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Review Article

Obesity and fertility

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Abstract

Objective **Reproductive function is intrinsically linked to body metabolism, as both energy deficiency and excess significantly impact pubertal onset and fertility. Obesity leads to secondary hypogonadism in males, also called "male obesity-related secondary hypogonadism" (MOSH)—a complex condition driven by systemic inflammation, insulin resistance, and suppressed gonadotropin secretion. In females, obesity is a primary risk factor for polycystic ovary syndrome (PCOS), the most prevalent anovulatory disorder. Furthermore, obesity can trigger non-PCOS ovulatory dysfunction, recently conceptualized as "female obesity-related secondary hypogonadism" (FOSH). Notably, even metabolically healthy obese (MHO) women exhibit a heightened risk of infertility. Consequently, managing obesity is fundamental to preserving reproductive health. In this context, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as promising therapeutic agents.**

Design and Methods **Based on this framework, this review evaluates: (i) the physiological interplay between metabolism and reproduction; (ii) the contemporary pathophysiological model of obesity-related male infertility; and (iii) the clinical challenges of obesity-related reproductive dysfunction in females.**

Results and Conclusions **Ultimately, while weight loss remains a cornerstone of fertility preservation, GLP-1 RAs represent a significant advancement, potentially offering reproductive benefits beyond weight reduction, whether used alone or in combination with lifestyle interventions or surgery.**

Keywords Obesity, reproduction, infertility, GLP-1, hypogonadism, PCOS, sexual dimorphism

Significance statement

Body metabolism is a critical regulator of reproductive function in both sexes. The relationship between body mass index (BMI) and gametogenesis follows an inverse J-shaped curve, as both underweight and overweight states impair sperm production in males and ovulatory function in females. While obesity in males is associated with male obesity-related secondary hypogonadism (MOSH), females may present with either polycystic ovary syndrome (PCOS) or female obesity-related secondary hypogonadism (FOSH). Notably, even metabolically healthy obesity confers a higher risk of infertility. Effective obesity management is therefore essential for reproductive health. In this scenario, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as promising therapeutic tools whose clinical benefits may extend beyond weight reduction alone.

Relationship between metabolism and reproduction

Critical fat mass hypothesis

Metabolism and reproduction are tightly interconnected functions. It is clear that not only a lack of energy stores but also persistent energy excess, such as in cases of morbid obesity, are associated with reproductive dysfunction.[1] The connection between metabolism and reproduction was initially postulated based on the work of Kennedy and Mitra, who showed that pups exposed to higher energy intake reached puberty earlier compared to those of the same age who had lower energy intake and delayed pubertal development.[2] These findings led to the "critical fat mass hypothesis," coined by Frisch et al., who found that a critical minimum weight appeared necessary for the onset and maintenance of normal menstrual cycles in human females.[3] Based on this background, current opinion holds that

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reproductive function depends on metabolic fuel availability and metabolic signals informing the hypothalamic-pituitary-gonadal (HPG) axis of energy reserves, such as leptin, insulin, and ghrelin.[4]

Integration of metabolic and endocrine signals in the regulation of the HPG axis

Leptin is a 167-amino acid peptide predominantly expressed in adipose tissue and secreted in direct proportion to the amount of stored body fat.[5] It signals energy sufficiency and represents an indispensable permissive factor for pubertal progression, as demonstrated by the fact that its administration reverses pubertal failure and infertility in leptin-deficient models.[6,7] However, leptin alone cannot trigger early puberty *per se*; it requires other intermediary factors, as GnRH neurons are devoid of leptin receptors (LepRs).[1] For instance, it has been shown that the selective elimination of LepRs from all neurons prevents puberty onset and causes infertility, but this is not the case when LepRs are knocked out in GnRH neurons only.[8] A paradigm shift in this field occurred with the discovery of the crucial role of kisspeptin signaling in reproduction. This was based on the evidence that humans and mice harboring mutations in the gene encoding kisspeptin (*KISS1*/*Kiss1*) or its receptor (*KISS1R/Gpr54*) do not undergo puberty and are infertile.[9-11] In the last decade, kisspeptin has been identified as a key player in the crosstalk between metabolism and reproduction.[12] This was based on the evidence that upon leptin stimulation, kisspeptin—encoded by the *KISS1/Kiss1* gene and secreted by Kiss1 neurons—increased and activated GnRH neurons, with subsequent stimulation of the pituitary-gonadal axis. This was also supported by the observation that low or absent leptin levels led to a significant reduction in *Kiss1* mRNA expression[8] and that leptin replacement in leptin-deficient models increased *Kiss1* mRNA expression.[13] Of note, *LepR* mRNA expression was found in ∼40% of mouse kisspeptin neurons in the arcuate nucleus.[13]

