# Liver X Receptors: A Possible Link between Lipid Disorders and Female Infertility

**Sarah Dallel** [1,2,3], **Igor Tauveron** [1,3], **Florence Brugnon** [4,5], **Silvère Baron** [1,2,*], **Jean Marc A. Lobaccaro** [1,2,*] and **Salwan Maqdasy** [1,2,3]

[1] Université Clermont Auvergne, GReD, CNRS UMR 6293, INSERM U1103, 28, Place Henri Dunant, BP38, F63001 Clermont-Ferrand, France; sarah.dallel@etu.uca.fr (S.D.); itauveron@chu-clermontferrand.fr (I.T.); smaqdasy@chu-clermontferrand.fr (S.M.)

[2] Centre de Recherche en Nutrition Humaine d'Auvergne, 58 Boulevard Montalembert, F-63009 Clermont-Ferrand, France

[3] Service d'Endocrinologie, Diabétologie et Maladies Métaboliques, CHU Clermont Ferrand, Hôpital Gabriel Montpied, F-63003 Clermont-Ferrand, France

[4] Université Clermont Auvergne, ImoST, INSERM U1240, 58, rue Montalembert, BP184, F63005 Clermont-Ferrand, France; fbrugnon@chu-clermontferrand.fr

[5] CHU Clermont Ferrand, Assistance Médicale à la Procréation-CECOS, Hôpital Estaing, Place Lucie et Raymond Aubrac, F-63003 Clermont-Ferrand CEDEX 1, France

* Correspondence: silvere.baron@uca.fr (S.B.); j-marc.lobaccaro@uca.fr (J.M.A.L.); Tel.: +33-473-407-412 (S.B.); +33-473-407-416 (J.M.A.L.)

check for updates

**Abstract:** A close relationship exists between cholesterol and female reproductive physiology. Indeed, cholesterol is crucial for steroid synthesis by ovary and placenta, and primordial for cell structure during folliculogenesis. Furthermore, oxysterols, cholesterol-derived ligands, play a potential role in oocyte maturation. Anomalies of cholesterol metabolism are frequently linked to infertility. However, little is known about the molecular mechanisms. In parallel, increasing evidence describing the biological roles of liver X receptors (LXRs) in the regulation of steroid synthesis and inflammation, two processes necessary for follicle maturation and ovulation. Both of the isoforms of LXRs and their bona fide ligands are present in the ovary. *LXR*-deficient mice develop late sterility due to abnormal oocyte maturation and increased oocyte atresia. These mice also have an ovarian hyper stimulation syndrome in response to gonadotropin stimulation. Hence, further studies are necessary to explore their specific roles in oocyte, granulosa, and theca cells. LXRs also modulate estrogen signaling and this could explain the putative protective role of the LXRs in breast cancer growth. Altogether, clinical studies would be important for determining the physiological relevance of LXRs in reproductive disorders in women.

**Keywords:** liver X receptors; cholesterol; female reproduction; breast cancer; ovarian hyperstimulation syndrome

## 1. Introduction

Infertility affects 15% of couples and remains one of the major issues of public health. The propagation of infertility from the last forty years [1] seems parallel to the increment of the prevalence of obesity, dyslipidemia, and metabolic syndrome [2,3]. A strong correlation exists between the lipid metabolism and the reproductive function in both men and women [4–8]. Cholesterol influences female fertility through multiple mechanisms, especially oocyte maturation, cell turnover during folliculogenesis, and hormonal function of the ovary and placenta. Indeed, a tight control of cholesterol turnover in the steroidogenic tissues is mandatory in order to maintain a normal ovarian

function. Hence, an excess or insufficiency of cholesterol is deleterious for cell function. The turnover starts from the cholesterol uptake through low density lipoprotein (LDL) and high density lipoprotein (HDL) receptors (LDLR and SR-BI, respectively), cholesterol esterification and storage, cholesterol ester hydrolase activity, cholesterol de novo synthesis pathway, and cholesterol efflux promoted by ATP-binding cassette (ABC) proteins. The latter are target genes of liver X receptors.

Liver X receptors (LXRα/NR1H3 and LXRβ/NR1H2) are nuclear receptors (NRs) for oxysterols, which are largely implicated in cholesterol homeostasis [9]. Because of their roles in the regulation of numerous metabolic functions, LXRs could represent part of the molecular link between lipid disorders and infertility. Thus, many arguments led to deeply investigating LXRs in female reproductive function, namely: (1) the close relationship between cholesterol and ovarian physiology [4,10,11]; (2) the increasing body of literature describing the novel biological roles of LXRs in the regulation of steroid synthesis and inflammation, two processes necessary for follicle maturation and ovulation [12–17]; (3) the fact that oxysterols, which are the physiological ligands [18], play a potential role in the maturation of the oocytes [19,20]; (4) and the role of LXRs in spermatogenesis suggests common germ cell pathways regulated by LXRs [7,14,17].

## 2. Fertility Disorders and Abnormal Lipid Homeostasis

Ovarian dysfunction is frequently observed in patients with metabolic syndrome and obesity, two frequent pathological situations linked to polycystic ovary syndrome (PCOS) [21,22], which is the main cause of amenorrhea and infertility in women [23–25]. These women share the main metabolic anomalies related to overweight and insulin resistance [26]. Indeed, 50–70% of women who suffer from PCOS are obese and 43% of them suffer from metabolic syndrome characterized by low HDL levels [6]. These patients also present inefficient folliculogenesis [27]. Furthermore, glycation end products in obese patients affect granulosa cell physiology counteracting a LH effect on such cells, and inducing the inflammatory cytokine secretion responsible for anovulation [28]. Furthermore, the oocytes of women with PCOS are smaller.

The Danish register of 47,000 couples identified a link between body mass index and infertility [29]. Moreover, the chances of success of assisted reproduction techniques to obtain a pregnancy are reduced in these women. They are resistant to gonadotrophin stimulation. The ovarian dysfunction in obese women is reflected by lower anti-Mullerian hormone (AMH) and inhibin B levels, two markers of granulosa cells reflecting the ovarian follicular reserve and the endocrine activity of the ovary [30,31]. The association between obesity and infertility seems to be correlated, at least in part, to anomalies in lipid metabolism [21]. Indeed, free cholesterol levels are positively correlated with the mean duration necessary to become pregnant [4].

Actually, the molecular evidences linking cholesterol anomalies and infertility came from mouse models. Cholesterol-rich diet alters the oocyte quality and reduces the ovulation rate in mice [32]. The follicles of these mice are apoptotic [33]. Furthermore, the oxidative stress seems to be higher in the oocytes of obese mice [34]. At the molecular level, the female mice deficient for *Abca1* encoding the ATP-binding cassette, A1, involved in cholesterol efflux, have low HDL levels and suffer from steroidogenesis defects, a reduced number of pups per litter, and placenta anomalies [10]. Likewise, the mice deficient for *Srb1* encoding the scavenger receptor class B type 1 (SRB1/SCARB1), also known as HDL-receptor, are infertile, with lower cholesteryl ester levels in the ovary and with defects in embryogenesis and implantation [35]. Conversely, excessive free cholesterol could also affect the meiosis in *Srb1*−/− or in wild type mice fed a cholesterol-rich diet [11]. The oocyte of *Srb1*−/− mice skips meiosis arrest and expulses spontaneously its second germinal vesicle, explaining the sterility in such mice.

Apolipoprotein E (Apoe)-deficient mice have a lower expression of *Cyp19a1*, encoding aromatase, and *Hsd3b*, encoding 3 β-hydroxysteroid dehydrogenase/Δ5-4-isomerase, which catalyzes the conversion of pregnenolone to progesterone, and the oxidative conversion of other

Δ5-ene-3-beta-hydroxy steroid. The folliculogenesis is enhanced, however, it is counteracted by excessive follicular atresia. Paradoxically, no modification in their fertility rates has been identified [36].

The analysis of infertile women revealed polymorphisms on SCARB1, consolidating the link between cholesterol, its receptor, and fertility. In another study, the HDL and apolipoprotein (APO) A-1 levels in the follicular fluid obtained during in vitro fertilization were negatively correlated with the embryonic development in the early stages [37]. Likewise, the APOE polymorphisms alter the plasma cholesterol and apolipoprotein levels [38], and are associated with reduced reproductive efficiency in women with *APOE2* protein subtype [39].

In summary, cholesterol metabolism anomalies are directly linked to oocyte maturation and to chances of fertility. Because various nuclear receptors (NRs) are involved in the control of cholesterol homeostasis, many research groups have looked for a putative implication of these transcription factors in the control of the female fertility. If the 'classical' steroid NRs, such as those of progesterone (PR/NR3C3), estrogens (ERα/NR3A1 and ERβ/NR3A2), and androgens (AR/NR3C4), have been extensively studied, the 'lipid' NRs, such as LXRs, FXR (bile acid receptor; NR1H4), SHP (small heterodimeric partner; NR0B1), and LRH1 (liver receptor homolog 1; NR5A2), have been the topic of investigations, mainly because of the phenotypes observed in the mice lacking the genes encoding these NRs. We will focus this review on LXRs.

