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Energy metabolism and fertility—a balance preserved for female health

Sara Della Torre, Valeria Benedusi, Roberta Fontana and Adriana Maggi

Abstract | In female animals, energy metabolism and fertility are tightly connected, and reciprocally regulated. However, the relative contributions of metabolic and reproductive pathways have changed over the course of evolution. In oviparous animals, metabolic factors take precedence over fertility, enabling egg production to be inhibited in a nutritionally poor environment. By contrast, in placental mammals, the opposite occurs: the need to feed a developing embryo and neonate forces metabolic pathways to adapt to these reproductive needs. This physiological necessity explains why in female mammals alterations of gonadal activity, including age-dependent cessation of ovarian functions, are associated with a disruption of metabolic homeostasis and consequent inflammatory reactions that trigger the onset of metabolic, cardiovascular, skeletal and neural pathologies. This Review discusses how metabolic homeostasis and reproductive functions interact to optimize female fertility and explains the pathogenic mechanisms underlying the disordered energy metabolism associated with human ovarian dysfunction owing to menopause, polycystic ovary syndrome and Turner syndrome. Finally, this article highlights how hormone replacement therapy might aid the restoration of metabolic homeostasis in women with ovarian dysfunction.

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Introduction

Although women have a greater life expectancy than men, the gap is narrowing.¹ From 1990 to 2011 the difference in life expectancy between men and women dropped from an average of 6.61 to 4.67 years in European countries and from 7 to 5 years in the USA.² The fact that women develop an increased susceptibility to weight gain as they age³ could potentially contribute to this phenomenon, because obesity is a well-known risk factor for a large number of metabolic, cardiovascular and skeletal disorders.⁴ Understanding the biological basis of weight gain in ageing women is, therefore, relevant to define appropriate strategies to combat obesity in this population.

One interesting hypothesis suggests that the female-specific propensity to weight gain (and, thereby, to metabolic dysfunction) might be the consequence of adaptations that enable reproduction and nurturing of offspring in food-scarce environments.³ Uncontrolled reproduction in a nutritionally poor environment would lead to competition for food between mothers and their offspring, which ultimately might result in extinction of the species. Female fertility and energy metabolism are, therefore, tightly interconnected; during the reproductive period of life, the physiological activity of the gonads, with their cyclic production of sex hormones, ensures a continuous regulation of food intake and energy expenditure. However, with the cessation of ovarian function,

gonadal control over energy metabolism decreases, with negative consequences. In women, weight gain and obesity are most prevalent around and after menopause.⁵ Moreover, pathologies that involve ovarian dysfunction, such as polycystic ovary syndrome (PCOS) and Turner syndrome, are generally associated with metabolic disorders.^{6,7} Thus, an obesogenic milieu might be particularly metabolically harmful in species adapted to survive in nutrient-poor environments.

The molecular mechanisms involved in the interactions between fertility and metabolism have been little investigated in mammals. However, the remarkable similarities in these mechanisms among oviparous species demonstrate that strong selection pressure has favoured the preservation of pathways that coordinate reproductive functions with energy availability. Indeed, mechanisms that limit female gonadal activity during times of calorie restriction should have been positively selected for in all species during evolution.⁸ An appreciation of the role of evolution in shaping these reproductive and metabolic pathways might, therefore, improve our understanding of human female physiology.

In this Review, we discuss how the reciprocal interactions between pathways that control fertility and energy metabolism are organized and underline the key roles of molecules such as estrogens and insulin-like growth factors (IGFs) in these pathways. We also discuss how this novel perspective could challenge current therapeutic strategies—amelioration of metabolic disorders, for example, might become an important goal of hormone replacement therapy (HRT), particularly in ageing women.

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Competing interests

A. Maggi declares an association with the following company: Pfizer. See the article online for full details of the relationship. The other authors declare no competing interests.

Key points

- Metabolic and reproductive pathways are tightly associated, and this relationship has been conserved throughout evolution
- Reproductive disorders can lead to changes in metabolic function
- Similarly, metabolic disorders can underlie changes in reproductive function
- Hormone replacement therapy for reproductive disorders might also have beneficial effects on energy metabolism

**Nutritional status—links to fertility
Mechanisms in oviparous species**

In oviparous species, the most important yolk proteins are vitellogenins, a family of large glycoproteins that provide nutrients (such as amino acids, carbohydrates, phosphates and sulphates) to the embryo, as well as lipids, hormones, vitamins and metals.⁹ Synthesis of vitellogenins takes place in metabolic organs that are functionally comparable to liver.¹⁰ Vitellogenins also have a key role in fat storage and mobilization; thus, egg maturation ceases when energy availability is restricted. Moreover,

vitellogenins and the molecular pathways directing their synthesis are well-conserved across all oviparous species, from invertebrates to vertebrates.¹¹ In liver-like tissues, stimuli from local sources and the nervous system (such as insulin-like peptides,¹² amino acids and nutritional signalling factors, such as target of rapamycin¹³),^{12,14} control vitellogenin production in concert with gonadal hormones (ecdysone and estrogens) to signal the state of egg development and maturation (Figure 1).

Mechanisms in placental mammals

In mammals, including primates, severe malnutrition and allostatic overload reduce fertility.¹⁵ Reproduction is still arrested in nutritionally unfavourable settings, but the mechanisms involved have increased complexity compared with those in oviparous species.