Although leptin is important for the activation of kisspeptin neurons, further studies have questioned whether leptin's effects on reproduction are mediated directly by kisspeptin only.[14,15] Historically, neuronal nitric oxide was the first essential regulator of the HPG axis and reproduction to be identified.[16] Further research has clarified that nitric oxide synthase (nNOS)-expressing neurons, which are located in the organum vasculosum of the lamina terminalis and the median preoptic nucleus, act as critical relays between metabolism and reproduction, where leptin-induced nitric oxide (NO) production facilitates GnRH release.[17] Interestingly, Bellefontaine et al. showed that genetic deletion or pharmacological inhibition of nNOS prevented leptin-induced LH release[15] and this effect appeared to be independent of kisspeptin and Kiss1R signaling. Nevertheless, nNOS neurons in the preoptic region express functional Kiss1R, indicating that the kisspeptin and nNOS pathways work together to establish the appropriate pattern of GnRH release.[17] In line with these findings, it has also been demonstrated that leptin effects on pubertal development are relayed by ventral premammillary nucleus neurons expressing the excitatory neurotransmitter glutamate, which may serve as an alternative pathway in this circuitry, conveying inputs on fluctuating levels of leptin directly to GnRH neurons.[14] Consequently, it is clear that metabolic signals to the reproductive axis are characterized by significant redundancy, as shown in Figure 1.

To add a further layer of complexity, the metabolic regulation of reproductive function also relies on pro-opiomelanocortin (POMC) neurons, which serve as essential sensors of leptin and other anorexigenic stimuli, such as GLP-1.[18,19] As demonstrated by Hill et al.,[20] the direct and concomitant action of insulin and leptin on POMC neurons is mandatory for maintaining normal glucose homeostasis and female fertility, as its disruption leads to hyperandrogenism and ovarian dysfunction. Furthermore, the melanocortin system, originating from these POMC neurons, acts as a critical relay to the GnRH pulse generator. Specifically, Israel et al. showed that melanocortin signaling (via MC4R) is required to translate leptin-derived metabolic cues into GnRH neuronal activity, thus establishing this pathway as an important component in the leptin-mediated regulation of GnRH neuron activity, initiation of puberty, and fertility.[21] Similarly, other anorexigenic stimuli, such as glucagon-like peptide-1 (GLP-1), may modulate reproductive function through the same pathways. Moreover, recent experimental evidence indicates that GLP-1 can directly regulate GnRH neurons as well[22-26] and acts on Kiss1 neurons to increase *Kiss1* mRNA expression.[27]

Body metabolism and the timing of puberty

Reproductive function depends on metabolic fuel availability. Consequently, the timing of puberty is sensitive to both underfeeding and overfeeding during early (postnatal) periods, which have been attributed to alterations in the hypothalamic expression of kisspeptin. For example, Castellano et al. showed that early overfeeding promoted puberty onset, as evidenced by an increase in kisspeptin expression.[28] Consistent with these observations, the age of puberty onset has progressively decreased over recent decades, showing a strong inverse correlation with the rising prevalence of obesity, particularly in girls.[29] The relationship between obesity and earlier puberty onset in girls can be ascribed to multiple factors. On the one hand, excessive adiposity leads to higher circulating levels of leptin and higher gonadotropin levels in obese children,[30] likely through the activation of kisspeptin signaling. On the other hand, excessive adiposity is associated with insulin resistance and hyperinsulinemia, which reduces the hepatic production of sex hormone-binding globulin (SHBG), leading to higher bioavailability of sex steroids.[31]

The timing of puberty onset has important health consequences,[32] particularly regarding future fertility.[33] A 25-year follow-up study conducted by He et al. shows that being obese before the age of 12 is associated with impaired fertility in later life.[33] This appears to be because early puberty onset in obese girls affects the long-term function of the HPG axis and reproductive system development. Specifically, increased estrogen production—due to the accelerated aromatization of adrenal and ovarian androgens in adipose tissue—promotes earlier menarche, pubarche, and thelarche. However, this premature maturation seems to exert unfavorable influences on the HPG axis, ovarian function, and oocyte quality in the long term. For instance, exposure of female rats to a post-weaning, high-fat diet has deleterious long-term