## 3. LXRs and Their Ligands in the Ovary

LXRα and LXRβ are two NRs whose natural ligands and activators are derived from specific oxidized forms of cholesterol [18,40], or dendrogenin A, the product of a stereo-selective condensation of 5,6α-epoxycholesterol with histamine [41]. The discovery of this ligand identified the existence of a new metabolic branch at the crossroad between cholesterol and histamine metabolism [42].

Both of the isoforms are found in the oocyte with a predominance of LXRβ [16,20]. This expression is induced by the human chorionic gonadotropin hormone (hCG), and plays an important role in steroidogenesis in humans [43] as well as mice [16]. Follicular fluid meiosis-activating sterol (FFMAS), which can activate LXRs, increases after stimulation by gonadotropins [44,45] (Figure 1). This increment is necessary for the oocyte to resume meiosis just before ovulation. Indeed, the luteinizing hormone (LH) surge during folliculogenesis, necessary for ovulation, induces meiosis resumption of the oocyte. This indirect effect is mediated by the FFMAS produced by granulosa cells. Thus, FFMAS stimulates its receptor on the oocytes and LXRα was suggested as a candidate [18,40]. Furthermore, FFMAS promotes embryo implantation [46].

During the luteal phase, LXR is thought to promote luteolysis by depriving the lutein cells from cholesterol, a key molecule for progesterone synthesis (Figure 2). This effect is counteracted by the activity hCG that inhibits the LXR activity in these cells, and increases the sterol response element binding protein 2 and LDLR expression to maintain a cholesterol supply [47].

Steffensen et al. [20] first described the phenotype of female mice lacking both LXRs. These mice are hypo fertile with a reduced number of pups per litter. This seems mainly due to the absence of LXRβ. With their folliculogenesis and ovulation being normal, these mice suggest putative defects in oocyte maturation and/or in meiosis resumption [46]. LXRs are thus intermediates that promote the action of gonadotropins on the oocyte. In the same line of evidence, Grondahl et al. tested ex vivo meiosis resumption of oocytes surrounded by their cumulus using FFMAS and the other LXR ligands, 22R-hydroxycholesterol, 16-hydroxycholesterol, 25-hydroxycholesterol, and 27-hydroxycholesterol. Meiosis resumption was induced only with FFMAS [19]. Conversely, Steffensen et al. showed that zymosterol, an intermediate in cholesterol biosynthesis and the structural analog of FFMAS, is capable of inducing meiosis resumption, however, in a LXR-dependent manner. In wild type mice, an FSH injection induces meiosis resumption and increases the *Lxrα* transcription levels. On the other side, the synthetic LXR agonist GW3965 induces meiosis resumption, even in the absence of the cumulus, suggesting that LXR in the oocyte is necessary for its maturation [20]. On the cumulus–oocyte complex retrieved from *Lxr−/−* mice, the meiosis resumption was abolished despite a treatment with FSH,

zymosterol, or GW3965 [20]. These findings suggest that FSH activates the FFMAS production from the cumulus, which then activates the LXR in the oocyte. Likewise, our team pointed out that deficient-LXR mice have a delayed sterility and an inefficient folliculogenesis under stimulation, with an important number of atretic oocytes on retrieval, after stimulation by gonadotropins [16]. Altogether, LXRs are important for oocyte maturation and survival.
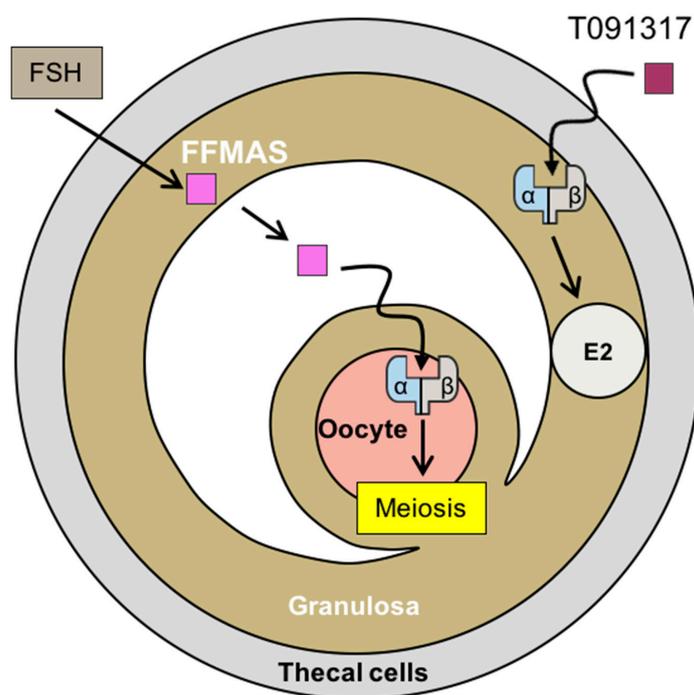


**Figure 1.** Role of liver X receptors (LXRs) in oocyte meiosis and in estradiol synthesis. When follicle-stimulating hormone (FSH )reaches its receptor on the granulosa cells, it increases the concentration of follicular fluid meiosis-activating sterol (FFMAS) by increasing its synthesis, a ligand of LXRα/β. This in turn induces the final steps of the oocyte meiosis. In addition, when the LXRα/β is activated by a ligand (in this figure T0901317, a synthetic ligand, purple square), they increase the production of estradiol. α/β—LXRα, or LXRβ; E2—estradiol; FFMAS—follicular fluid meiosis-activating sterol (pink square).

As in the testes [14,17] and adrenal glands [12], LXRs are also involved in the regulation of steroid synthesis in the ovary [16]. Indeed, the synthetic LXR ligand T0901317 induces the estradiol synthesis in wild type mice by activating the transcription of the steroidogenic acute regulatory protein (StAR), a transport protein that regulates cholesterol transfer within the mitochondria, which is the rate-limiting step in the production of steroid hormones. In the ovary, LXRs also control the transcription of cytochrome P450 side-chain cleavage (Cyp11A1), a mitochondrial enzyme that catalyzes the conversion of cholesterol to pregnenolone, the first reaction in the process of steroidogenesis.

Interestingly, LXRs seem to control any excessive estradiol synthesis during gonadotropin stimulation. Indeed, the gonadotropin stimulation of the *Lxr*−/− mice leads to an exaggerated hormonal response, with an excessive estradiol secretion [16]. This effect contributes to the phenotype of ovarian hyper stimulation syndrome (OHSS), observed in LXR-deficient mice. After a gonadotropin stimulation, the ovaries of the *Lxr*−/− mice harvest large hemorrhagic follicles with an exaggerated inflammatory and ovulatory response. This signals a diagnosis of OHSS, which is characterized by the excessive accumulation of vasoactive and angiogenic substances activating the vascular epithelial growth factor (VEGF) and interleukin (IL) 6 signaling, leading to a systemic inflammatory response, and variable clinical manifestations of cardiovascular collapse, septic shock, and thromboembolism in the most severe cases [48–53].
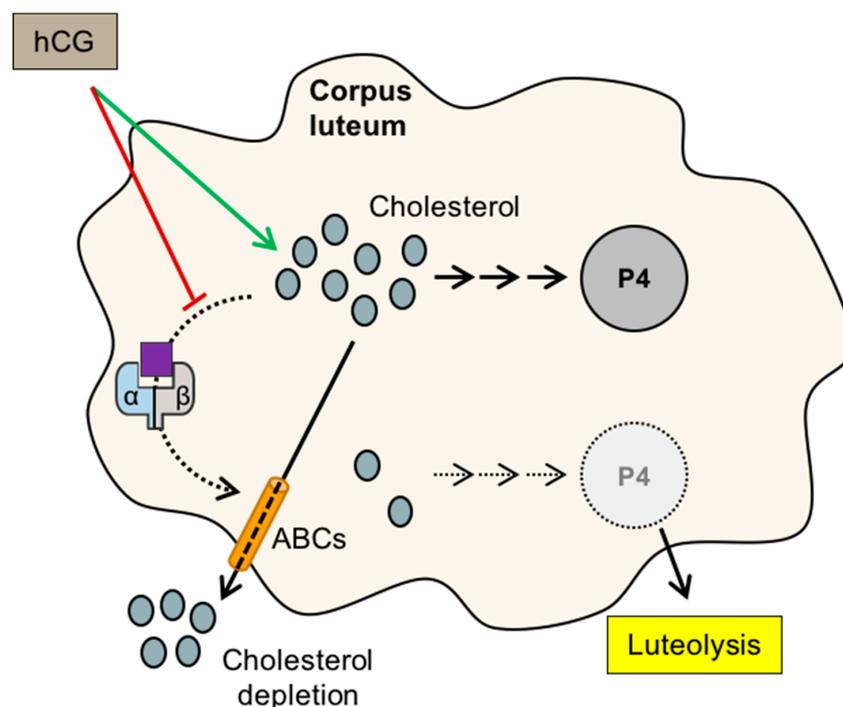
**Figure 2.** Role of LXRs in progesterone production and luteolysis. When the human chorionic gonadotropin hormone (hCG) reaches its receptor, it increases (green arrow) the concentration of cholesterol, by acting on low density lipoprotein receptor (LDLR) (uptake) and sterol response binding element (SREBP2) (de novo synthesis), and favors the production of progesterone (P4). Activation of LXRα/β by one of their bona fide ligands, produced from the cholesterol oxidation, stimulates the production of ATP-binding cassette transporter (ABC) proteins, inducing a cholesterol depletion within the cell, a decrease in progesterone synthesis, and finally, the luteolysis. hCG also inhibits LXR transcriptional activity. α/β—LXRα or LXRβ; ABCs—ATP-binding cassette transporters; hCG—human chorionic gonadotropin; P4—progesterone. LXR ligands are represented by the purple square.