In the mammalian liver, estrogen-regulated synthesis of apolipoproteins¹⁶ seems to have a role in maintaining reproductive capacity, as defective hepatic production of VLDL leads to female sterility.¹⁷ Interestingly,

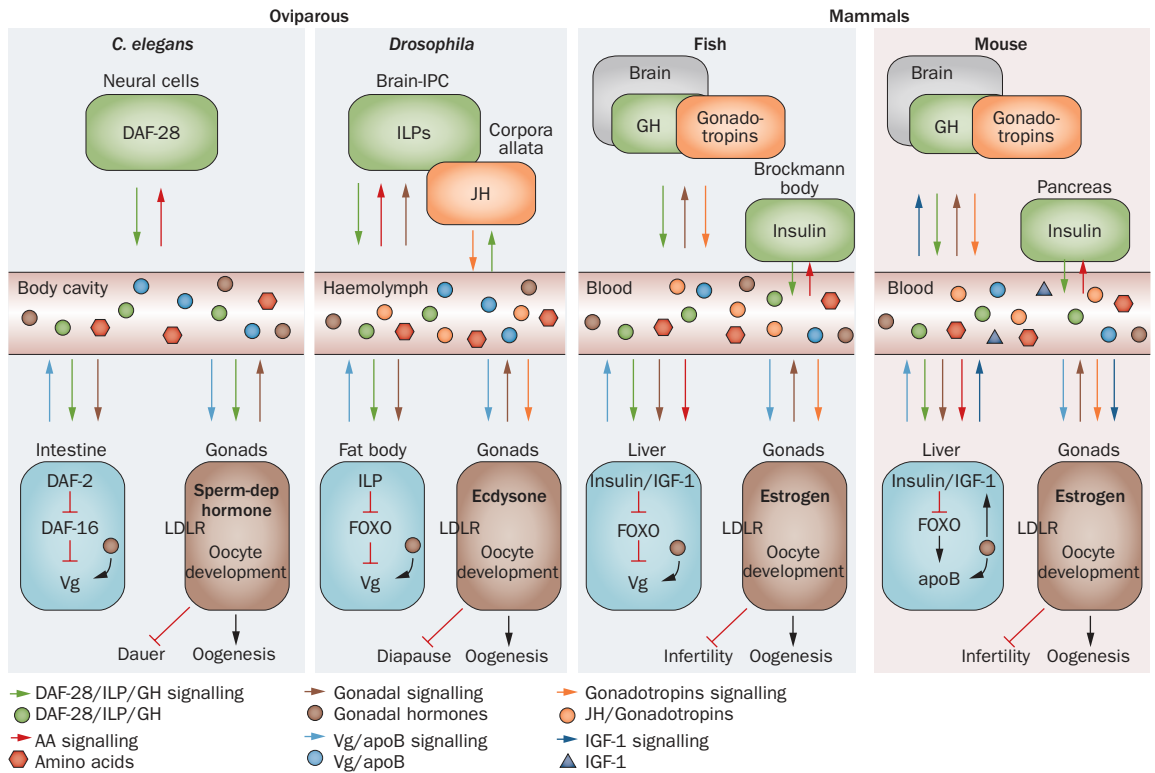


Figure 1 | The mutual control of nutritional status and reproduction throughout evolution. In oviparous animals, vitellogenin synthesis takes place in the organ functionally comparable to the mammalian liver,⁹ and is regulated by nutritional cues together with gonadal hormones (such as ecdysone or estrogens).¹³ Once synthesized, these lipid transport proteins are secreted into the circulatory system to reach the gonads where they regulate the maturation of the egg. Vitellogenins and the proteins they transport provide the embryo with energy necessary for its development. In all oviparous animals, therefore, nutritional cues have a direct control over reproduction regulating oogenesis, or inducing infertility or a dormant fertility state (dauer and diapause). In placental mammals, the liver regulates gonadal function through the synthesis of the lipid transport protein apoB (a member of the vitellogenin family) and the synthesis of IGF-1.^{144–146} Estrogens, together with dietary intake, regulate liver production of both apoB and IGF-1. In addition, estrogens have a strong influence on the activity of all organs relevant for energy metabolism and provide the embryo with the energy molecules necessary for its growth. In mammals the control of energy metabolism on reproduction, typical of oviparous animals, is maintained, but reproductive functions become the key driver of metabolic functions. Abbreviations: AA, amino acids; apoB, apolipoprotein B-100; E2, estradiol; GH, growth hormone; IGF, insulin-like growth factor; ILPs, insulin-like peptides; IPC, insulin-producing cells; JH, juvenile hormones; LDLR, LDL receptor; Sperm-dep, sperm dependent; Vg, vitellogenin.

apolipoprotein B-100 (apoB100) contains a vitellogenin domain,¹⁸ and placenta formation is impaired in *apoB*-knockout mice.¹⁹ Moreover, dietary intakes of amino acids can also regulate fertility.²⁰ Hepatic synthesis of IGF-1, which is essential for the reproductive cycle, is regulated by amino-acid-dependent activation of estrogen receptor (ER) α in the liver.²¹ These mechanisms resemble those in oviparous species. However, in placental animals, the central regulation of energy expenditure and reproduction takes precedence over these ancestral, nutrition-based, mechanisms of

fertility control. Peripheral messages converge in the brain nuclei responsible for their integration and for production of the efferent signals that ultimately control allostatic regulation in the organism. Several tissues and organs communicate nutritional status to the central nervous system. White adipose tissue secretes the anorexigenic hormone leptin in amounts proportional to the amount of energy stored as fat.²² The stomach produces the orexigenic hormone ghrelin.²³ The intestine secretes peptide YY in response to food intake, which induces satiety.²⁴ Finally, the pancreas releases insulin, which has a similar action to leptin in the hypothalamus.²⁵ All these signals converge and are integrated in the brainstem and arcuate nucleus which, together with other hypothalamic nuclei, regulate both ovulation and energy homeostasis. For example, sensors of energy status in the arcuate nucleus—such as cocaine and amphetamine-regulated transcript (CART)–pro-opiomelanocortin (POMC) neurons and agouti-related peptide (AgRP)–neuropeptide Y (NPY) neurons—direct the synthesis of gonadotropins in the pituitary by regulating the activity of gonadotropin-releasing hormone (GnRH) neurons located in the preoptic area (Figure 2).²⁶

