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Adverse Effects of Excessive FSH in Extragonadal Diseases

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Abstract

Levels of Follicle-Stimulating Hormone (FSH) rise during menopausal transition. Many studies have shown that FSH in various extragonadal tissues and organs plays a critical role in the pathogenesis of multiple diseases. Papers published in the PubMed and Web of Science were systematically searched in this narrative literature review. Here, we summarize the effects of FSH on disease pathogenesis, including liver diseases, Alzheimer's disease, osteoporosis, cardiovascular disease, adiposity, and cancer, while proposing that FSH-induced harm is ubiquitous. Recently, several elegant studies reported that blocking the action of FSH with a polyclonal antibody potently prevents pathophysiological changes during menopausal transition in animal studies. This review will help broaden the appreciation of the harmful effects of FSH and thus potentially expand therapeutic trials of FSH blocking agents.

Keywords: Follicle-stimulating hormone (FSH); FSH receptors; Menopausal transition; Extragonadal actions

Introduction

Levels of Follicle-Stimulating Hormone (FSH) rise during menopausal transition (the term "menopausal transition" was defined at 2011 Stages of Reproductive Aging Workshop (STRAW) + 10 system [1]), and women experience menstrual cycle changes and significant physiological changes involving various cells and tissues. These changes can seriously affect women's quality of life and health. Current menopausal hormone therapy presents limited efficacy and are often associated with a broad range of side effects [2]. Hence, new therapeutic interventions are urgently needed, and interventions targeting FSH might be able to reduce risks following changes during menopausal transition.

FSH is secreted from gonadotrope cells in the anterior pituitary and plays a key role in the control of gonadal function and reproduction [3,4]. The function of FSH is mediated through the FSH receptor (FSHR), which belongs to the G Protein-Coupled Receptor (GPCR). FSHR is generally expressed in gonads, namely, the ovary and testis. By now, it has been showed that FSHR is expressed in numerous extragonadal cells and tissues, such as the liver [5, 6], hippocampus [7,8], osteoclasts [9], adipocytes [10], and endothelial cells [11] (Table 1).

FSH is a heterodimer consisting of an alpha subunit and a beta subunit. It is the beta subunit of FSH that endows FSH with the ability to combine with FSHR and exerts its specific biological function [12]. Recently, emerging animal studies have revealed that blocking the action of FSH with an FSH-beta antibody or knocking out FSHR potently prevents dyslipidaemia [5], Alzheimer's disease [7], osteoporosis [13,14], atherosclerosis [15], obesity [13] and other diseases [16]. Increasing data are carried out to test the effects of blocking FSH. Thus, in this review, we summarize these results, while providing a deeper insight into the extragonadal actions of FSH in different tissues.

Methods

Data Sources and Searches

The concept of this review stemmed from limitation of current menopausal hormone therapy and extensive role of FSH in extragonadal tissues. PubMed and Web of Science were systematically searched using keywords: FSH, FSHR, menopausal transition, postmenopause, menopausal hormone therapy, liver, nonalcoholic fatty liver disease (NAFLD), lipid, glucose, glycogenolysis, gluconeogenesis, cognitive impairment (or cognitive dysfunction), Alzheimer's disease, neurodegenerative, bone loss, osteoporosis, cardiovascular diseases, atherosclerosis, coronary, endothelial cells, fat, adiposity (or adipose, adipocytes), metabolic syndrome, cancer, tumor, malignant, carcinogenesis, proliferation, invasion and migration. Relevant studies were also identified from review articles.

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Table 1: FSHR expression and function.