Although VEGF levels and increased IL6 signaling (through its receptor sIL-6Rα) are linked to OHSS, no molecular driver has been identified yet. Furthermore, the literature information are contradictory in linking these two cytokines to OHSS [54]. As LXRs have anti-inflammatory properties from inhibiting IL6, COX2, tumor necrosis factor TNFα [55], and the downstream of VEGF signaling [56], they could potentially be implicated in the prevention of OHSS [13,57–59]. Altogether, the genetic models enlighten the LXRs as key factors for the endocrine and exocrine functions of the ovary, and suggest that these NRs could be considered gatekeepers against an exaggerated ovarian response to gonadotropins. Even though clinical investigations should be performed, the exact roles of LXRs in femal ovarian physiology is thus questioned.

## 4. LXRs, Uterus, and Placenta

The endometrium trophicity is influenced by estrogens and progesterone in each menstrual cycle, in to be prepared for eventual pregnancy. When implantation takes place, the placenta develops in the endometrium permitting maternofetal exchange during pregnancy. Myometrium is necessary during labor. Obesity is related to many complications associated with pregnancy (e.g., gestational diabetes mellitus, tromboembolic problems, and hypertensive disorders such as preeclampsia or eclampsia) [60]. Hence, obese patients and/or those with a metabolic syndrome usually suffer from dystocia, contractility defects during labor that could affect the perinatal morbidity, and mortality [61,62]. Likewise, before pregnancy, the body mass index [63,64] and its increase [65]

during pregnancy have been associated with a higher risk for caesarean delivery at the term of pregnancy, for failure to progress in the labor.

Interestingly rats fed a hypercaloric diet to induce obesity have an increased accumulation of transcripts implicated in lipid homeostasis and inflammation, such as fatty acid translocase CD36, lipoprotein lipase, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), in the uterus [66]. This accumulation is also observed in ob/ob and db/db mouse models, which are prone to develop obesity as well as metabolic syndrome [67]. An abnormal accumulation of cholesterol in the muscular cells of the myometrium has been associated to contractility defects [68,69]. We showed that the females lacking LXRβ presented a similar phenotype of characterized by a higher accumulation in the myometrium, resulting from the absence of the upregulation of *Abca1* and *Abcg1* (Figure 3). Together with this 'adipose'-like phenotype of the muscular cells, the LXRβ-deficient mice exhibited a lower capacity to contract under stimulation with oxytocin and prostaglandin (PG) F2α analog [70]. This link between lipid accumulation in the myometrium and resistance to oxytocin induction during labor was suggested by Andreasen et al., who described a need for more oxytocin infusion to induce labor in overweight and obese women than in normal weight [60].
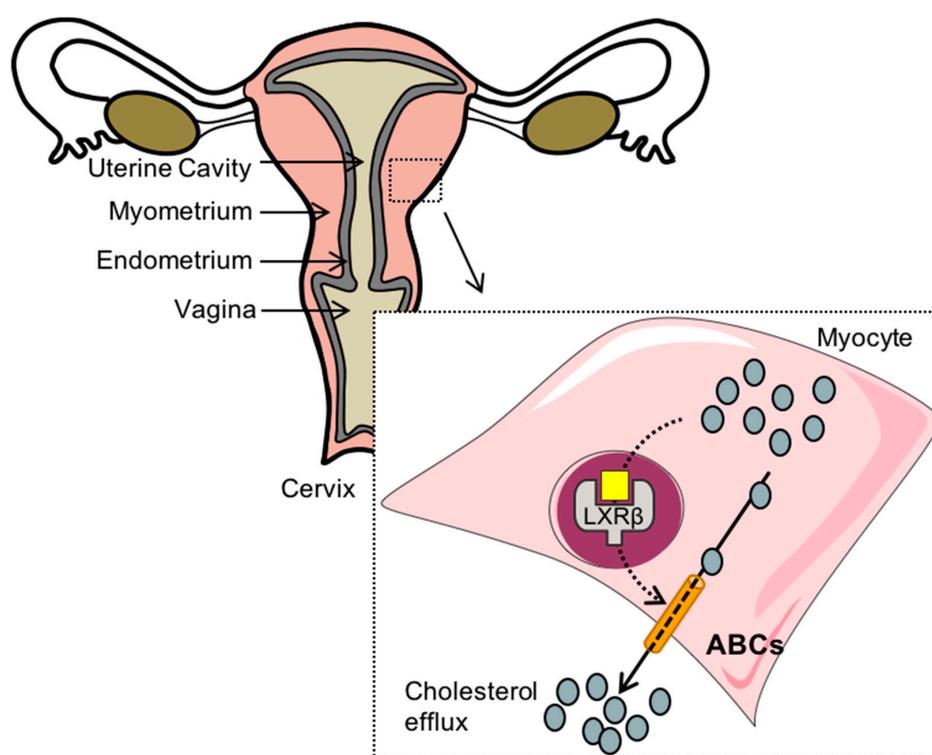


**Figure 3.** LXRβ controls the cholesterol homeostasis within the myometrium. When cholesterol (grey) raises to a critical concentration, its enzymatic transformation into LXR-activating oxysterols induces a higher accumulation of ATP-binding caste transporters and the efflux of cholesterol. A defect in the LXRβ-signaling pathway is linked to a higher accumulation of cholesteryl esters, a decrease response to oxytocin and prostaglandin (PG) F2α, and a defect in the contractility during the labor. ABCs—ATP-binding cassette transporters; LXRβ—liver X receptor β. Oxysterols are represented by the yellow square.

Nutrient and hormone exchanges between maternal and fetal circulation take place through the placenta, which also constitutes a barrier against toxins, in order to protect the fetus. Cholesterol is supplied by maternal circulation for steroid synthesis, by the placenta [71]. Among the various metabolic disorders during pregnancy, preeclampsia is one of the most important and affects 5% of pregnant women [72,73]. This pathology usually occurs in women with obesity and diabetes,

and is characterized by hypertension and proteinuria [74,75]. The hallmark of this syndrome is an insufficient trophoblast invasion with contractile spiral uterine arteries, leading to acute atherosis (atherosclerosis-like), vasoconstriction, and hypertension [75,76]. Elevated oxidized LDL (rich in sterols) levels reduce vessel invasion and produce preeclampsia [77]. Early and progressive LXRα and LXRβ expression in the placenta (seven days post-coitum in mice, six weeks of pregnancy in women) participate to maintain the cholesterol available for trophoblast cells, and modulates arterial invasion [78,79]. Many oxysterols, especially 25-hydroxycholesterol, increase in the placenta during pregnancy [80]. Furthermore, LXRs activate the ABC protein expression in trophoblast cells for eliminating excessive cholesterol and toxic sterols [78,81]. LXRβ also controls trophoblast invasion [77,82,83]. Interestingly, the *LXRα* and *ABCA1* genes are overexpressed in the placenta tissue of the women that suffered from preeclampsia [79], while another study demonstrated a reduction in LXRβ in these patients [84]. Endoglin/CD105 is membrane receptor that induces endothelial relaxation [78,85,86]. The production of soluble Endoglin/CD105 by the membrane metalloproteinase-14 induces the squelching of TGF-β1, endothelial dysfunction, and impaired relaxation, altogether, preeclampsia [78,85,86]. We pointed out that Endoglin/CD105 is an atypical LXR target gene, which could explain how LXR could reduce the trophoblast invasion and the risk of preeclampsia [78,85,86]. Interestingly, a single nucleotide polymorphism within the sequences encoding LXRβ has been significantly associated with the risk of preeclampsia in a study of over 155 women that presented this disorder [87].