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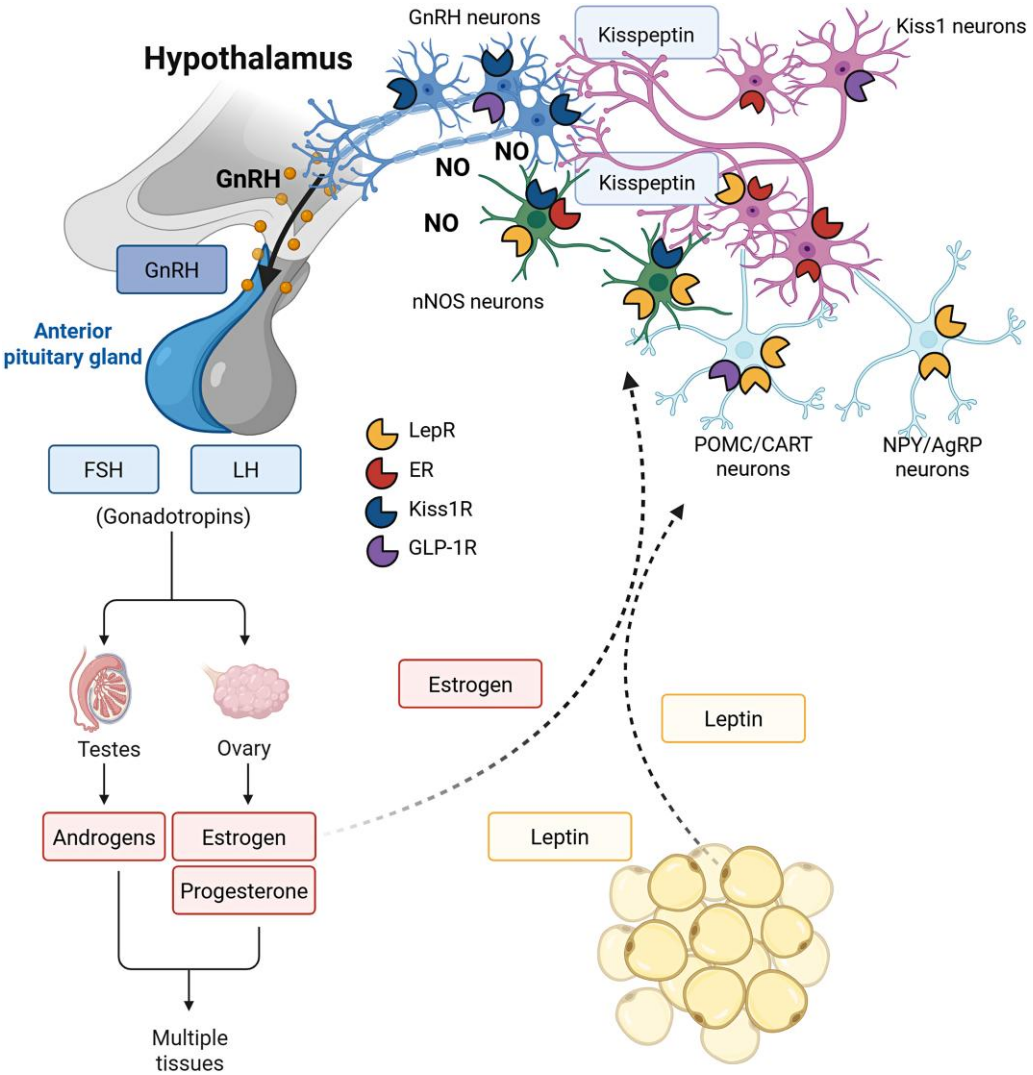


Figure 1 Integration of metabolic and endocrine signals in the regulation of the Hypothalamic-Pituitary-Gonadal (HPG) axis. The figure illustrates the neuroendocrine network governing reproductive function. Leptin, secreted by adipose tissue, exerts indirect effects on GnRH neurons via intermediary neuronal populations expressing the leptin receptor (LepR), including Kiss1 neurons, nNOS-expressing neurons (producing nitric oxide, NO), and POMC/CART neurons, while inhibiting orexigenic NPY/AgRP neurons. Kisspeptin acts directly on GnRH neurons via the Kiss1R to stimulate GnRH pulsatile release, which in turn triggers the pituitary secretion of LH and FSH. Notably, GLP-1 receptors (GLP-1R) are specifically located on Kiss1 and POMC/CART neurons, highlighting their role as direct targets for metabolic regulation, whereas NPY/AgRP neurons are primarily modulated through indirect inhibitory circuits. Estrogen feedback is mediated by estrogen receptors (ER) on these regulatory populations. This figure was created with biorender.com. Abbreviations: AgRP, agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; ER, estrogen receptor; FSH, follicle-stimulating hormone; GLP-1R, glucagon-like peptide-1 receptor; GnRH, gonadotropin-releasing hormone; Kiss1R, kisspeptin receptor; LepR, leptin receptor; LH, luteinizing hormone; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; NPY, neuropeptide Y; POMC, pro-opiomelanocortin.

effects on ovulation, potentially involving the downregulation of ovarian *Kiss1* mRNA and kisspeptin.[34] Moreover, DBA/2J female mice, which are prone to obesity-induced infertility, showed a marked decrease in *Kiss1* gene expression in both the rostral periventricular region of the third ventricle and the arcuate nucleus, alongside a reduction in kisspeptin-immunoreactive neurons following diet-induced obesity.[8] Additionally, childhood obesity is a significant factor contributing to the presence and severity of PCOS in adolescence and adulthood, increasing the risk of anovulatory infertility.