Gene	Expression in extragonadal cells and tissues	Direct extragonadal activity of FSH
Human FSHR *Gene ID: 2492*	Liver [5,6]	
	Cortex [7]	
	Neuroblastoma cells [7]	
	Endothelium of vascular anomalies [11], human umbilical vascular endothelial cells (HUVECs) [12]	FSH directly upregulated VCAM-1 expression in HUVECs [12].
	Tumor cells, including: Breast cancer, Colon cancer, Kidney cancer, Lung cancer, Prostate cancer, Leiomyosarcoma [11]	
Mouse FSHR *Gene ID: 14309*	Liver [5,6]	Results characterized a novel role of FSH, independent of estrogen, as a potential regulator of hepatic cholesterol biosynthesis. Blocking FSH signaling could significantly reduce cholesterol biosynthesis in the liver, thereby ameliorating high serum level of cholesterol [5].
	Cortex and hippocampus [7]	The study not only suggest a causal role for rising serum FSH levels in the exaggerated Alzheimer's disease pathophysiology during menopause, but also reveal an opportunity for treating Alzheimer's disease [7].
	Osteoclasts and osteoclast orecursors [9]	High circulating FSH causes hypogonadal bone loss [9]. Blocking antibody to the β-subunit of FSH prevents bone loss by inhibiting bone resorption and stimulating bone synthesis [13,14].
	Inguinal and visceral white adipose tissue (WAT) and brown adipose tissue (BAT) [13], and 3T3.L1 cells [10, 13]	FSH inhibits Ucp1 expression by reducing cAMP levels [10, 13]. FSHβ antibody caused a sharp, timedependent increase in Ucp1 in both BAT and WAT, resulting in a marked reduction in adiposity, coupled with the production of mitochondria-rich, Ucp1-high thermogenic adipose tissue [13].
Rat FSHR *Gene ID: 25449*	Cortical neurons [7]	
	Hippocampus [8]	

Data extraction and summary

Two authors independently screened the search results for eligible studies. Two authors extracted details of study design, patient population or animal studies, and summarized identified studies into figures and tables. Two authors reviewed the concept and design, and wrote and revised the manuscript.

Change in FSH across the Menopausal Transition

Aging women experience the transition from a reproductive to a nonreproductive phase (menopause), as manifested by the World Health Organization (WHO) defined Menopausal Transition (MT) at the 2011 STRAW + 10system [1]. The MT stage is primarily described by patterns of uterine bleeding and is anchored to the termination of bleeding and the Final Menstrual Period (FMP) [17]. The definition of entry into the early menopause transition was refined as the onset of menstrual cycle length variability with a persistent difference of 7 days or more in the length of consecutive cycles, and the persistence was defined as at least one recurrence within 10 cycles of the first variable length cycle [1]. The MT stage begins approximately 2 yr before FMP. FSH has a primary function in procreation, wherein it induces estrogen production in the ovary. As the ovary ages, FSH levels rise, resulting from progressive dysregulation of the hypothalamic-pituitary-ovarian system. In the Study of Women's Health Across the Nation (SWAN) [17], the FSH pattern across the menopausal transition began with an increase 6.10 yr before the FMP, an acceleration 2.05 yr before the FMP, deceleration beginning 0.20 yr before the FMP, and stabilization 2.00 yr after the FMP. The mean E2 concentration did not change until 2.03 yr before the FMP when it began decreasing, achieving a maximal rate of change at the FMP, and then decelerating to achieve stability 2.17 yr after the FMP (Figure 1). In general, the change in FSH levels occurs earlier than that of estrogen levels.

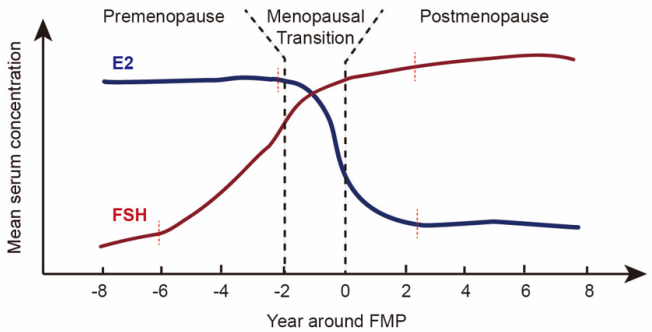

Figure 1: Hormonal Changes around menopause. Based on menstrual status and hormone level, sexually mature women can be divided into three stages, that is, premenopause, menopause transition and postmenopause. With transition into menopause, FSH pattern began with an increase 6.10yr before the FMP, an acceleration 2.05yr before the FMP, and stabilization 2.00 yr after the FMP. The mean E2 concentration did not change until 2.03yr before the FMP when it began decreasing, and decelerating to achieve stability 2.17yr after the FMP [17].