In placental mammals, the nutritional burden associated with development of the embryo and growth of the offspring has been transferred to the mother. Consequently, the regulatory mechanisms linking energy availability and reproductive function had to be adapted to take into account the variable energy demands of each stage of the reproductive cycle (periodic ovulation, pregnancy and lactation).²⁶ Thus, the need to have highly reciprocal control of both energy sensing and reproduction might have favoured the selection of ER α and ER β as the nexus through which these two functions are linked. Indeed, these receptors can be activated by nutritional signalling molecules (such as amino acids and IGF-1), as well as gonadal hormones,²¹ and can regulate expression of a diverse range of genes.²⁶ ER α and ER β are exceptionally versatile sensory and regulatory effectors that are widely expressed in mammalian tissues.²⁷

The essential role of estrogens and their receptors in reproduction has long been known. However, emerging evidence suggests that estrogen signalling also has a central role in the control of energy metabolism. The concentration of various circulating estrogen metabolites such as estradiol, estrone, estriol and their ratio depends on fertility status.²⁸ The exact role of each of these metabolites is unclear; therefore, in this Review, the term estrogens refers to all estrogenic compounds. The major naturally occurring estrogens in women are estrone, estradiol (which has the most potent effect on ER α and ER β), and estriol (which has the least potency). In addition, pregnant women produce estetrol. Estradiol is the predominant estrogen produced during the reproductive years (mean levels of which rise from a nadir of 106.5 ± 25.7 pmol/l of plasma during menstruation, to a peak of 1167.4 ± 99.1 pmol/l of plasma around mid-cycle). Changes in estrone concentrations follow a similar, although less marked, pattern (from a nadir of 148.0 ± 14.8 pmol/l during menstruation, to a peak

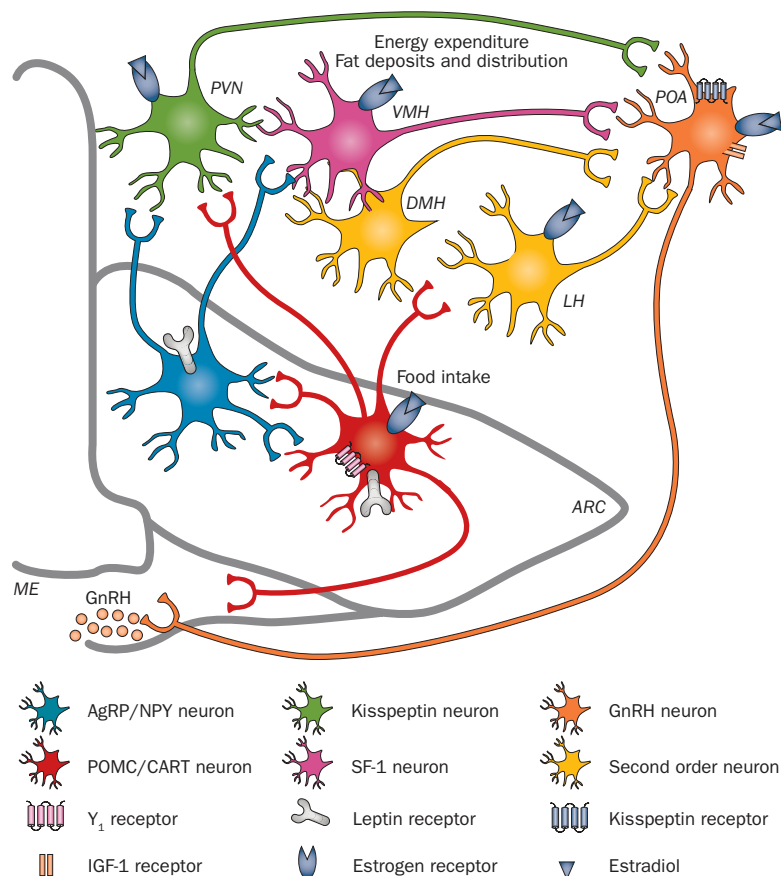


Figure 2 | ER α in hypothalamic circuits regulates energy metabolism and reproduction. Estrogen inhibits food intake via ER α signalling on POMC/CART neurons (red) that signal to second-order neurons (yellow) in the lateral hypothalamus, to kisspeptin neurons (green) in the paraventricular nucleus and to orexigenic AgRP/NPY neurons (blue) in the arcuate nucleus. Conversely, AgRP/NPY neurons, when activated, inhibit the POMC-CART neuron possibly through the Y₁ receptor. Estrogens act on SF-1 neurons (purple) in the ventromedial hypothalamus to regulate energy expenditure and fat distribution. ER α in the arcuate nucleus is a critical regulator of food intake, whereas ER α in the ventromedial hypothalamus regulates energy expenditure.³⁹ Finally, POMC/CART (through kisspeptin and second-order neurons) and SF-1 neurons signal energetic status to GnRH neurons (orange) that are responsible for the pituitary release of gonadotropins, thereby regulating plasma estrogen levels. AgRP/NPY and POMC/CART neurons express receptors for leptin that allow them to be sensitive to the amount of energy stored in fat. Abbreviations: AgRP, agouti-related protein; CART, cocaine and amphetamine-regulated transcript; DMH, dorsomedial hypothalamus; ER α , estrogen receptor α ; GnRH, gonadotrophin releasing hormone; LH, lateral hypothalamus; ME, median eminence; NPY, neuropeptide Y; POA, preoptic area; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; SF-1, steroidogenic factor-1; VMH, ventromedial hypothalamus.