## 5. LXRs, Modulation of Estrogen Activity, and Breast Cancer

Even though breast cancer cannot be defined as a woman reproductive disease per se, it has been directly associated to the circulating levels of estrogens and the levels and/or mutations of ERα by their roles in the growth and proliferation of epithelial cells. Hence, pharmacological management partly targets the estrogen pathway by using selective estrogen receptor modulators (SERM; e.g., tamoxifen or raloxifen) or degraders (SERD; e.g., fulvestran), LHRH analogs, and/or aromatase inhibitors [88,89]. Nevertheless, these therapies induce menopausal symptoms and some breast cancers are negative for ERα [90]. A significant correlation between ERα positive breast cancer/obesity/metabolic syndrome from one side, and statin, an inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase and cholesterol de novo synthesis, from the other side, have been revealed by various studies [91–94]. Beside the excessive aromatization of estrogen by the adiposity, and the excessive production of insulin-like growth factors and inflammatory cytokines [95], LXRs could represent a molecular link. Indeed, LXRs and ERα exert reciprocal effects on each other. As mentioned above, LXRs are gatekeepers against excessive E2 production after hormonal stimulation. LXR activation reduces ERα expression [96]. Furthermore, LXRs decrease the free estrogen level by increased sulfotransferase activity (EST or SULT1E1) [97]. On the other side, E2 decreases the LXR mRNA expression [98–101]. The ERα in the liver is recruited to the SREBP1c promoter, through direct binding to LXR, and prevents coactivator recruitment to LXR in an estrogen dependent manner [100].

LXRs were also identified to have an anti-proliferative effect in both ER positive and ER negative cells lines [96,102]. They could block cell proliferation-invasion by downregulating the cell cycle and cholesterol metabolism genes. The hypothesis of the LXR protective effect, through its anti-proliferative, pro-apoptotic role is based on cholesterol deprivation, as cholesterol is indispensable for cell proliferation [103–105]. Furthermore, the LXR activation reduced different breast cancer cell lines in vitro, by the suppression of cyclin proteins, ERα, and increased P53 protein levels [96]. LXR manipulation could help in estrogen deprivation, necessary for breast cancer treatment [106]. The molecular mechanism seems to be linked to LXRβ, which inhibits the proliferation of human breast cancer cells through the PI3K–Akt pathway [107] or an E2F-mediated mechanism [102,107]. Altogether, this thus indicates a positive impact of LXRs for protection against the development of breast cancer (Figure 4), even though 27-hydroxycholesterol, which is a LXR-ligand, acts as ERα ligand SERM [108] in breast cancer, cannot exclude a negative role of LXRs when 27-hydroxycholesterol increases, which

has never been described so far. Despite this possibility, modulating the cholesterol levels by statin treatment, or LXRs agonists, has been evoked as potential therapeutic option to prevent and/or repress tumor growth [109].
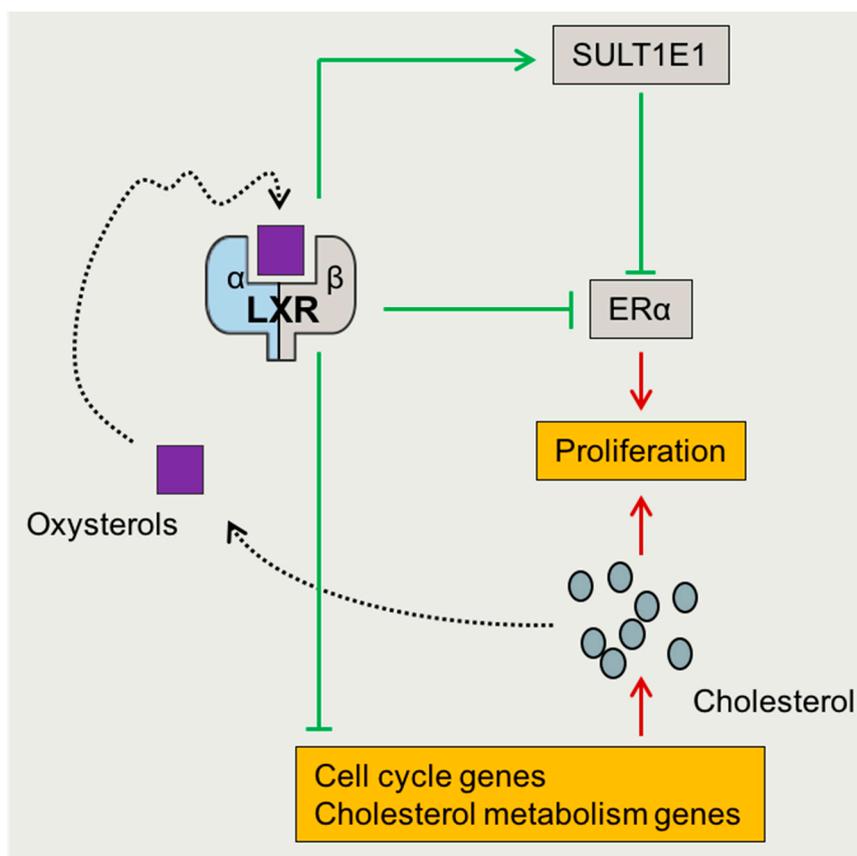


**Figure 4.** LXRs have beneficial effects on breast cancer proliferation. While increased synthesis and/or concentration of cholesterol induce cell proliferation, activation of LXRs blocks estrogen receptor (ER) $\alpha$ transcriptional effects directly by decreasing its transcription and by increasing sulfotransferase Family 2A Member 1 (SULT1A1), which in turn decreases the levels of circulating estrogens. ER$\alpha$—estrogen receptor $\alpha$; LXR$\alpha$/$\beta$—liver X receptor $\alpha$/$\beta$; SULT1E1—sulfotransferase E1.

## 6. Conclusions

This review highlights the roles of both LXRs in female physiology (oocyte maturation, fertility, and delivery) and the potential abnormal regulations of their signaling pathways in female pathophysiology. Reduced LXR activity could indeed expose the oocyte to higher cholesterol and estradiol concentrations, and alter the oocyte meiosis and survival. Furthermore, LXRs are gatekeepers against ovarian hyper stimulation. LXR signaling could be a perspective for future clinical studies to identify women at high risk of OHSS development, as well as how LXR modulation in parallel to the protocols of hormone stimulation during procreation assistance could abolish an excessive response. The beneficial role of LXRs in breast cancer has been suggested from genetic models and cell lines. More clinical investigations will be necessary before translating these findings to the clinics. Moreover, the fact that LXRs are ubiquitous transcription factors with pleiotropic physiological activities makes it mandatory to identify selective LXR modulators (SLiMs), as this was done for the SERMs and ER. For that, new pharmacology paradigms will be necessary as well.

**Author Contributions:** S.D. and S.M. wrote the article; I.T. and F.B. read the paper and corrected it; S.B. and J.M.A.L. wrote the paper and supervised the scientific work leading to this review.

**Conflicts of Interest:** The authors declare no conflict of interest.

## Abbreviations

| | |
|---|---|
| ABCA1/G1 | ATP-binding cassetteA1/G1 |
| AMH | anti-Mullerian hormone |
| APO | apolipoprotein |
| COX | cyclooxygenase |
| Cyp11A1 | cytochrome P450 side-chain cleavage |
| Cyp19a1 | cytochrome P450 aromatase |
| ER | estrogen receptor |
| EST | estrogen sulfotransferase |
| FFMAS | follicular fluid meiosis-activating sterol |
| hCG | human chorionic gonadotropin |
| HDL | high density lipoprotein |
| Hsd3b | 3 β-hydroxysteroid dehydrogenase/Δ5-4-isomerase |
| IL6 | interleukin 6 |
| iNOS | inducible nitric oxide synthase |
| JAK/STAT | janus kinase/signal transducer and activator of transcription protein |
| LDL | low density lipoprotein |
| LDLR | LDL receptor; LXR, liver X receptor |
| *Lxr−/−* mice | LXR-deficient mice |
| NR | nuclear receptor |
| OHSS | ovarian hyper stimulation syndrome |
| PCOS | polycystic ovary syndrome |
| PI3K | phosphoinositide 3-kinase |
| SCARB1 | scavenger receptor class B type |
| SREBP | sterol response element binding protein |
| SLiMs | selective liver X receptor modulators |
| StAR | steroidogenic acute regulatory protein |
| SULT2A1 | Sulfotransferase Family 2A Member 1 |
| VEGF | vascular endothelial growth factor |
| 27OHC | 27-hydroxycholesterol |