FSH and Liver Diseases

The liver plays a central role in cholesterol and lipid homeostasis, and nonalcoholic fatty liver disease (NAFLD) is associated with dysregulation of several metabolic processes [18] (Figure 2). The liver is considered as a "control center" for the maintenance of whole-body cholesterol homeostasis. This organ is the main site for *de novo* cholesterol biosynthesis, clears cholesterol-containing chylomicron remnants and Low-Density Lipoprotein (LDL) particles from plasma and is the major contributor to high density lipoprotein formation. FSH, by binding to hepatic FSHR, drives 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-controlling enzyme in the cholesterol biosynthesis pathway, nascent transcription and *de novo* cholesterol biosynthesis, leading to an increase in cholesterol accumulation. Moreover, blocking FSH signaling with an FSHβ antibody or ablating the FSH receptor (*Fshr*) gene could effectively prevent hypercholesterolemia induced by FSH injection or high-cholesterol diet feeding in mice [5]. FSH may also interact with FSHR in hepatocytes, and reduce LDLR levels, which subsequently

Table 2: FSH and diseases.

Disease	FSH-induced pathological changes	Studies on FSH blockade and outcome
Hypercholesterolemia	Binds to hepatic FSHR, and drives HMG-CoA reductase, leading to *de novo* cholesterol biosynthesis in liver [5] interacts with FSHR in hepatocytes and reduces LDLR levels, resulting in an elevated circulating LDL-C level [6]	Both FSHβ antibody and ablating *Fshr* gene effectively prevent hypercholesterolemia induced by FSH injection or high-cholesterol diet feeding [5]
NAFLD	Increases the prevalence of NAFLD in perimenopausal women [21] independently associates with NAFLD [22]	No
T2DM	Binding to FSHR and targeting GRK2, increases hepatic *Pepck* and *G6pase* transcription via CRTC2, and consequently enhances hepatic gluconeogenesis [27] FSH levels were associated with HbA1c, a measure of long-term glucose load [29]	No
Alzheimer's disease	Elevated concentrations of FSH in patients with Alzheimer's disease [31-33] acts directly on hippocampal and cortical neurons to accelerate amyloid-β and Tau deposition and impair cognition [7]	Blocking FSH action in these mice abrogates the Alzheimer's disease-like phenotype by inhibiting the neuronal C/EBPβ–δ-secretase pathway [7]
Depression	Associates with negative mood and with increased recruitment of cognitive association regions during emotion processing [29]	No
Osteoporosis	Activates MEK/Erk, NF-κB and Akt pathways through FSHR, directly regulating bone mass [9] Relates to lower bone mineral density among pre- and early-perimenopausal women [38,39] Stimulates osteoclast development and activity by enhancing RANK [40] Stimulates macrophages to release TNF-α that expanded the number of bone marrow osteoclast precursors and enhanced osteoblast formation, subsequently leading to the high turnover bone loss [41,42]	Blocking FSHR mediated effects on mesenchymal stem cells and stimulates bone formation [14] blocking FSH with a specific antibody targeting its β subunit increases bone mass [13, 16]
Cardiovascular Disease	A positive correlation between FSH levels and risk of atherosclerosis in clinical studies [45-47] Directly upregulates VCAM-1 expression in HUVECs and increases human monocyte adhesion through the FSHR/Gas/cAMP/PKA and PI3K/Akt/mTOR/NF-kB signalling pathways, resulting in the development of AS in postmenopausal women [12] Accelerates adiposity and lipid accumulation, which may contribute to cardiovascular dysfunction [10] Promotes dyslipidemia by increasing circulating LDL-C level which is an independent risk factor for atherosclerosis [5,6] Affects plaque formation and intimal neovascularization [51] reduces vascular calcification [53,54]	No
Adiposity	Stimulates lipid biosynthesis and increases fat storage through the FSHR/Gαi/Ca2+/CREB pathway in mouse 3T3-L1 preadipocytes [10] Promotes UCP1 expression in adipocytes [13] Positively correlates with visceral fat [59, 60] Increases fat mass in male patients with Klinefelter syndrome [61]	Blockade of FSH signalling with an FSHβ antibody reduces high-fat diet-induced obesity in wild-type mice and adiposity [13]
Cancer	Promotes the proliferation and preventes the apoptosis of ovarian cancer cells by activating survivin through the SAPK/JNK and PI3K/AKT pathways [65] Induces the epithelial-mesenchymal transition of ovarian cancer cells through the FSHR-PI3K/Akt-Snail signalling pathway [67] promotes the cancer cell ability and migration ability [73] Activates FAK through a Gαi/β and c-Srcsignalling cascade, and promotes tumor cell migration and invasion in breast cancer [74] Promotes the proliferation, migration, and invasion of cancer cells by activating FSHR [76]	No