of 628.8 ± 48.1 pmol/l at mid-cycle).²⁹ With menopause, estradiol levels decrease markedly, although estrone levels remain comparable to those observed in fertile women. The transcriptional programme regulated by ER α and ER β might be modulated in response to changing levels of circulating hormones, which characterize the different stages of female fertility.^{26,30,31} Accordingly, the set of genes controlled by ER α and ER β might substantially change in response to different concentrations and ratios of hormones. Hence, in the same target tissue, the intracellular activity of these receptors might vary at each reproductive stage or during the estrous cycle, leading to an alternate activation of pathways that control energy metabolism.²⁶

After loss of estrogen production due to ovariectomy³² or menopause,³³ adipose tissue mass rapidly increases, and its distribution changes. These effects can be reversed by the administration of HRT.³² The influence of estrogens on energy metabolism is believed to be largely mediated by ER α . Mice lacking ER α have increased body weight and food intake compared with wild-type littermates,³⁴ and administration of ER α -selective agonists (but not ER β -selective agonists) has anorexigenic effects in these mice.^{35,36} Interestingly, mice lacking ER β have variable degrees of reduced fertility, show abnormal follicular maturation and very few *corpora lutea*,³⁷ whereas mice lacking ER α are infertile and have markedly hypoplastic reproductive organs and tissues,²⁷ again highlighting the close association between regulation of energy balance and fertility.

Estrogen-mediated metabolic effects occur at multiple levels. In the brainstem, estrogens potentiate or attenuate the effect of various peptides that signal satiety or hunger, respectively (such as cholecystokinin, which is released from the small intestine in response to food ingestion,³⁸ or ghrelin,³⁹ production of which is stimulated by fasting). In the arcuate and ventromedial nuclei, estrogens stimulate POMC and steroidogenic factor 1 (SF-1) neurons,⁴⁰ thereby repressing the synthesis of orexigenic neuropeptides (such as AgRP and NPY).⁴¹ POMC expression is regulated by ER α ; in mice lacking this receptor, leptin and insulin no longer increase POMC expression.⁴² Moreover, mice lacking ER α specifically in POMC neurons are hyperphagic and have reduced sensitivity to leptin, despite POMC expression being maintained in the hypothalamus.⁴⁰ Thus, the anorexigenic effect of estrogens on POMC neurons is clearly mediated by ER α , although whether the underlying mechanism involves direct regulation of POMC expression or potentiated effects of other anorexigenic hormones, such as leptin, or both remains unclear. POMC neurons also express CART, and, to our knowledge, no data describe whether ER α or ER β (or both) are involved in CART regulation, even if CART expression is modulated by estradiol.⁴³ AgRP and NPY are essential targets for the anorexigenic effect of estrogens. AgRP–NPY neurons do not express ER α *in vivo*.⁴¹ However, given that ER α is abundantly expressed in the arcuate nucleus of the hypothalamus,⁴⁴ whereas expression of ER β is barely detectable at this location, estrogens might conceivably regulate AgRP–NPY neurons through ER α on other neuronal

subtypes (such as kisspeptin neurons in the ventromedial hypothalamus that innervate AgRP–NPY neurons). The mechanisms through which estrogens regulate GnRH neurons to control fertility are unclear. Estrogen decreases GnRH expression in GT1-7 cells (a hypothalamic cell line that expresses ER α and ER β), an effect that might be mediated by ER α .⁴⁵ Although GnRH neurons seem to express only ER β *in vivo*,⁴⁶ a role for both ER α and ER β receptors in regulating GnRH neuronal activity as well as GnRH secretion remains probable. Different mechanisms are potentially required, including direct actions of estrogen through ER β -expressing GnRH neurons, and indirect actions of estrogen through ER α -expressing afferents of GnRH neurons.

Moreover, estrogen signalling potentiates leptin sensitivity, possibly by increasing expression of the leptin receptor in the hypothalamus.⁴⁷ The overall effects of increased estrogen signalling are induction of an anorexigenic response and fat redistribution to subcutaneous rather than visceral depots. In the arcuate nucleus, anteroventricular periventricular nucleus and preoptic area, estrogen signalling integrates with afferent signals from peripheral organs and tissues, such as the stomach, pancreas and adipose tissue and, through kisspeptin neurons, controls the release of GnRH⁴⁸ in response to an individual's metabolic status. These effects are mediated mainly by ER α , which is abundantly expressed in these hypothalamic nuclei (Figure 2).⁴⁹

ER α and ER β are expressed and active in all metabolic organs. In adipose tissue, estrogens increase subcutaneous fat deposition in lower body areas and decrease lipolytic activity (which maintains fat stores in case periods of food scarcity occur during pregnancy or lactation). When estrogen signalling decreases, the subcutaneous fat redistributes to visceral areas;^{31,34,50} this phenomenon has been observed in women after natural or oophorectomy-induced menopause;^{32,33} in animal models of selective ablation of ER α ;^{27,34} in humans with loss-of-function ER α polymorphisms;⁵¹ and in ovariectomized mice, the phenotype of which can be partially rescued by treatment with 17 β -estradiol.³² Studies in cultured adipocytes show that estrogens have a direct antilipogenic and pro-lipolytic activity *in vitro*, associated with inducing the expression of hormone-sensitive lipases and decreasing the activity of lipoprotein lipase.^{52,53} These same effects of estrogens in fatty acid metabolism are observed in animal models.^{52–54} However, the exact contributions of ER α and ER β to these activities remain to be defined. Although the results of studies in mice genetically engineered to lack ER α suggest that ER α is the main receptor involved in the control of adipose tissue distribution,³⁴ other studies, mainly in cultured adipocytes, suggest that estradiol also has antilipogenic and antiadipogenic effects mediated by ER β .⁵⁵