## References

1. Petraglia, F.; Serour, G.I.; Chapron, C. The changing prevalence of infertility. *Int. J. Gynaecol. Obstet.* **2013**, *123*, S4–S8. [CrossRef] [PubMed]

2. Kasturi, S.S.; Tannir, J.; Brannigan, R.E. The metabolic syndrome and male infertility. *J. Androl.* **2008**, *29*, 251–259. [CrossRef] [PubMed]

3. Norman, R.J.; Noakes, M.; Wu, R.; Davies, M.J.; Moran, L.; Wang, J.X. Improving reproductive performance in overweight/obese women with effective weight management. *Hum. Reprod. Update* **2004**, *10*, 267–280. [CrossRef] [PubMed]

4. Schisterman, E.F.; Mumford, S.L.; Browne, R.W.; Barr, D.B.; Chen, Z.; Louis, G.M.B. Lipid concentrations and couple fecundity: The LIFE study. *J. Clin. Endocrinol. Metab.* **2014**, *99*, 2786–2794. [CrossRef] [PubMed]

5. Eisenberg, M.L.; Kim, S.; Chen, Z.; Sundaram, R.; Schisterman, E.F.; Buck Louis, G.M. The relationship between male BMI and waist circumference on semen quality: Data from the LIFE study. *Hum. Reprod.* **2014**, *29*, 193–200. [CrossRef] [PubMed]

6.  Apridonidze, T.; Essah, P.A.; Iuorno, M.J.; Nestler, J.E. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **2005**, *90*, 1929–1935. [CrossRef] [PubMed]

7.  Maqdasy, S.; Baptissart, M.; Vega, A.; Baron, S.; Lobaccaro, J.-M.A.; Volle, D.H. Cholesterol and male fertility: What about orphans and adopted? *Mol. Cell. Endocrinol.* **2013**, *368*, 30–46. [CrossRef] [PubMed]

8.  Pitteloud, N.; Hardin, M.; Dwyer, A.A.; Valassi, E.; Yialamas, M.; Elahi, D.; Hayes, F.J. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. *J. Clin. Endocrinol. Metab.* **2005**, *90*, 2636–2641. [CrossRef] [PubMed]

9.  Wang, B.; Tontonoz, P. Liver X receptors in lipid signalling and membrane homeostasis. *Nat. Rev. Endocrinol.* **2018**. [CrossRef] [PubMed]

10. Christiansen-Weber, T.A.; Voland, J.R.; Wu, Y.; Ngo, K.; Roland, B.L.; Nguyen, S.; Peterson, P.A.; Fung-Leung, W.P. Functional loss of ABCA1 in mice causes severe placental malformation, aberrant lipid distribution, and kidney glomerulonephritis as well as high-density lipoprotein cholesterol deficiency. *Am. J. Pathol.* **2000**, *157*, 1017–1029. [CrossRef]

11. Yesilaltay, A.; Dokshin, G.A.; Busso, D.; Wang, L.; Galiani, D.; Chavarria, T.; Vasile, E.; Quilaqueo, L.; Orellana, J.A.; Walzer, D.; et al. Excess cholesterol induces mouse egg activation and may cause female infertility. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, E4972–E4980. [CrossRef] [PubMed]

12. Cummins, C.L.; Volle, D.H.; Zhang, Y.; McDonald, J.G.; Sion, B.; Lefrançois-Martinez, A.-M.; Caira, F.; Veyssière, G.; Mangelsdorf, D.J.; Lobaccaro, J.-M.A. Liver X receptors regulate adrenal cholesterol balance. *J. Clin. Investig.* **2006**, *116*, 1902–1912. [CrossRef] [PubMed]

13. Joseph, S.B.; Castrillo, A.; Laffitte, B.A.; Mangelsdorf, D.J.; Tontonoz, P. Reciprocal regulation of inflammation and lipid metabolism by liver X receptors. *Nat. Med.* **2003**, *9*, 213–219. [CrossRef] [PubMed]

14. Maqdasy, S.; El Hajjaji, F.-Z.; Baptissart, M.; Viennois, E.; Oumeddour, A.; Brugnon, F.; Trousson, A.; Tauveron, I.; Volle, D.; Lobaccaro, J.-M.A.; et al. Identification of the functions of Liver X Receptor β in Sertoli cells using a targeted expression-rescue model. *Endocrinology* **2015**, *156*, 4545–4557. [CrossRef] [PubMed]

15. Mouzat, K.; Baron, S.; Marceau, G.; Caira, F.; Sapin, V.; Volle, D.H.; Lumbroso, S.; Lobaccaro, J.-M. Emerging roles for LXRs and LRH-1 in female reproduction. *Mol. Cell. Endocrinol.* **2013**, *368*, 47–58. [CrossRef] [PubMed]

16. Mouzat, K.; Volat, F.; Baron, S.; Alves, G.; Pommier, A.J.C.; Volle, D.H.; Marceau, G.; DeHaze, A.; Déchelotte, P.; Duggavathi, R.; et al. Absence of nuclear receptors for oxysterols liver X receptor induces ovarian hyperstimulation syndrome in mice. *Endocrinology* **2009**, *150*, 3369–3375. [CrossRef] [PubMed]

17. Volle, D.H.; Mouzat, K.; Duggavathi, R.; Siddeek, B.; Déchelotte, P.; Sion, B.; Veyssière, G.; Benahmed, M.; Lobaccaro, J.-M.A. Multiple roles of the nuclear receptors for oxysterols liver X receptor to maintain male fertility. *Mol. Endocrinol. Baltim.* **2007**, *21*, 1014–1027. [CrossRef] [PubMed]

18. Janowski, B.A.; Willy, P.J.; Devi, T.R.; Falck, J.R.; Mangelsdorf, D.J. An oxysterol signalling pathway mediated by the nuclear receptor LXR alpha. *Nature* **1996**, *383*, 728–731. [CrossRef] [PubMed]

19. Grøndahl, C.; Ottesen, J.L.; Lessl, M.; Faarup, P.; Murray, A.; Grønvald, F.C.; Hegele-Hartung, C.; Ahnfelt-Rønne, I. Meiosis-activating sterol promotes resumption of meiosis in mouse oocytes cultured in vitro in contrast to related oxysterols. *Biol. Reprod.* **1998**, *58*, 1297–1302. [CrossRef] [PubMed]

20. Steffensen, K.R.; Robertson, K.; Gustafsson, J.-A.; Andersen, C.Y. Reduced fertility and inability of oocytes to resume meiosis in mice deficient of the *Lxr* genes. *Mol. Cell. Endocrinol.* **2006**, *256*, 9–16. [CrossRef] [PubMed]

21. Sarfati, J.; Young, J.; Christin-Maitre, S. Obesity and female reproduction. *Ann. Endocrinol.* **2010**, *71* (Suppl. 1), S49–S53. [CrossRef]

22. Teede, H.J.; Meyer, C.; Hutchison, S.K.; Zoungas, S.; McGrath, B.P.; Moran, L.J. Endothelial function and insulin resistance in polycystic ovary syndrome: The effects of medical therapy. *Fertil. Steril.* **2010**, *93*, 184–191. [CrossRef] [PubMed]

23. March, W.A.; Moore, V.M.; Willson, K.J.; Phillips, D.I.W.; Norman, R.J.; Davies, M.J. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum. Reprod.* **2010**, *25*, 544–551. [CrossRef] [PubMed]

24. Azziz, R.; Woods, K.S.; Reyna, R.; Key, T.J.; Knochenhauer, E.S.; Yildiz, B.O. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 2745–2749. [CrossRef] [PubMed]

25. Conway, G.; Dewailly, D.; Diamanti-Kandarakis, E.; Escobar-Morreale, H.F.; Franks, S.; Gambineri, A.; Kelestimur, F.; Macut, D.; Micic, D.; Pasquali, R.; et al. The polycystic ovary syndrome: A position statement from the European Society of Endocrinology. *Eur. J. Endocrinol.* **2014**, *171*, 1–29. [CrossRef] [PubMed]

26. Cardozo, E.; Pavone, M.E.; Hirshfeld-Cytron, J.E. Metabolic syndrome and oocyte quality. *Trends Endocrinol. Metab.* **2011**, *22*, 103–109. [CrossRef] [PubMed]

27. Silvestris, E.; de Pergola, G.; Rosania, R.; Loverro, G. Obesity as disruptor of the female fertility. *Reprod. Biol. Endocrinol.* **2018**, *16*, 22. [CrossRef] [PubMed]

28. Merhi, Z. Advanced glycation end products and their relevance in female reproduction. *Hum. Reprod.* **2014**, *29*, 135–145. [CrossRef] [PubMed]