Abbreviation: FSHR: Follicle-Stimulating Hormone Receptor; HMG-Coa: 3-Hydroxy-3-Methylglutaryl Coenzyme A; LDLR: Low Density Lipoprotein Receptor; LDL-C: Low Density Lipoprotein Cholesterol; NAFLD: Nonalcoholic Fatty Liver Disease; T2DM: Type 2 Diabetes Mellitus; RANKL: Receptor Activator of The Nuclear Factor Kb Ligand; Huvecs: Human Umbilical Vein Endothelial Cells; CREB: Camp Regulatory Element-Binding Protein; UCP1: Uncoupling Protein 1; FAK: Focal Adhesion Kinase.

attenuates the endocytosis of LDL-Cholesterol (LDL-C), resulting in an elevated circulating LDL-C level [6]. In clinical studies, it has been proven that compared with premenopausal women, early postmenopausal women had a 2-fold risk of low-density lipoprotein cholesterol, which is strongly correlated with elevated FSH levels [19,20]. The prevalence of NAFLD increased in perimenopausal women (the term "perimenopause" was defined at 2011 STRAW + 10 system [1]) compared with premenopausal women [20]. A cross-sectional study suggested that the 'normal' diurnal rhythm of FSH was independently associated with NAFLD in an elderly population, which provides a novel insight into the diurnal rhythm of FSH in the pathogenesis of NAFLD [21]. Conversely, low FSH levels may decrease the risk of NAFLD in elder men [22].

The liver is the primary organ involved in glycogenolysis and gluconeogenesis, a main mechanism through which humans maintain blood glucose levels [23]. In order to achieve glucose homeostasis, the liver switches from producing glucose via glycogenolysis and gluconeogenesis in the fasted condition to the uptake of glucose via glycogen synthesis [18]. Glycogenolysis in the liver is controlled by the activities of Glucokinase (GK), Phosphofructokinase (PFK), and Pyruvate Kinase (PK) [24]. In hepatic gluconeogenesis, conversion of pyruvate to phosphoenolpyruvate is catalyzed by Pyruvate Carboxylase (PC) and phosphoenolpyruvate carboxykinase (PEPCK) [25]. In mouse models, FSH, through FSHR and targeting GRK2, increases hepatic *Pepck* and *G6pase*transcription via CRTC2, and consequently enhances hepatic gluconeogenesis [26]. Excessive hepatic gluconeogenesis is a major contributor to the hyperglycaemia observed in type 2 diabetes mellitus [27]. One clinical study demonstrated that FSH levels were associated with HbA1c, a measure of long-term glucose load [28].

FSH and Cognitive Impairment

The aging brain is susceptible to age-related neurodegenerative diseases. The role of FSH in the pathogenesis of cognitive dysfunction

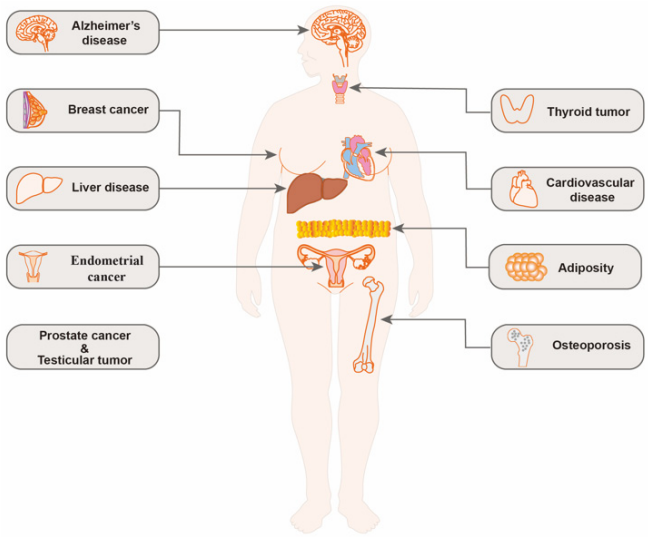

Figure 2: FSH is involved in the pathogenesis of numerous diseases. Evidence shows that FSH alone is involved in the pathogenesis of numerous diseases other than gonadal disfunction, including Alzheimer's disease, liver disease, cardiovascular disease, osteoporosis, adiposity, both gonadal and extrogonadal tumors and even COVID-19.