ER α involvement in the control of lipid metabolism is certainly relevant in the liver,²⁶ where this receptor isoform is predominant.²⁷ In addition to controlling the synthesis of lipid transport proteins, such as VLDL, hepatic ER α signalling also regulates the expression of numerous genes, the products of which are involved

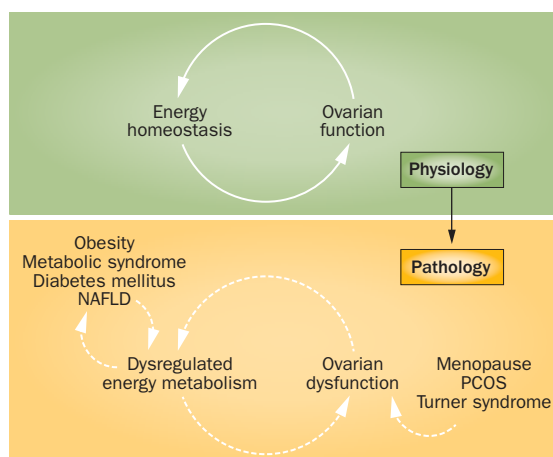


Figure 3 | Reciprocal regulation of energy metabolism and reproduction. Reproduction and energy metabolism are controlled to guarantee a metabolic status that is finely tuned to reproductive needs. The alteration of ovarian functions that characterizes menopause and other endocrine disorders changes these metabolic pathways, which might lead to obesity, metabolic syndrome, diabetes mellitus or NAFLD. Changes in energy metabolism might further impair reproductive activity. Abbreviations: NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome.

in pathways of cholesterol and fatty acids synthesis, according to the phase of the menstrual cycle and fertility status.²⁶ The oscillation of lipid biosynthesis induced during the menstrual cycle by fluctuating estrogen levels is necessary to maintain healthy fat metabolism. Menopause, ovariectomy and suppression of ER α activity in the liver are all associated with increased hepatic fat deposition.²⁶ These observations suggest that the changes in estrogen metabolism that accompany each stage of reproductive activity in women might regulate ER α transcriptional activity in the liver, thereby promoting the release or the storage of energy in the form of fat, as necessary for reproductive function.²⁶

ER α and ER β are expressed in all tissues relevant to glucose metabolism, including skeletal muscle and liver.²⁷ However, the most studied extragonadal site of estrogen action is the pancreas, where its important protective effect has been known for decades.⁵⁶ In pancreatic β cells, estrogens have an antiapoptotic action,⁵⁷ repress both lipid biosynthesis and the accumulation of fat, preventing lipotoxicity,⁵⁸ and directly stimulate insulin biosynthesis.⁵⁹ This last effect might be important in late pregnancy, when high estrogen levels could synergize with high prolactin levels to promote β -cell insulin production, to meet the increased metabolic demand.⁶⁰ Of particular relevance with regard to the potential therapeutic use of hormonal interventions is that the beneficial effects of estrogens on pancreatic β cells are observed with physiological plasma estrogen levels, as estrogen concentrations above or below the physiological range are associated with metabolic dysfunction.⁶¹ Animal studies have shown that after ovariectomy, sensitivity to insulin is progressively impaired. The administration of estradiol

to reach early gestational concentrations of the hormone (734–918 pmol/l) improves insulin sensitivity whereas a 100-fold higher physiological dose than normal cycle concentration decreases insulin sensitivity.⁶² Randomized controlled clinical trials should be carried out to better evaluate the long-term effects of oral contraceptives or HRT in women. The use of contraceptives can deteriorate glucose tolerance;⁶³ however, low estrogen doses (for example 0.625 mg/day), when administered orally can improve tolerance.⁶⁴ Moreover, the Heart Estrogen Progestin replacement study⁶⁵ and the Women's Health Initiative found a lower incidence of diabetes mellitus in women taking HRT.⁶⁶ Finally, high estrogen levels during late pregnancy (1,278–7,192 pg/ml)⁶⁷ decrease insulin sensitivity, which might lead to gestational diabetes mellitus. However, the mechanism mediating these effects requires clarification. Normalization of glycaemia must also take into consideration hormonal status, because sex hormones counteract the effects of insulin.⁶⁸

Metabolic effect of reproductive status Menopause

Given that mammalian reproductive functions also regulate energy homeostasis, the fact that cessation of ovarian function leads to the manifestation of metabolic disorders is not surprising. Indeed, postmenopausal women have increased vulnerability to a large number of pathologies, including disorders of the cardiovascular, skeletal, immune and nervous systems.⁶⁹ How menopause triggers the onset of such diverse pathologies is unclear; perhaps declining levels of circulating estrogens weaken ER α and ER β activity and thereby cause subtle alterations of energy metabolism in multiple tissues. Over time, such changes could lead to overt pathology owing to the diversity of organs involved. However, in our opinion, for each individual woman, the risk of developing a specific disease is influenced by genetic and environmental factors, as well as her overall health status (Figure 3).