Interestingly, the relationship between obesity and the timing of puberty onset is less clear in boys, partly due to the sexual dimorphism of the kisspeptin system.[35-37] Current evidence on the effect of obesity on male pubertal timing is contradictory, with reports of both earlier and delayed puberty. As discussed in the review by Reinherr et al., the potential earlier onset of puberty by a few months was reported predominantly in boys who were overweight rather than boys with obesity. In contrast to girls, puberty onset in boys could be influenced by the degree of weight gain, with earlier maturation in boys who are overweight, and later maturation in boys with obesity, as compared to boys with normal weight.[29,38] Adipose tissue has an aromatase action, which increases androgen conversion to estrogens, and excess estradiol concentrations in boys with increased body fat mass can exert negative feedback on the HPG axis. Lee et al. speculated that greater estrogen production in boys with obesity

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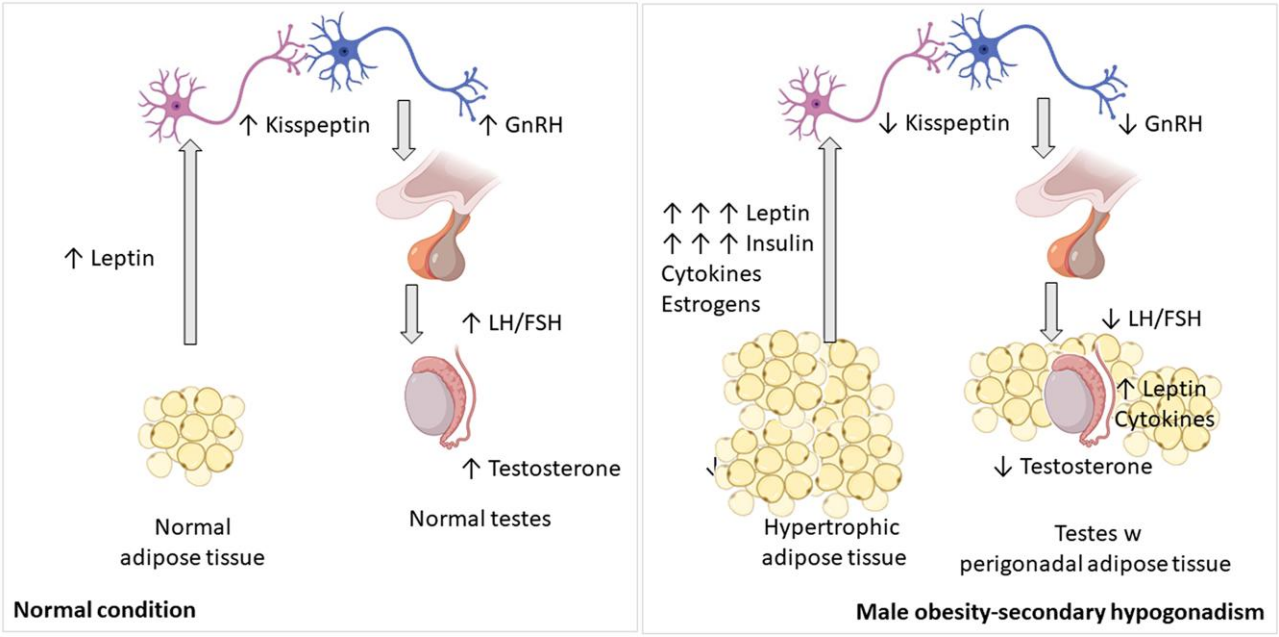


