 transporters may facilitate adequate cholesterol efflux, enabling partial female reproductive ability, although embryos may experience developmental disorders. Despite the presence of ABCA1, ABCG1, and ABCG4 transporters in SCARB1 KO mice, the absence of a proper HDL-C acceptor could pose a significant issue in this model [59]. In the R/O chicken with marked hypercholesterolemia, impaired cholesterol efflux could be a contributing factor to the phenotype. Overall, studies on all these mutant models underscore the importance of HDL content, composition, and concentration for reproductive health in female mammals (Agarwala et al., 2015).

Research has shown that there is an excess of cholesterol in the oocytes of SCARB1 KO mice that begins during the antral phase of follicular maturation and persists until ovulation. This anomaly can be reversed both *in vivo*, through the normalization of circulating HDL-C levels via medication, and *in vitro*, through co-incubation of oocytes with wild-type HDL (Tolani et al., 2013). These findings, along with prior evidence of the lack of receptors involved in the uptake of HDL-C in granulosa cells or oocytes, suggest that follicular fluid (FF) HDLs are linked to cholesterol efflux. Messenger RNA transcripts and proteins for ABCA1, the primary protein aiding in the transport of cholesterol from cells to HDL, are present in oocytes, supporting this notion. Additionally, females with ABCA1 KO demonstrate excess cholesterol and reduced viability. The hypothesis is that for maintaining cholesterol levels within a normal range in oocytes, efflux to functional FF HDL and ABCA1 transporters is essential (Catalano et al., 2008).

Conclusion

In exploring the intricate relationship between HDL metabolism and female fertility through animal models, this review has unveiled compelling insights into the mechanisms intertwining cholesterol regulation and reproductive health. The studies highlighted the critical role of factors such as SCARB1, ABCA1, and liver X receptor in maintaining HDL homeostasis and their direct implications for oocyte quality, embryo development, and overall reproductive outcomes.

Strengths of the studies lie in their ability to delineate the specific contributions of HDL components and pathways in female reproduction, shedding light on the complex interplay between cholesterol metabolism and fertility. The findings underscore the importance of HDL-mediated cholesterol efflux, highlighting the significance of precise regulation in maintaining optimal cholesterol levels within follicular environments crucial for oocyte maturation and fertility.

Nevertheless, certain areas of uncertainty persist, such as the exact mechanisms underlying cholesterol surplus in oocytes and the

interplay between various HDL-related proteins in regulating female reproductive processes. Additionally, controversies may arise in reconciling findings from different animal models and translating them to human reproductive physiology, necessitating further research to elucidate these discrepancies.

Future research directions could focus on elucidating the distinct roles of ABCA1, SCARB1, and other HDL-related proteins in mediating cholesterol efflux in different stages of oocyte development and embryo implantation. Exploring novel therapeutic interventions, such as pharmacological modulation of HDL metabolism or targeted gene editing, may offer promising avenues for addressing infertility associated with dysregulated HDL levels.

Clinical Implications

The insights gained from studies on HDL metabolism in female infertility have profound clinical implications for reproductive medicine. Understanding the intricate mechanisms of cholesterol regulation in reproductive tissues can inform the development of targeted interventions for improving oocyte quality, embryo viability, and overall fertility outcomes in women facing difficulties conceiving. Incorporating assessments of HDL function and composition into infertility evaluations may offer new diagnostic tools for identifying underlying mechanisms contributing to reproductive challenges. Additionally, personalized treatment strategies targeting HDL metabolism abnormalities could offer novel therapeutic avenues for enhancing fertility outcomes in affected individuals, paving the way for precision medicine approaches in reproductive health.

By providing a comprehensive overview of the research findings on HDL metabolism and female infertility, this review contributes to the growing body of knowledge in the field, offering valuable insights that could shape future research endeavors and clinical approaches aimed at improving reproductive outcomes in women experiencing fertility challenges.

Author contributions

A.V.P. prepared the original draft. V.N.S., V.A.K., V.Y.G., I.A.S., and A.N.O. reviewed and edited the writing.

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Competing financial interests

The authors have no conflict of interest.

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