Altered lipid metabolism

Menopause is associated with increased body weight, decreased lean mass⁷⁰ and abdominal fat accumulation.^{33,71} Several enzymes involved in fat turnover are reduced in adipose tissue from postmenopausal women (such as acetyl-coenzyme A carboxylase 1, long-chain-acyl-coenzyme A dehydrogenase and hormone-sensitive lipase).⁷² Increased insulin resistance is also evident, possibly prompted by nonphysiological fatty acid deposits,⁷³ high levels of circulating free fatty acids, and increased production of reactive oxygen species from mitochondrial β -oxidation of fatty acids.⁷⁴ Macrophages are recruited by the increased fat mass⁷⁵ and, in combination with adipocytes, secrete proinflammatory cytokines and chemokines.^{76–78} Fatty acids also accumulate in the liver, where they facilitate the development of diffuse hepatic steatosis, characteristic of postmenopausal women.⁷⁹ This steatosis further contributes to the proinflammatory state, which facilitates the onset of the pathologies associated with climacterium such as atherosclerosis, osteoporosis and metabolic dysfunctions. Furthermore,

in the liver, cessation of estrogenic control of cholesterol, fatty acid²⁶ and lipoprotein metabolism leads to a decrease in production of HDL2 (large, antiatherogenic lipid particles)⁸⁰ and an increase of HDL3 (small, proatherogenic particles).^{79,80} Total cholesterol, LDL, triglycerides,^{81,82} apoB100 and apoB100-containing lipoproteins and lipoprotein(a),⁸³ a complex of an LDL-like particle and apoA,⁸¹ are also increased, which contribute to the development of an atherogenic lipid profile and an increased risk of cardiovascular disease. The loss of estrogen's anti-inflammatory action in circulating monocytes and microglia^{84,85} is another important pathophysiological element that, together with the altered lipid transport associated with reduced levels of apoE, might lead to brain neurodegenerative pathologies. For example, the incidence of disorders such as Alzheimer disease is similarly low in both female and male individuals ≤ 50 years old, but increases after this age and thereafter is considerably higher in women.⁸⁶

Impaired muscle and bone physiology

After menopause, skeletal muscle function is reduced, as is muscle strength and mass, an effect that is reversed by HRT.⁸⁷ Additionally, the decline in expression of the glucose transporter GLUT-4,⁸⁸ which is associated with impaired muscle ER α activity, together with a generalized proinflammatory milieu might participate in the increased risk of insulin resistance typical in postmenopausal women. The proinflammatory state and increased levels of circulating cytokines (IL-1, IL-6 and TNF) also have repercussions in other organs, such as bone, where they contribute to a decrease in BMD and increase in osteoclast number.⁸⁹

Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is a metabolic condition that leads to liver damage. The spectrum of NAFLD ranges from simple steatosis, through non-alcoholic steatohepatitis and cirrhosis, to liver failure and hepatocellular carcinoma. NAFLD is characterized by hepatic lipid accumulation (fat comprises 5–10% of the total organ weight), which is associated with insulin resistance in the liver,⁹⁰ increased lipogenesis⁹⁰ and reduced secretion of triglycerides.⁹¹ Insufficient suppression of lipolysis in adipocytes⁷² further contributes to the formation of lipid deposits in the liver. These alterations result in impaired mitochondrial fatty acid oxidation⁹² and upregulation of both peroxisomal β -oxidation and microsomal ω -oxidation. Together with production of lipotoxic lipid intermediates, increased production of ROS, and induction of a proinflammatory response, these changes further contribute to progression of NAFLD and insulin resistance.⁹³

NAFLD can occur in individuals of all ages and ethnic groups, and has a prevalence of about 30%;⁹⁴ this disorder is more common in men, in whom it has a 2.0–3.5-fold higher prevalence than in women.^{95,96} After menopause, the incidence of NAFLD increases significantly to reach the levels seen in men.⁹⁷ HRT reduces the risk of hepatic steatosis⁹⁸ and the prevalence of NAFLD⁹⁹ in this

population. These and other data, including the association of NAFLD with altered ovarian function,⁹⁹ suggest that estrogens protect against the development of NAFLD.

The exact aetiology of NAFLD in postmenopausal women is unclear. However, estrogen deficiency certainly contributes to the loss of inhibition of *de novo* fatty acid synthesis,^{26,100} decreased VLDL-mediated export of lipids,^{97,101} and reduced fatty acid oxidation^{97,100} in the liver. This view is supported by studies in ovariectomized rodents, in which administration of estrogens prevented hepatic fat accumulation by inhibiting expression of genes that encode proteins involved in lipogenesis, including sterol regulatory element-binding protein 1c, peroxisome proliferator-activated receptor (PPAR) γ , stearoyl-coenzyme A desaturase 1, acetyl-coenzyme A carboxylase and fatty acid synthase.^{26,100} Estrogens also facilitate VLDL-mediated export of lipids from the liver, by increasing hepatic VLDL-triglyceride production and expression of microsomal triglyceride transfer protein.^{97,101} Finally, estrogens sustain the β -oxidation of fatty acids by inducing expression of PPAR- α .¹⁰⁰

Polycystic ovary syndrome

NAFLD is often associated with PCOS,¹⁰² which affects up to 10% of women of reproductive age.¹⁰³ PCOS is a major metabolic and reproductive disorder characterized by hyperandrogenism, chronic anovulation and polycystic ovaries,¹⁰⁴ as well as metabolic disturbances—50% of women with PCOS have overweight or obesity,¹⁰⁵ and dyslipidaemia (increased levels of LDL and decreased levels of HDL) is also commonly observed.¹⁰⁶ In the USA, 39% of women with PCOS have hepatic steatosis,¹⁰² and 50% have insulin resistance and metabolic syndrome.⁶ Indeed, insulin resistance, independent of obesity, is the metabolic disorder that is most strongly correlated with PCOS.¹⁰⁷ This decreased insulin signalling might be due to serine hyperphosphorylation of the insulin receptor and its substrate IRS-1.¹⁰⁸