Figure 2 Pathophysiological mechanisms of Male Obesity-related Secondary Hypogonadism (MOSH). The figure illustrates the transition from normal physiological conditions (left panel) to the dysregulated state associated with obesity (right panel). In the healthy state, leptin signals energy sufficiency to the hypothalamus, maintaining appropriate Kisspeptin and GnRH pulsatility, which in turn stimulates the pituitary-gonadal axis to ensure normal testosterone production and spermatogenesis. In the context of obesity, hypertrophic adipose tissue leads to a state of chronic low-grade inflammation and hormonal imbalance. Specifically, the marked increase in leptin (hyperleptinemia), insulin, and pro-inflammatory cytokines, coupled with increased estrogen levels (due to peripheral aromatization of androgens in the adipose tissue), exerts a potent negative feedback on the hypothalamic-pituitary-gonadal (HPG) axis. This results in the suppression of Kisspeptin and GnRH release, leading to reduced LH and FSH secretion and, ultimately, a significant decline in testosterone levels and impaired testicular function. This figure was created with biorender.com. Abbreviations: FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HPG, hypothalamic-pituitary-gonadal; LH, luteinizing hormone; MOSH, male obesity-related secondary hypogonadism.

than in boys at a healthy weight could suppress the pubertal process; however, this might not be the case for boys who are overweight.[38] Consistent with this, animal studies show that high-fat diets are detrimental to male fertility. Compared with controls, males fed a high-fat diet exhibit smaller testes and accessory sex glands relative to body size, reduced semen quality, and decreased mating and fertilization success.[39] This is consistent with the rapid decline in semen quality observed over the last 50 years, which has been attributed to environmental causes, including the rising prevalence of obesity, rather than genetic factors.

Obesity and fertility in the male sex

Male obesity-related secondary hypogonadism

Male hypogonadism can be defined as a clinical syndrome that results from a failure of the testes to produce adequate amounts of testosterone, which is frequently associated with impaired sperm production. Cross-sectional studies have confirmed that hypogonadism is strongly associated with obesity[40] and today, the prevalence of hypogonadism secondary to obesity is estimated as high as 40%-50% in obese subjects.[41] As previously mentioned, semen quality has declined significantly since 1940.[42] Specifically, mean sperm concentration dropped from around 113 million/mL in 1940 to 66 million/mL in 1990, while mean ejaculate volume decreased from 3.4 mL to 2.7 mL. Environmental factors have likely contributed to this downward trend, including exposure to toxins/endocrine-disrupting chemicals but also smoking, alcohol consumption, and unhealthy lifestyle habits—such as high-fat diets and physical inactivity—that lead to obesity.[42,43] In particular, an extensive meta-analysis on the relationship between BMI and semen quality found that there is a J-shaped association between BMI and the risk of oligozoospermia or azoospermia.[44]

Notably, the relationship between obesity and gonadal dysfunction is recognized as bidirectional. While excessive adiposity impairs gonadal function, infertility and gonadal failure can, in turn, adversely affect metabolic health.[45] Also infertility treatment with gonadotropins, particularly follicle-stimulating hormone (FSH), might increase visceral fat accumulation and alter lipid metabolism, creating a self-perpetuating cycle that exacerbates weight gain and metabolic decline.[46]

Mechanisms of male obesity-related secondary hypogonadism

The mechanisms by which obesity leads to male hypogonadism and infertility involve predominantly central changes. This condition has been recently named “male obesity-related secondary hypogonadism” or MOSH,[41] as shown in Figure 2. While historically attributed mainly to increased peripheral aromatase activity

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and the subsequent conversion of testosterone to estradiol with HPG axis suppression,[47,48] contemporary integrative models suggest a more multifaceted pathophysiology relying not only on peripheral, but also on central and testicular changes.[45] This is also supported by the evidence that the use of the aromatase inhibitor leflutrozole increased testosterone in subjects with MOSH, but did not relieve symptoms of sexual dysfunction, indicating that aromatase activity is only partially responsible for sexual dysfunction among obese men.[49] It is well known that excessive adiposity triggers a state of chronic low-grade inflammation, insulin-resistance, and hyperleptinemia.[50] These changes are responsible for the altered function of the HPG axis in MOSH. It has been shown that local leptin levels negatively regulate *LepR* expression in the hypothalamus.[51] Consistent with this, Zhai et al demonstrated that high-fat-diet-fed mice with hyperleptinemia exhibited a downregulation of *LepR* and *Gpr54* in the hypothalamus, with subsequent reduction of GnRH, kisspeptin, Gpr54, and LepR, confirming that increased leptin levels may account for the decreased secretion of GnRH and be involved in secondary hypogonadism (SH) in obese males.[52] Likewise, low-grade inflammation also impairs kisspeptin signaling and the HPG axis. In particular, TNF-α reduces the expression of the *GPR54* in vitro at a hypothalamic level.[53] This is worsened by hyperinsulinemia, which reduces SHBG[54] and total testosterone but increases estradiol.[55] Of note, it has been recently shown that lower SHBG of morbidly obese subjects affected testosterone but not estradiol[55] and that SHBG has direct anti-inflammatory effects per se.[56] Nevertheless, obesity also has testicular effects, as low-grade inflammation seems to impair testicular function directly. In particular, the testicles of obese men show higher expression of pro-inflammatory cytokines that alter spermatogenesis.[57] They attract macrophages and neutrophils, which infiltrate the seminiferous epithelium and epididymal lumen, thus affecting sperm maturation and function. In addition, leptin has also testicular effects, as it suppresses testosterone synthesis in Leydig cells.[58,59] Moreover, obesity is associated with an increased scrotal and suprapubic adipose tissue, which increases the testicular temperature, impairing sperm quality.[60] Finally, sexual dysfunction, encompassing erectile dysfunction and loss of libido, represents a further barrier to fertility.