29. Ramlau-Hansen, C.H.; Thulstrup, A.M.; Nohr, E.A.; Bonde, J.P.; Sørensen, T.I.A.; Olsen, J. Subfecundity in overweight and obese couples. *Hum. Reprod.* **2007**, *22*, 1634–1637. [CrossRef] [PubMed]

30. Gracia, C.R.; Freeman, E.W.; Sammel, M.D.; Lin, H.; Nelson, D.B. The relationship between obesity and race on inhibin B during the menopause transition. *Menopause* **2005**, *12*, 559–566. [CrossRef] [PubMed]

31. Freeman, E.W.; Gracia, C.R.; Sammel, M.D.; Lin, H.; Lim, L.C.-L.; Strauss, J.F. Association of anti-mullerian hormone levels with obesity in late reproductive-age women. *Fertil. Steril.* **2007**, *87*, 101–106. [CrossRef] [PubMed]

32. Minge, C.E.; Bennett, B.D.; Norman, R.J.; Robker, R.L. Peroxisome proliferator-activated receptor-gamma agonist rosiglitazone reverses the adverse effects of diet-induced obesity on oocyte quality. *Endocrinology* **2008**, *149*, 2646–2656. [CrossRef] [PubMed]

33. Jungheim, E.S.; Schoeller, E.L.; Marquard, K.L.; Louden, E.D.; Schaffer, J.E.; Moley, K.H. Diet-induced obesity model: Abnormal oocytes and persistent growth abnormalities in the offspring. *Endocrinology* **2010**, *151*, 4039–4046. [CrossRef] [PubMed]

34. Igosheva, N.; Abramov, A.Y.; Poston, L.; Eckert, J.J.; Fleming, T.P.; Duchen, M.R.; McConnell, J. Maternal diet-induced obesity alters mitochondrial activity and redox status in mouse oocytes and zygotes. *PLoS ONE* **2010**, *5*, e10074. [CrossRef] [PubMed]

35. Trigatti, B.; Rayburn, H.; Viñals, M.; Braun, A.; Miettinen, H.; Penman, M.; Hertz, M.; Schrenzel, M.; Amigo, L.; Rigotti, A.; et al. Influence of the high density lipoprotein receptor SR-BI on reproductive and cardiovascular pathophysiology. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 9322–9327. [CrossRef] [PubMed]

36. Zhang, T.; Dai, P.; Cheng, D.; Zhang, L.; Chen, Z.; Meng, X.; Zhang, F.; Han, X.; Liu, J.; Pan, J.; et al. Obesity occurring in apolipoprotein E-knockout mice has mild effects on fertility. *Reproduction* **2014**, *147*, 141–151. [CrossRef] [PubMed]

37. Fujimoto, V.Y.; Kane, J.P.; Ishida, B.Y.; Bloom, M.S.; Browne, R.W. High-density lipoprotein metabolism and the human embryo. *Hum. Reprod. Update* **2010**, *16*, 20–38. [CrossRef] [PubMed]

38. Mahley, R.W.; Rall, S.C. Apolipoprotein E: Far more than a lipid transport protein. *Annu. Rev. Genom. Hum. Genet.* **2000**, *1*, 507–537. [CrossRef] [PubMed]

39. Corbo, R.M.; Ulizzi, L.; Scacchi, R.; Martínez-Labarga, C.; De Stefano, G.F. Apolipoprotein E polymorphism and fertility: A study in pre-industrial populations. *Mol. Hum. Reprod.* **2004**, *10*, 617–620. [CrossRef] [PubMed]

40. Janowski, B.A.; Grogan, M.J.; Jones, S.A.; Wisely, G.B.; Kliewer, S.A.; Corey, E.J.; Mangelsdorf, D.J. Structural requirements of ligands for the oxysterol liver X receptors LXRalpha and LXRbeta. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 266–271. [CrossRef] [PubMed]

41. De Medina, P.; Paillasse, M.R.; Segala, G.; Voisin, M.; Mhamdi, L.; Dalenc, F.; Lacroix-Triki, M.; Filleron, T.; Pont, F.; Saati, T.A.; et al. Dendrogenin A arises from cholesterol and histamine metabolism and shows cell differentiation and anti-tumour properties. *Nat. Commun.* **2013**, *4*, 1840. [CrossRef] [PubMed]

42. Poirot, M.; Silvente-Poirot, S. The tumor-suppressor cholesterol metabolite, dendrogenin A, is a new class of LXR modulator activating lethal autophagy in cancers. *Biochem. Pharmacol.* **2018**, *153*, 75–81. [CrossRef] [PubMed]

43. Drouineaud, V.; Sagot, P.; Garrido, C.; Logette, E.; Deckert, V.; Gambert, P.; Jimenez, C.; Staels, B.; Lagrost, L.; Masson, D. Inhibition of progesterone production in human luteinized granulosa cells treated with LXR agonists. *Mol. Hum. Reprod.* **2007**, *13*, 373–379. [CrossRef] [PubMed]

44. Leonardsen, L.; Wiersma, A.; Baltsen, M.; Byskov, A.G.; Andersen, C.Y. Regulation of spontaneous and induced resumption of meiosis in mouse oocytes by different intracellular pathways. *J. Reprod. Fertil.* **2000**, *120*, 377–383. [CrossRef] [PubMed]

45. Grøndahl, C. Oocyte maturation. Basic and clinical aspects of in vitro maturation (IVM) with special emphasis of the role of FF-MAS. *Dan. Med. Bull.* **2008**, *55*, 1–16. [PubMed]

46. Marín Bivens, C.L.; Lindenthal, B.; O'Brien, M.J.; Wigglesworth, K.; Blume, T.; Grøndahl, C.; Eppig, J.J. A synthetic analogue of meiosis-activating sterol (FF-MAS) is a potent agonist promoting meiotic maturation and preimplantation development of mouse oocytes maturing in vitro. *Hum. Reprod.* **2004**, *19*, 2340–2344. [CrossRef] [PubMed]

47. Xu, Y.; Hernández-Ledezma, J.J.; Hutchison, S.M.; Bogan, R.L. The liver X receptors and sterol regulatory element binding proteins alter progesterone secretion and are regulated by human chorionic gonadotropin in human luteinized granulosa cells. *Mol. Cell. Endocrinol.* **2018**. [CrossRef] [PubMed]

48. Artini, P.G.; Monti, M.; Fasciani, A.; Battaglia, C.; D'Ambrogio, G.; Genazzani, A.R. Vascular endothelial growth factor, interleukin-6 and interleukin-2 in serum and follicular fluid of patients with ovarian hyperstimulation syndrome. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2002**, *101*, 169–174. [CrossRef]

49. Bar-Joseph, H.; Ben-Ami, I.; Ron-El, R.; Shalgi, R.; Chuderland, D. Pigment epithelium-derived factor regulation by human chorionic gonadotropin in granulosa cells. *Reproduction* **2016**, *151*, 179–185. [CrossRef] [PubMed]

50. Chen, C.D.; Chen, H.F.; Lu, H.F.; Chen, S.U.; Ho, H.N.; Yang, Y.S. Value of serum and follicular fluid cytokine profile in the prediction of moderate to severe ovarian hyperstimulation syndrome. *Hum. Reprod.* **2000**, *15*, 1037–1042. [CrossRef] [PubMed]

51. Chuderland, D.; Ben-Ami, I.; Kaplan-Kraicer, R.; Grossman, H.; Ron-El, R.; Shalgi, R. The role of pigment epithelium-derived factor in the pathophysiology and treatment of ovarian hyperstimulation syndrome in mice. *J. Clin. Endocrinol. Metab.* **2013**, *98*, E258–E266. [CrossRef] [PubMed]

52. Miller, I.; Chuderland, D.; Ron-El, R.; Shalgi, R.; Ben-Ami, I. GnRH Agonist Triggering Modulates PEDF to VEGF Ratio Inversely to hCG in Granulosa Cells. *J. Clin. Endocrinol. Metab.* **2015**, *100*, E1428–E1436. [CrossRef] [PubMed]

53. Wei, L.-H.; Chou, C.-H.; Chen, M.-W.; Rose-John, S.; Kuo, M.-L.; Chen, S.-U.; Yang, Y.-S. The role of IL-6 trans-signaling in vascular leakage: Implications for ovarian hyperstimulation syndrome in a murine model. *J. Clin. Endocrinol. Metab.* **2013**, *98*, E472–E484. [CrossRef] [PubMed]

54. Pellicer, A.; Albert, C.; Mercader, A.; Bonilla-Musoles, F.; Remohí, J.; Simón, C. The pathogenesis of ovarian hyperstimulation syndrome: In vivo studies investigating the role of interleukin-1beta, interleukin-6, and vascular endothelial growth factor. *Fertil. Steril.* **1999**, *71*, 482–489. [CrossRef]