and disease has gradually been revealed by researchers. According to 2023 Alzheimer's disease facts and figures, the estimated lifetime risk for Alzheimer's dementia was approximately twice higher for women than for men [29]. In a small study, serum levels of FSH and LH in 40 male residents of long-term care facilities with a primary diagnosis of dementia were significantly higher than those in 29 age-matched controls [30]. Consistent with those results, elevated concentrations of FSH have been reported in patients with Alzheimer's disease [31,32]. The dentate gyrus of the mammalian hippocampus continuously generates new neurons during adulthood. These adult-born neurons become functionally active and are thought to contribute to learning and memory [33]. A study found that pyramidal neurons from the CA1 to CA4 region and granule neurons in the dentate gyrus could express FSH and its receptor, and the majority of hippocampal neurons coexpressed FSH and its receptor [8]. Recently, Xiong *et al.* found that FSH acts directly on hippocampal and cortical neurons to accelerate amyloid-β and Tau deposition and impair cognition in mice displaying features of Alzheimer's disease. Blocking FSH action in these mice abrogates the Alzheimer's disease-like phenotype by inhibiting the neuronal C/EBPβ–δ-secretase pathway [7]. The above studies not only suggest a causal role for rising serum FSH levels in the exaggerated Alzheimer's disease pathophysiology during menopause but also reveal an opportunity for treating Alzheimer's disease.

Depression is a mood disorder characterized by listlessness and slow thinking, and the metabolism of the nervous system and changes in some neurotransmitters are the pathophysiological basis of geriatric depression [34]. Disturbances of emotion regulation and depressive symptoms are common during the menopause transition. Neurological regulation of cognitive and emotional function may be impacted by changes in hormone concentrations related to menopause. During the menopause transition, FSH levels are associated with negative mood, a tendency towards negative interpretation of emotionally neutral images, and with increased recruitment of cognitive association regions during emotion processing [28].

FSH and Osteoporosis

Postmenopausal women are prone to osteoporosis. Findings from prospective examinations of bone mineral density across the menopausal transition demonstrate an early and accelerated rate of bone loss [35]. It has been reported that bone loss occurs approximately 2-3 years before the FMP [36], when estrogen levels are relatively normal and FSH levels are significantly elevated [17]. Previous studies have shown that higher serum FSH levels, but not lower serum estradiol levels, are associated with lower bone mineral density among pre- and early-perimenopausal women enrolled in SWAN [37,38]. In addition, lumbar spines BMD loss was 5.6% in natural postmenopause, 3.9% in surgical postmenopause, or 3.2% in late perimenopause, and the results indicated that pine and hip BMD losses during the menopause transition were most strongly related to the interaction between initial FSH levels and longitudinal FSH changes and not to E2 or androgen levels or changes [38]. All the above data indicate that FSH plays a role in bone loss related to menopause.

There are compelling data to confirm the association between FSH levels and bone metabolism. FSH, by enhancing receptor activator of the nuclear factor kB ligand (RANKL), stimulates osteoclast development and activity [39]. Sun *et al.* reported that FSH directly regulates bone mass in haploinsufficient *FSHβ*$^{+/-}$ mice with normal ovarian function, but with a 50% reduction in serum FSH levels, and the underlying mechanism may rely on FSH activating MEK/Erk, NF-κB and Akt pathways through FSHR [9]. A blocking antibody to the FSHβ subunit, when injected intraperitoneally, significantly reduced ovariectomy- induced bone loss in mice, and stimulated bone formation, likely by blocking FSHR mediated effects on mesenchymal stem cells [40]. Bone formation and resorption are influenced by inflammatory processes. A further study reported that FSH stimulated macrophages to release TNF-α that, in turn, expanded the number of bone marrow osteoclast precursors and enhanced osteoblast formation, subsequently leading to the high turnover bone loss [41,42]. In addition, blocking FSH with a specific antibody targeting its β subunit increases bone mass [13,14]. All these studies provide the framework for the future development of an FSH-based therapeutic that could potentially target bone.