How to treat MOSH

Male obesity-related secondary hypogonadism is considered a form of functional hypogonadism,[61] implying potential reversibility as it is not due to intrinsic genetic or structural lesions of the testes. Clinically, affected men typically present with increased central adiposity and nonspecific symptoms such as low libido, fatigue, mood disturbances, and infertility, as summarized in the European Academy of Andrology guidelines on functional hypogonadism.[62] Testosterone, which should be measured only in the presence of signs and symptoms of hypogonadism, is slightly reduced, and LH and FSH concentrations are most often normal. Based on EAA guidelines,[62] diagnosis of MOSH requires signs and symptoms consistent with androgen deficiency and low testosterone levels confirmed on at least two occasions, after exclusion of organic causes.[41,62] In this setting, the optimal therapeutic approach remains a subject of debate. Although testosterone replacement therapy (TRT) can address androgen deficiency and symptoms of hypogonadism, the ideal treatment would be to remove the cause of functional hypogonadism and restore HPG axis function, as this would promote the entire testicular function, not only in terms of testosterone but also sperm production.[46]

Several studies have shown that weight loss raises testosterone levels, with the most significant improvements observed when weight reduction exceeded 20%.[61,63] Consistent with this, Corona et al. reported that lifestyle changes resulting in an average weight loss of 9.8%, increased testosterone by 2.9 nmol/L, while bariatric surgery, yielding a 32% weight loss, increased testosterone by 8.7 nmol/L.[64] The European Male Ageing Study further demonstrated that in overweight men aged ~58 years, a 5% weight loss over 4.4 years was associated with an increase in testosterone by 2 nmol/L.[65] This effect was attributed to the improvement of insulin resistance and the increase in sex hormone-binding globulin.[65] Conversely, a 15% weight loss increased total testosterone by 5.7 nmol/L, free testosterone by 52 pmol/L, and LH by 2.2 IU/L, significantly improving sexual function, as assessed by the International Index of Erectile Function (IIEF), which increased by 3.1 points.[65] Notably, the most robust results are achieved through bariatric surgery. In a prospective study on 64 men aged 49 years with a BMI of 46 kg/m^2, a 30% weight loss after gastric bypass increased testosterone by 10.8 nmol/L and improved sexual function by 7.5 points on a 20-point scale.[66]

In addition, weight loss improves semen parameters. A recent meta-analysis of twelve studies, including 345 subjects (mean age 38 years; mean baseline BMI 45 kg/m^2), confirmed that weight loss leads to a significant increase in sperm concentration and progressive motility, while decreasing the sperm DNA fragmentation index.[67] Likewise, in a study evaluating the effect of sustained weight loss on semen parameters, obese men who lost an average of 16.5 kg via a low-calorie diet showed a 1.5-fold increase in sperm concentration and 1.4-fold increase in sperm count. In addition, these improvements were kept for 52 weeks in men who maintained the weight loss with either exercise or liraglutide.[68]

The use of GLP-1RAs

In the current era of glucagon-like peptide-1 (GLP-1) receptor agonists and dual agonists for weight loss, a few studies have compared them to testosterone replacement therapy (TRT) regarding hormonal and semen parameters. A recent randomized trial has compared liraglutide (3.0 mg/day) to TRT (50 mg/day) in the treatment of obese men with functional hypogonadism. After 16 weeks, liraglutide achieved an 8 kg weight loss compared to 1 Kg with TRT.[69] While both treatments increased total testosterone ($+2.6 \pm 3.5$ nmol/L with liraglutide vs $+5.9 \pm 7.2$ nmol/L with TRT), only liraglutide increased LH and FSH and resolved metabolic syndrome in two participants. Another study compared semaglutide (1 mg/week) to intramuscular testosterone undecanoate in obese men with type 2 diabetes and MOSH. After 24 weeks, both interventions increased total testosterone and improved Aging Male Symptoms scores; however, only TRT significantly improved IIEF-15 scores. On the other hand, only semaglutide significantly improved sperm morphology, whereas in the TRT group, sperm concentration and count declined.[70]