The cause of anovulation in women with PCOS has not been clearly identified, but might involve an increase in GnRH pulse frequency, possibly caused by low progesterone levels in these patients, which augment both luteinizing hormone release from the pituitary and ovarian androgen production.¹⁰⁹ Insulin might increase luteinizing hormone production and synergize with it to stimulate androgen synthesis by ovarian theca cells, thereby further impairing the development of ovarian follicles.^{110,107} This observation further emphasizes the tight interconnection between metabolic and reproductive disturbances in patients with PCOS. The presence of metabolic disorders worsens the clinical and biochemical manifestations of PCOS. Being overweight contributes to hyperandrogenism, insulin resistance and dyslipidaemia;^{105,110} conversely, a reduction in excess body weight ameliorates these abnormal metabolic and reproductive features of PCOS.¹⁰⁵

The oral contraceptive pill has been the mainstay of therapy for women with PCOS for several years—combinations of estrogens and progestins ameliorate hirsutism, acne and oligomenorrhoea in these patients.^{110,111}

Additionally, HRT, possibly by reducing abdominal fat deposits, is thought to counteract the worsening of hyperinsulinaemia that occurs with ageing in women with PCOS.¹¹² Concerns about the use of oral contraceptive therapy in patients with PCOS have been raised by the observation of increased triglyceride and cholesterol levels,¹¹³ a phenomenon that is not in line with either observations from experimental studies of HRT or with the notion that endogenous estrogens protect against dyslipidaemia.⁸¹ Further studies should be carried out to clarify the extent to which these alterations in patients' lipid profiles were related to the specific compound used (ethinyl estradiol), its dosage and route of administration.

Metformin, an antidiabetic agent, can effectively restore ovarian function in women with metabolic disorders—indeed, metformin not only reduces insulin levels but also directly stimulates ovarian steroidogenesis.¹¹⁴ However, the effects of this therapy on reproductive outcomes seem to be limited, as live birth rates do not improve in metformin-treated women with PCOS (despite improved clinical pregnancy rates).¹¹⁵ Metformin in combination with oral contraceptives can also mitigate the reproductive and metabolic symptoms of PCOS.¹¹¹ This observation, which is in line with the theory that gonadal hormones are essential for a well-balanced metabolism, also requires confirmation in additional studies including a statistically relevant number of patients with PCOS.¹¹¹

Turner syndrome

Turner syndrome is a common genetic disorder affecting 1 in 2,500 live-born girls¹¹⁶ that is caused by the total or partial absence of one X chromosome (genotype 45,XO). The most common features of Turner syndrome are infertility due to gonadal dysgenesis, short stature,¹¹⁷ metabolic disorders, webbed neck and other physical abnormalities.¹¹⁸ Reduced dosage of genes on the X chromosome, which in 46,XX female individuals escape X-inactivation (and are, therefore, functionally diploid), is thought to cause most Turner syndrome features.¹¹⁹ However, candidate X-chromosome genes responsible for specific Turner syndrome features are yet to be identified.¹²⁰

The clinical features of patients with Turner syndrome include obesity,¹²¹ low lean body mass and increased BMI, waist circumference¹²² and visceral adipose tissue,⁹⁹ moreover, triglycerides and LDL levels are elevated, but HDL levels are decreased.¹²³ Patients with Turner syndrome also have smaller lipid particle sizes than do 46,XX individuals.¹²³ Interestingly, the extent of the differences in lipid levels and particle sizes between 46,XX and 45,XO individuals is very similar to that between men and women.⁸¹ Thus, haploinsufficiency of X-chromosome genes whose products are involved in lipid metabolism is probably the cause of dyslipidaemia in patients with Turner syndrome, in agreement with the fact that men generally have a more atherogenic lipid profile than do women.¹²⁴ As a result, patients with Turner syndrome have a sevenfold increased risk of mortality from ischaemic heart disease.¹²¹

Moreover, 80% of patients with Turner syndrome have abnormal liver function,¹²⁵ which is associated with intracellular hepatic lipid accumulation,^{99,125} elevated levels of

liver enzymes,¹²⁶ and increased incidence of NAFLD,⁹⁹ cirrhosis,¹²² liver hyperplasia and inflammation.¹²⁷ The hepatic abnormalities seem to be caused by the lack of estradiol production, as estradiol treatment ameliorates these abnormalities.¹²⁸

Although many clinical features in patients with Turner syndrome recapitulate the metabolic syndrome, paradoxically, such patients have decreased levels of fasting glucose, insulin and leptin (despite their high visceral adiposity), even compared with women who have premature ovarian failure.¹²⁹ However, the low insulin levels are thought to result from defective β -cell secretory function¹³⁰ or a glucose-storage defect,¹³¹ and the decreased leptin levels are probably attributable to low fasting insulin levels.¹³² Impaired glucose homeostasis is also frequent^{121,122} and results in an increased risk of diabetes mellitus,^{122,126} which is the cause of death in 25% of patients with Turner syndrome.¹³³

Current guidelines for the treatment of Turner syndrome recommend growth hormone therapy and suggest the initiation of estrogen-based HRT in patients aged 12–14 years.¹³⁴ Patients with Turner syndrome require high doses of growth hormone to achieve optimal development because they are resistant to its metabolic effects.^{7,135} Growth hormone therapy aids the decrease of adiposity and abdominal fat, and increases lean mass and circulating IGF-1 levels,⁷ whereas HRT is necessary for female sexual development, normalization of BMD and improvement of neurocognitive functions.¹¹⁸ Furthermore, estrogen therapy has important beneficial effects on the metabolic derangements associated with Turner syndrome, resulting from decreasing visceral adipose tissue,⁷ increasing HDL levels¹²¹ and maintaining normal liver metabolism.¹²⁸ Indeed, estradiol therapy improves liver function¹²⁸ and regulates the release of growth factors and antiapoptotic factors, which maintain the integrity of hepatocytes and promote their proliferation.¹³⁶