55. Landis, M.S.; Patel, H.V.; Capone, J.P. Oxysterol activators of liver X receptor and 9-cis-retinoic acid promote sequential steps in the synthesis and secretion of tumor necrosis factor-alpha from human monocytes. *J. Biol. Chem.* **2002**, *277*, 4713–4721. [CrossRef] [PubMed]

56. Walczak, R.; Joseph, S.B.; Laffitte, B.A.; Castrillo, A.; Pei, L.; Tontonoz, P. Transcription of the vascular endothelial growth factor gene in macrophages is regulated by liver X receptors. *J. Biol. Chem.* **2004**, *279*, 9905–9911. [CrossRef] [PubMed]

57. Beyer, C.; Huang, J.; Beer, J.; Zhang, Y.; Palumbo-Zerr, K.; Zerr, P.; Distler, A.; Dees, C.; Maier, C.; Munoz, L.; et al. Activation of liver X receptors inhibits experimental fibrosis by interfering with interleukin-6 release from macrophages. *Ann. Rheum. Dis.* **2015**, *74*, 1317–1324. [CrossRef] [PubMed]

58. Noghero, A.; Perino, A.; Seano, G.; Saglio, E.; Lo Sasso, G.; Veglio, F.; Primo, L.; Hirsch, E.; Bussolino, F.; Morello, F. Liver X receptor activation reduces angiogenesis by impairing lipid raft localization and signaling of vascular endothelial growth factor receptor-2. *Arterioscler. Thromb. Vasc. Biol.* **2012**, *32*, 2280–2288. [CrossRef] [PubMed]

59. Nunomura, S.; Okayama, Y.; Matsumoto, K.; Hashimoto, N.; Endo-Umeda, K.; Terui, T.; Makishima, M.; Ra, C. Activation of LXRs using the synthetic agonist GW3965 represses the production of pro-inflammatory cytokines by murine mast cells. *Allergol. Int.* **2015**, *64* (Suppl. 1), 11–17. [CrossRef] [PubMed]

60. Andreasen, K.R.; Andersen, M.L.; Schantz, A.L. Obesity and pregnancy. *Acta Obstet. Gynecol. Scand.* **2004**, *83*, 1022–1029. [CrossRef] [PubMed]

61. Sebire, N.J.; Jolly, M.; Harris, J.P.; Wadsworth, J.; Joffe, M.; Beard, R.W.; Regan, L.; Robinson, S. Maternal obesity and pregnancy outcome: A study of 287,213 pregnancies in London. *Int. J. Obes. Relat. Metab. Disord.* **2001**, *25*, 1175–1182. [CrossRef] [PubMed]

62. Zhang, J.; Bricker, L.; Wray, S.; Quenby, S. Poor uterine contractility in obese women. *Int. J. Obstet. Gynaecol.* **2007**, *114*, 343–348. [CrossRef] [PubMed]

63. Barau, G.; Robillard, P.-Y.; Hulsey, T.C.; Dedecker, F.; Laffite, A.; Gérardin, P.; Kauffmann, E. Linear association between maternal pre-pregnancy body mass index and risk of caesarean section in term deliveries. *Int. J. Obstet. Gynaecol.* **2006**, *113*, 1173–1177. [CrossRef] [PubMed]

64. Doherty, D.A.; Magann, E.F.; Francis, J.; Morrison, J.C.; Newnham, J.P. Pre-pregnancy body mass index and pregnancy outcomes. *Int. J. Gynaecol. Obstet.* **2006**, *95*, 242–247. [CrossRef] [PubMed]

65. Kabiru, W.; Raynor, B.D. Obstetric outcomes associated with increase in BMI category during pregnancy. *Am. J. Obstet. Gynecol.* **2004**, *191*, 928–932. [CrossRef] [PubMed]

66. Shankar, K.; Zhong, Y.; Kang, P.; Lau, F.; Blackburn, M.L.; Chen, J.-R.; Borengasser, S.J.; Ronis, M.J.J.; Badger, T.M. Maternal obesity promotes a proinflammatory signature in rat uterus and blastocyst. *Endocrinology* **2011**, *152*, 4158–4170. [CrossRef] [PubMed]

67. Garris, D.R.; Garris, B.L. Cytolipotoxicity-induced involution of the female reproductive tract following expression of obese (ob/ob) and diabetes (db/db) genotype mutations: Progressive, hyperlipidemic transformation into adipocytic tissues. *Reprod. Toxicol.* **2004**, *18*, 81–91. [CrossRef] [PubMed]

68. Smith, R.D.; Babiychuk, E.B.; Noble, K.; Draeger, A.; Wray, S. Increased cholesterol decreases uterine activity: Functional effects of cholesterol alteration in pregnant rat myometrium. *Am. J. Physiol. Cell Physiol.* **2005**, *288*, C982–C988. [CrossRef] [PubMed]

69. Noble, K.; Zhang, J.; Wray, S. Lipid rafts, the sarcoplasmic reticulum and uterine calcium signalling: An integrated approach. *J. Physiol.* **2006**, *570*, 29–35. [CrossRef] [PubMed]

70. Mouzat, K.; Prod'homme, M.; Volle, D.H.; Sion, B.; Déchelotte, P.; Gauthier, K.; Vanacker, J.-M.; Lobaccaro, J.-M.A. Oxysterol nuclear receptor LXRbeta regulates cholesterol homeostasis and contractile function in mouse uterus. *J. Biol. Chem.* **2007**, *282*, 4693–4701. [CrossRef] [PubMed]

71. Costa, M.A. The endocrine function of human placenta: An overview. *Reprod. Biomed. Online* **2016**, *32*, 14–43. [CrossRef] [PubMed]

72. Abalos, E.; Cuesta, C.; Grosso, A.L.; Chou, D.; Say, L. Global and regional estimates of preeclampsia and eclampsia: A systematic review. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2013**, *170*, 1–7. [CrossRef] [PubMed]

73. Khan, K.S.; Wojdyla, D.; Say, L.; Gülmezoglu, A.M.; Van Look, P.F.A. WHO analysis of causes of maternal death: A systematic review. *Lancet* **2006**, *367*, 1066–1074. [CrossRef]

74. Myatt, L. Role of placenta in preeclampsia. *Endocrine* **2002**, *19*, 103–111. [CrossRef]

75. Myatt, L.; Webster, R.P. Vascular biology of preeclampsia. *J. Thromb. Haemost.* **2009**, *7*, 375–384. [CrossRef] [PubMed]

76. Pijnenborg, R.; Vercruysse, L.; Hanssens, M. The uterine spiral arteries in human pregnancy: Facts and controversies. *Placenta* **2006**, *27*, 939–958. [CrossRef] [PubMed]

77. Pavan, L.; Hermouet, A.; Tsatsaris, V.; Thérond, P.; Sawamura, T.; Evain-Brion, D.; Fournier, T. Lipids from oxidized low-density lipoprotein modulate human trophoblast invasion: Involvement of nuclear liver X receptors. *Endocrinology* **2004**, *145*, 4583–4591. [CrossRef] [PubMed]

78. Marceau, G.; Volle, D.H.; Gallot, D.; Mangelsdorf, D.J.; Sapin, V.; Lobaccaro, J.-M.A. Placental expression of the nuclear receptors for oxysterols LXRalpha and LXRbeta during mouse and human development. *Anat. Rec. A Discov. Mol. Cell. Evol. Biol.* **2005**, *283*, 175–181. [CrossRef] [PubMed]

79. Plösch, T.; Gellhaus, A.; van Straten, E.M.E.; Wolf, N.; Huijkman, N.C.A.; Schmidt, M.; Dunk, C.E.; Kuipers, F.; Winterhager, E. The liver X receptor (LXR) and its target gene ABCA1 are regulated upon low oxygen in human trophoblast cells: A reason for alterations in preeclampsia? *Placenta* **2010**, *31*, 910–918. [CrossRef] [PubMed]

80. Schroepfer, G.J. Oxysterols: Modulators of cholesterol metabolism and other processes. *Physiol. Rev.* **2000**, *80*, 361–554. [CrossRef] [PubMed]

81. Woollett, L.A. Review: Transport of maternal cholesterol to the fetal circulation. *Placenta* **2011**, *32* (Suppl. 2), S218–S221. [CrossRef] [PubMed]

82. Fournier, T.; Handschuh, K.; Tsatsaris, V.; Guibourdenche, J.; Evain-Brion, D. Role of nuclear receptors and their ligands in human trophoblast invasion. *J. Reprod. Immunol.* **2008**, *77*, 161–170. [CrossRef] [PubMed]