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Nevertheless, a retrospective study by Giagulli et al. on obese men with type 2 diabetes and MOSH showed that patients treated with liraglutide experienced not only a weight loss but also a significant improvement in the IIEF-15 score compared with the group receiving only testosterone and metformin.[71] That being said, the effects of diet and glucose-lowering drugs on erectile dysfunction have been recently reviewed by other Authors.[72]

Collectively, these works imply that GLP-1RAs provide a dual benefit in MOSH management: they facilitate testosterone increase while maintaining or improving sperm quality, contrasting sharply with TRT, which may suppress spermatogenesis.[73] It goes without saying that while TRT effectively manages symptoms of hypogonadism, it is inherently contraceptive due to its suppressive effect on LH and FSH, further impairing spermatogenesis. In contrast, GLP-1RAs address the root cause of MOSH by reducing adipose-driven negative feedback, thereby restoring the endogenous HPG axis and improving reproductive potential. It has to be noted that acute GLP-1 injections in healthy eugonadal men do not alter LH pulsatility and testosterone levels, indicating that the primary mechanism in MOSH is likely indirect, mediated through weight loss and metabolic improvement rather than a direct and continuous effect on the HPG axis.

Obesity and fertility in the female sex

Obesity increases androgen levels in the female sex

Sex hormones show a clear dimorphic response to obesity in males and females. While MOSH is characterized by androgen deficiency, androgen concentrations are increased in women with obesity. In particular, the SWAN study, a longitudinal community-based study which included 359 women (47.2% black), aged 42-60 years, showed that there was a clear linear relationship between testosterone and visceral fat as assessed by computed tomography in women at different stages of the menopausal transition.[74] Likewise, in obese peripubertal girls, BMI significantly and positively correlated with calculated free testosterone.[75] There are several mechanisms whereby obesity is associated with increased androgen production. First, low-grade inflammation increases ovarian androgen production.[76] Second, the peripheral conversion of androstenedione to testosterone, which is due to 17β-HSD5, increases in obesity, as the expression of *17β-HSD5* increases in relation to BMI.[77] Third, obesity is associated with insulin resistance, and high insulin levels lead to high androgen levels. Insulin increases androgens by different mechanisms: it stimulates ovarian steroidogenesis, it promotes androstenedione production by favoring the 17,20-lyase activity of CYP17A1, and it favors a high LH to FSH ratio, which further promotes androstenedione and testosterone production (dependent on LH) over estrone and estradiol (dependent on FSH) in the ovaries.[31] For instance, insulin seems to enhance the transcription of the *LHB* gene. In addition, insulin reduces SHBG, and this increases bioavailable testosterone levels.

The relationship between insulin and hyperandrogenemia was initially demonstrated by Nestler et al., as the suppression of insulin by diazoxide significantly reduced testosterone and the androstenedione:estrone ratio, in obese women with polycystic ovary syndrome (PCOS).[78] Consistent with this, the use of insulin-sensitizing agents like metformin has been shown to lower androgen levels and improve the ovulatory response (to clomiphene) in obese women with PCOS.[79,80] A recent meta-analysis including 1123 women with PCOS undergoing infertility treatment has shown that metformin was associated with increased clinical pregnancy rates among women with a BMI $\geq$ 26 (OR, 1.7; 95% CI, 1.1-2.6).[81] Based on this evidence, metformin is currently recommended in PCOS women with a BMI $\geq$ 25 kg/m^2, especially for anthropometric and metabolic parameters.[82]

Not only PCOS but also female-obesity secondary hypogonadism (FOSH)

PCOS is the most common form of chronic anovulation associated with androgen excess, affecting between 8%-13% of women of reproductive age.[83] This condition is characterized by a derangement of the LH to FSH ratio (ie, higher mean concentration of LH and low or low-normal FSH), an accumulation of follicles arrested at various stages of development without reaching full maturation, and impaired steroidogenesis in response to steady-state levels of LH. Women with obesity have increased odds of PCOS ($\sim$ 2.8-fold, 95% CI 1.9-4.1),[84] because acquired insulin resistance associated with significant weight gain may promote ovulatory dysfunction in genetically susceptible women. Interestingly, although obesity can promote PCOS development in genetically susceptible women, it can also lead to another form of infertility, which has been recently called “female obesity-related secondary hypogonadism”, or FOSH, as it shares similar mechanisms to those underlying MOSH. In particular, non-PCOS women with obesity display an attenuation of the pituitary response to GnRH stimulation, as well as lower LH and lower FSH.[85] This can be ascribed to the fact that on the one hand, elevated fatty acids, insulin, androgens, and proinflammatory cytokines may reduce basal and GnRH-stimulated LH levels.[83] On the other hand, chronic hyperleptinemia, as found in obesity, can downregulate hypothalamic leptin signaling and lead to leptin resistance and decreased hypothalamic function.[83] Last, it has been suggested that increased clearance of endogenous LH is likely to contribute to lower LH levels in women with obesity.[83] As such, in women with PCOS, obesity appears to exert a suppressive effect on the HPG axis; specifically, obese women with PCOS exhibit lower LH pulse amplitude and mean LH levels compared to their lean PCOS counterparts, but similar LH pulse frequency, which is higher than that of non-PCOS women.[86] For this reason, the diagnosis of PCOS can be less clear-cut in women with obesity, and it may overlap with FOSH,[83] as shown in Figure 3.