FSH and Cardiovascular Disease

It has been widely accepted that the risk of cardiovascular disease significantly increases in postmenopausal women [43]. Traditionally, the reduction in estrogen levels associated with menopausal transition was considered as a major contributor [44]. However, estrogen replacement therapy may modestly increase the risk for stroke [45]. Previous studies have reported a positive correlation between FSH levels and subclinical atherosclerosis, including coronary artery calcium and the carotid intima-media thickness in women [46,47]. A recent SWAN study suggested that women with a lower FSH rise over their menopausal transition may be at lower risk of atherosclerosis than those with a medium or high FSH rise [15]. These studies suggest that it may be much more important to examine the correlation between FSH trajectory and cardiovascular disease, which may reveal an opportunity for treating cardiovascular disease.

FSH may increase the risk of cardiovascular disease through

several distinct mechanisms. First, it is known that activated endothelial cells, expressing a variety of adhesion molecules including vascular cell adhesion molecule 1 (VCAM-1), play an important role in the initiation and progression of atherosclerosis [48]. FSH directly upregulated VCAM-1 expression in human umbilical vein endothelial cells (HUVECs) and subsequently increased human monocyte adhesion through the FSHR/Gas/cAMP/PKA and PI3K/Akt/mTOR/NF-kB signalling pathways, resulting in the development of AS in postmenopausal women [16]. Second, FSH accelerates adiposity and lipid accumulation, which may contribute to cardiovascular dysfunction [49]. FSHR was functionally expressed in human and mouse fat tissues and adipocytes. FSH increased lipid biosynthesis and lipid droplet formation through the Gαi/Ca2+/CREB pathway in mouse 3T3-L1 preadipocytes [10]. A recent elegant study has showed that blockade of FSH signalling with a specific antibody reduced high-fat diet-induced adiposity, including significantly reducing total fat volume, subcutaneous fat volume, and visceral fat volume, but interscapular brown adipose tissue remained unchanged [16]. Interestingly, FSH has been shown to promote dyslipidemia by inhibiting hepatic cholesterol metabolism, leading to an elevated circulating LDL-C level [5,6] that is an independent risk factor for atherosclerosis [50]. Third, FSH promotes angiogenesis which may be related to plaque formation and intimal neovascularization [51]. It has been shown that FSH signalling through FSHR in HUVECs promotes angiogenesis that is independent of VEGF [52]. The last but not the least, FSH reduces vascular calcification which is important in determining atherosclerotic plaque stability. Studies have demonstrated that vascular calcification shares many similarities to bone remodeling [53,54]. Previous data have suggested that osteoclasts, through a signaling cascade involving FSH, may be recruited to calcified regions where they can resorb mineral deposition, subsequently increasing the incidence of plaque rupture [55].

FSH and Adiposity

Adipose tissue, colloquially known as "fat", is an extraordinarily flexible and heterogeneous organ [56]. Adiposity, especially central (abdominal) adiposity, is associated with several metabolic pathologies, including hyperglycemia, low HDL cholesterol, hypertriglyceridemia, and hypertension, which together are often called "metabolic syndrome" [57]. During the transition from a reproductive to a nonreproductive phase (menopause), many women experience an increase in visceral adiposity [58]. In the SWAN study, FSH was positively correlated with visceral fat in women, using waist circumference as a surrogate [59,60]. In male patients with Klinefelter syndrome, a high level of serum FSH is accompanied by increased fat mass, which is independent of testosterone [61]. Combined, the data indicate that a high serum FSH level is a risk factor for fat accumulation.