83. Aye, I.L.M.H.; Waddell, B.J.; Mark, P.J.; Keelan, J.A. Oxysterols inhibit differentiation and fusion of term primary trophoblasts by activating liver X receptors. *Placenta* **2011**, *32*, 183–191. [CrossRef] [PubMed]

84. Weedon-Fekjær, M.S.; Johnsen, G.M.; Anthonisen, E.H.; Sugulle, M.; Nebb, H.I.; Duttaroy, A.K.; Staff, A.C. Expression of liver X receptors in pregnancies complicated by preeclampsia. *Placenta* **2010**, *31*, 818–824. [CrossRef] [PubMed]

85. Henry-Berger, J.; Mouzat, K.; Baron, S.; Bernabeu, C.; Marceau, G.; Saru, J.-P.; Sapin, V.; Lobaccaro, J.-M.A.; Caira, F. Endoglin (CD105) expression is regulated by the liver X receptor alpha (NR1H3) in human trophoblast cell line JAR. *Biol. Reprod.* **2008**, *78*, 968–975. [CrossRef] [PubMed]

86. Venkatesha, S.; Toporsian, M.; Lam, C.; Hanai, J.; Mammoto, T.; Kim, Y.M.; Bdolah, Y.; Lim, K.-H.; Yuan, H.-T.; Libermann, T.A.; et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat. Med.* **2006**, *12*, 642–649. [CrossRef] [PubMed]

87. Mouzat, K.; Mercier, E.; Polge, A.; Evrard, A.; Baron, S.; Balducchi, J.-P.; Brouillet, J.-P.; Lumbroso, S.; Gris, J.-C. A common polymorphism in NR1H2 (LXRbeta) is associated with preeclampsia. *BMC Med. Genet.* **2011**, *12*, 145. [CrossRef] [PubMed]

88. Burstein, H.J.; Mangu, P.B.; Somerfield, M.R.; Schrag, D.; Samson, D.; Holt, L.; Zelman, D.; Ajani, J.A. American Society of Clinical Oncology American Society of Clinical Oncology clinical practice guideline update on the use of chemotherapy sensitivity and resistance assays. *J. Clin. Oncol.* **2011**, *29*, 3328–3330. [CrossRef] [PubMed]

89. Obiorah, I.; Jordan, V.C. Progress in endocrine approaches to the treatment and prevention of breast cancer. *Maturitas* **2011**, *70*, 315–321. [CrossRef] [PubMed]

90. Foulkes, W.D.; Smith, I.E.; Reis-Filho, J.S. Triple-negative breast cancer. *N. Engl. J. Med.* **2010**, *363*, 1938–1948. [CrossRef] [PubMed]

91. Bianchini, F.; Kaaks, R.; Vainio, H. Overweight, obesity, and cancer risk. *Lancet Oncol.* **2002**, *3*, 565–574. [CrossRef]

92. Kitahara, C.M.; Berrington de González, A.; Freedman, N.D.; Huxley, R.; Mok, Y.; Jee, S.H.; Samet, J.M. Total cholesterol and cancer risk in a large prospective study in Korea. *J. Clin. Oncol.* **2011**, *29*, 1592–1598. [CrossRef] [PubMed]

93. Ferraroni, M.; Gerber, M.; Decarli, A.; Richardson, S.; Marubini, E.; Crastes de Paulet, P.; Crastes de Paulet, A.; Pujol, H. HDL-cholesterol and breast cancer: A joint study in northern Italy and southern France. *Int. J. Epidemiol.* **1993**, *22*, 772–780. [CrossRef] [PubMed]

94. Nielsen, S.F.; Nordestgaard, B.G.; Bojesen, S.E. Statin use and reduced cancer-related mortality. *N. Engl. J. Med.* **2012**, *367*, 1792–1802. [CrossRef] [PubMed]

95. Renehan, A.G.; Roberts, D.L.; Dive, C. Obesity and cancer: Pathophysiological and biological mechanisms. *Arch. Physiol. Biochem.* **2008**, *114*, 71–83. [CrossRef] [PubMed]

96. Vedin, L.-L.; Lewandowski, S.A.; Parini, P.; Gustafsson, J.-A.; Steffensen, K.R. The oxysterol receptor LXR inhibits proliferation of human breast cancer cells. *Carcinogenesis* **2009**, *30*, 575–579. [CrossRef] [PubMed]

97. Song, W.C. Biochemistry and reproductive endocrinology of estrogen sulfotransferase. *Ann. N. Y. Acad. Sci.* **2001**, *948*, 43–50. [CrossRef] [PubMed]

98. Kramer, P.R.; Wray, S. 17-Beta-estradiol regulates expression of genes that function in macrophage activation and cholesterol homeostasis. *J. Steroid Biochem. Mol. Biol.* **2002**, *81*, 203–216. [CrossRef]

99. Lundholm, L.; Movérare, S.; Steffensen, K.R.; Nilsson, M.; Otsuki, M.; Ohlsson, C.; Gustafsson, J.-A.; Dahlman-Wright, K. Gene expression profiling identifies liver X receptor alpha as an estrogen-regulated gene in mouse adipose tissue. *J. Mol. Endocrinol.* **2004**, *32*, 879–892. [CrossRef] [PubMed]

100. Han, S.-I.; Komatsu, Y.; Murayama, A.; Steffensen, K.R.; Nakagawa, Y.; Nakajima, Y.; Suzuki, M.; Oie, S.; Parini, P.; Vedin, L.-L.; et al. Estrogen receptor ligands ameliorate fatty liver through a nonclassical estrogen receptor/Liver X receptor pathway in mice. *Hepatol. Baltim.* **2014**, *59*, 1791–1802. [CrossRef] [PubMed]

101. D'Eon, T.M.; Souza, S.C.; Aronovitz, M.; Obin, M.S.; Fried, S.K.; Greenberg, A.S. Estrogen regulation of adiposity and fuel partitioning. Evidence of genomic and non-genomic regulation of lipogenic and oxidative pathways. *J. Biol. Chem.* **2005**, *280*, 35983–35991. [CrossRef] [PubMed]

102. Nguyen-Vu, T.; Vedin, L.-L.; Liu, K.; Jonsson, P.; Lin, J.Z.; Candelaria, N.R.; Candelaria, L.P.; Addanki, S.; Williams, C.; Gustafsson, J.-Å.; et al. Liver × receptor ligands disrupt breast cancer cell proliferation through an E2F-mediated mechanism. *Breast Cancer Res.* **2013**, *15*, R51. [CrossRef] [PubMed]

103. El Roz, A.; Bard, J.-M.; Valin, S.; Huvelin, J.-M.; Nazih, H. Macrophage apolipoprotein E and proliferation of MCF-7 breast cancer cells: Role of LXR. *Anticancer Res.* **2013**, *33*, 3783–3789. [PubMed]

104. El Roz, A.; Bard, J.-M.; Huvelin, J.-M.; Nazih, H. LXR agonists and ABCG1-dependent cholesterol efflux in MCF-7 breast cancer cells: Relation to proliferation and apoptosis. *Anticancer Res.* **2012**, *32*, 3007–3013. [PubMed]

105. El Roz, A.; Bard, J.M.; Huvelin, J.M.; Nazih, H. The anti-proliferative and pro-apoptotic effects of the trans9, trans11 conjugated linoleic acid isomer on MCF-7 breast cancer cells are associated with LXR activation. *Prostaglandins Leukot. Essent. Fatty Acids* **2013**, *88*, 265–272. [CrossRef] [PubMed]

106. Gong, H.; Guo, P.; Zhai, Y.; Zhou, J.; Uppal, H.; Jarzynka, M.J.; Song, W.-C.; Cheng, S.-Y.; Xie, W. Estrogen deprivation and inhibition of breast cancer growth in vivo through activation of the orphan nuclear receptor liver X receptor. *Mol. Endocrinol. Baltim.* **2007**, *21*, 1781–1790. [CrossRef] [PubMed]

107. Hassan, T.S.; Paniccia, A.; Russo, V.; Steffensen, K.R. LXR Inhibits Proliferation of Human Breast Cancer Cells through the PI3K-Akt Pathway. *Nucl. Recept. Res.* **2015**, *2*, 101154. [CrossRef]

108. Nelson, E.R.; Wardell, S.E.; Jasper, J.S.; Park, S.; Suchindran, S.; Howe, M.K.; Carver, N.J.; Pillai, R.V.; Sullivan, P.M.; Sondhi, V.; et al. 27-Hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology. *Science* **2013**, *342*, 1094–1098. [CrossRef] [PubMed]

109. Warner, M.; Gustafsson, J.-A. On estrogen, cholesterol metabolism, and breast cancer. *N. Engl. J. Med.* **2014**, *370*, 572–573. [CrossRef] [PubMed]