Current and future aims of HRT

Estrogens regulate both reproductive and metabolic functions, which have adapted to the reproductive cycle with fluctuating production of the metabolites relevant for energy storage or utilization.²⁶ Estradiol is the molecule most likely to be responsible for the beneficial effects of estrogens on metabolism, because it is the most potent and predominant form of estrogen during the fertile age, and its levels substantially decrease after menopause. However, the literature on levels of individual estrogen metabolites and their physiological effects is limited and often conflicting. Furthermore, we still do not understand the exact consequences of either the termination of ovarian activity or the oscillation of metabolic functions. Experimental and clinical observations show that ovariectomy disrupts the rhythm of ER α activation in the liver²⁶ and induces rapid disorganization of lipid metabolism characterized by accumulation of hepatic fat deposits.^{26,79} Decreased circulating estrogens and the lack of estrogen receptor oscillatory activity that occurs after menopause might trigger a derangement of energy metabolism in organs that are targets of estrogen action, such as adipose

tissue, muscle and hypothalamus. Functional deterioration leading to the onset of specific pathologies (cancer, immune, neuropsychiatric, cardiovascular and cerebrovascular diseases) are also observed with desynchrony of the circadian rhythm, which is generated by clock genes and proteins that regulate sleep and wakefulness, body temperature, blood pressure, digestive secretion, immune responses and metabolism.^{137–141} In analogy with such findings, the observed lack of efficacy of HRT with regard to menopause-associated dysmetabolism might plausibly be caused by their inability to reinstate the oscillatory activity of ER α and ER β in sexually mature individuals²¹ and the consequent reciprocal control of genes regulating both fertility and energy metabolism.

The aim of all forms of HRT used to date has been to keep hormone levels constant. However, in some organs, cyclical modulation of ER α and ER β signalling might be necessary to activate the expression of large numbers of genes whose products maintain energy homeostasis. For example, hepatic ER α becomes associated with distinct classes of promoters during different phases of the estrous cycle,²⁶ which might be necessary to poise ER α signalling for rapid selection of the transcriptome most appropriate for the specific energy requirements of each stage of the reproductive cycle. Previous studies in our laboratory suggest that selective estrogen receptor modulators, either alone or in combination with natural hormones, might have a substantial effect on the relative phasing and intensity of ER α and ER β activity in target organs.^{26,142} These findings raise the possibility that the complex actions of ER α and ER β in the whole organism might eventually be reproduced pharmacologically. However, currently a clear understanding of the pattern of ER α and ER β activity that would have the most favourable effect on women's health during ageing is lacking. In the absence of such knowledge, we believe that the analysis of the effects of existing forms of HRT on a single parameter (such as the period or amplitude of ER α or ER β activity in different organs) is not sufficient to establish the superiority of one treatment over another. Specific methodologies and algorithms for the comparative analysis of multivariate parameters of synthetic ER α and ER β ligand activity should also

be developed.¹⁴³ Initial animal studies have shown that screening, based on the whole-body analysis of ER α and ER β , by molecular imaging is a viable method.¹⁴³ This innovative technique might aid the development of novel HRT modalities better able to mimic estrogens' effects during the reproductive cycle.

Conclusions

This Review underlines the close link between energy metabolism and reproduction, to provide a comprehensive view of the role of estrogens in mammalian physiology. Given the association between energy production and reproductive activity, a main aim of HRT should be restoration of the metabolic functions characteristic of women still undergoing reproductive cycling. However, in postmenopausal women, current forms of HRT cannot reinstate the low morbidity from skeletal, cardiovascular and metabolic diseases typical in women of fertile age. Improved understanding of the exact physiological role of estrogens is, therefore, required to develop new types of HRT that can address metabolic as well as hormonal derangements.

Review criteria

The articles selected for this Review were English-language, full-text articles and abstracts identified by searching PubMed and personal databases. The keywords used included “estrogen”, “estrogen receptor”, “estradiol”, “fertility”, “reproduction”, “energy”, “metabolism”, “menopause”, “ovarian activity”, “ovariectomy”, “hormone replacement therapy”, “SERMs”, “obesity”, “steatosis”, “lipids”, “insulin resistance”, “apolipoproteins”, “POMC”, “NPY”, “AgRP”, “GnRH”, “CART”, “SF-1”, “neurons”, “PYY”, “ghrelin”, “leptin”, “fat”, “amino acids”, “IGF-1”, “GH”, “hypothalamus”, “liver”, “adipose tissue”, “pancreas”, “metabolic syndrome”, “NAFLD”, “PCOS”, “Turner syndrome”, “fatty acids”, “ β -oxidation”, “lipogenesis”, “LH”, “androgens”, “oral contraceptive”, “metformin”, “circadian rhythm”, “vitellogenin”, “fat body”, “juvenile hormones”, “ecdysone”, “*Drosophila*”, “mouse”, “insulin-like-peptides”, “mTOR”, “gonadotropins”, and “FOXO”.

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Author contributions

All authors researched the data for the article and contributed substantially to discussions of its content. A. Maggi wrote the manuscript, and S. Della Torre, V. Benedusi and R. Fontana reviewed and/or edited the manuscript before submission.