Compelling data have revealed a potential mechanism of FSH on fat accumulation. It has been proven that adipocytes express FSHR [10,62]. Liu *et al.* demonstrated that FSH treatment, by activating FSHR, stimulates lipid biosynthesis and increases fat storage through the Gαi/Ca^{2+}/cAMP Regulatory Element-Binding protein (CREB) pathway in mouse 3T3-L1 preadipocytes [10], which may contribute to the increased risk of metabolic diseases during menopause. An elegant study performed by Liu *et al.* has shown that blockade of FSH signalling with a polyclonal neutralizing antibody targeting the β-subunit of FSH reduces high-fat diet-induced obesity in wild-type mice and adiposity in ovariectomized mice [13]. Since adipose thermogenesis by brown fat and beige fat is highly dependent on the cAMP signallingpathway and the subsequent expression of Uncoupling Protein 1 (UCP1) [63], the inhibition of the FSH signalling promotes UCP1 expression in adipocytes [13]. The data provided compelling evidence that visceral adiposity can be alleviated by pharmacological inhibition of the FSH signalling.

FSH and Cancer

Since the key role of FSH is to control gonadal function and reproduction, previous studies showed that FSH is pivotal for carcinogenesis, proliferation, invasion and migration in ovarian cancer [64-66]. On the one hand, FSH promoted the proliferation and prevented the apoptosis of ovarian cancer cells by activating survivin through the SAPK/JNK and PI3K/AKT pathways. FSH also downregulated the expression of programmed cell death gene 6 (PDCD6) and death receptor 5 (DR5), two molecules required for the induction of apoptosis [65]. On the other hand, FSH induced the epithelial-mesenchymal transition of ovarian cancer cells through the FSHR-PI3K/Akt-Snail signalling pathway [67]. Studies have proved the expression of FSHR in tumor testicular tissues and the role of FSH in the carcinogenesis of testicular tumors [68,69]. Studies shown that normal thyroid follicles do not show the immunostaining for FSHR, however, most of follicular cancers showed the FSHR immunopositivity of tumoral cells [70,71]. The results indicate that the ectopic FSHR immunostaining seems to be useful to differentiate malignant from benign lesions, especially follicular cancers from follicular adenomas [71]. FSH also plays an important role in tumorigenesis and development in nongonadal tumors. A clinical study by Yongjing Lai *et al.* suggested that a high FSH level is a risk factor for endometrial cancer [72], and that FSH promotes the cancer cell ability and migration ability [73]. FSH, via FSHR, activates focal adhesion kinase (FAK) through a Gα i/β and c-Src-dependent signalling cascade, and then promotes tumor cell migration and invasion in breast cancer [74]. Of special interest is an elegant study that reported FSHR expression in vascular endothelial cells in tumors beyond those of prostate and ovarian cancer [75,76], which may promote the proliferation, migration, and invasion of cancer cells [76]. The rationale for developing a strategy for cancer therapy is based on FSHR expressed on the luminal endothelial cell surface of blood vessels located in the peritumoral area rather than endothelial markers expressed in the core of tumors, which indicates that FSHR is a common marker of peritumoral vessels. Therapeutic agents coupled to anti-FSHR humanized antibodies may in principle be applicable to a wide range of tumor types.

Concluding Remarks and Future Perspectives

Recently, the extragonadal effects of FSH in multiple tissues and organs have gradually been noticed. As described above, epidemiological data and evidence from clinical trials, animal studies, and *in vitro* experiments have showed the extragonadal actions of FSH in multiple diseases. Animal studies found the benefits of FSH blockade (Table 2), thus, we need to increase early phase trials so that we may determine if FSH blockade has a significant influence on outcomes.

During the menopause transition from a reproductive to a nonreproductive phase (menopause), many women experience a significant increase in serum FSH levels. In this review, we have highlighted our current understanding of the potential pathological roles of FSH in women. However, our understanding of the molecular mechanisms through which FSH increases the risk of extragonadal tissues and organs is far from complete. The vast technological advancements will provide valuable new information on the molecular pathophysiology of FSH in extragonadal tissues, such as the liver and brain. Animal studies have shown that blocking FSH increases bone mass, reduces cholesterol and body fat, and induces thermogenic adipose tissue. However, whether FSH-blocking strategies prevent cardiovascular disease in women remains to be further elucidated in humans. Therefore, further studies are needed to reveal the underlying mechanisms of FSH and to predict new related diseases induced by rising FSH during menopausal transition.

Author Statements

Author Contributions

Y.J.G.: project development, data collection, and manuscript writing. S.L.W.: project development, and manuscript writing. W.L., R.Y. and Y.Q.H.: data collection, and manuscript writing.

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Disclosure

The authors declare no competing interests.

Data Availability Statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

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