Obesity and reproductive health

Obesity has a significant impact on reproductive health,[87,88] as shown in a recent study based on the 2017-2020 NHANES database and 1463 women aged 20 to 45, of whom 172 were found to be infertile. After adjusting for all factors except body measurements, the authors found that for each one-unit increase in

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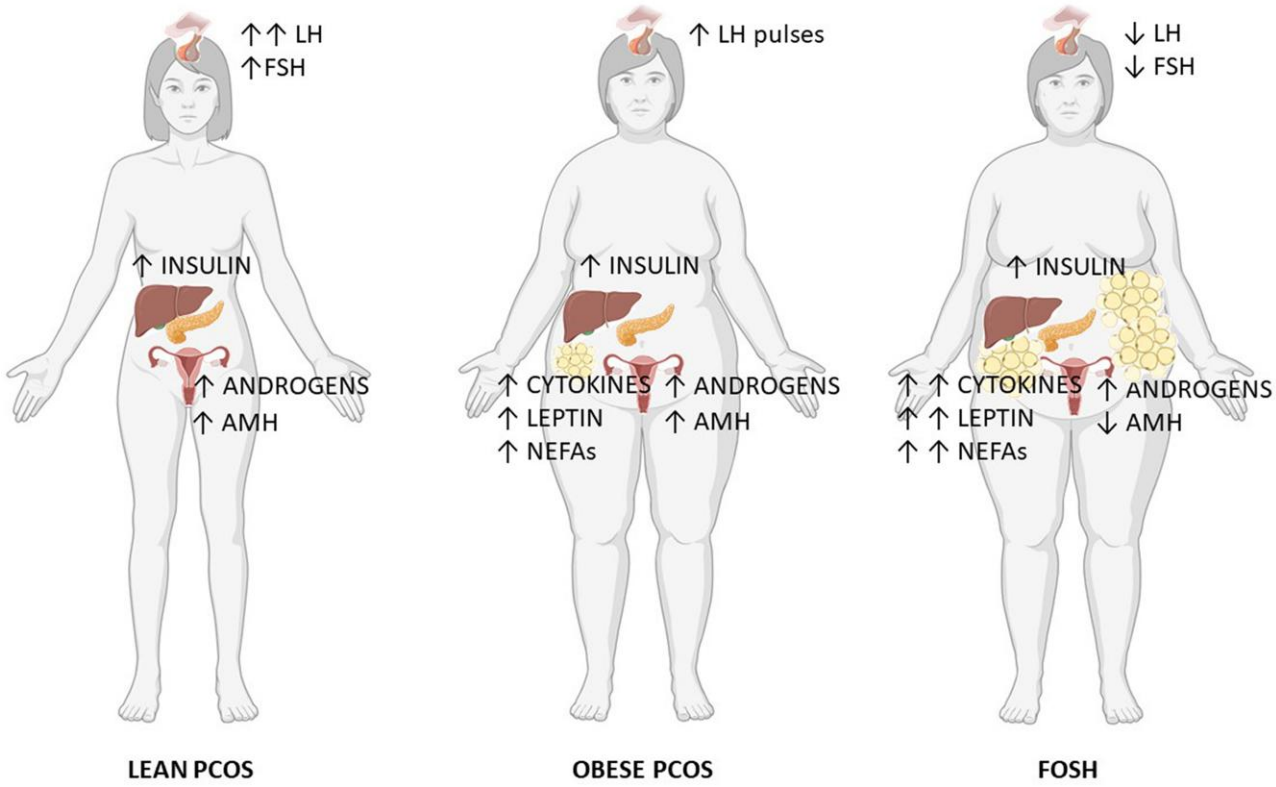


Figure 3 Comparison of hormonal and metabolic profiles in Lean PCOS, Obese PCOS, and Female Obesity-related Secondary Hypogonadism (FOSH). The figure illustrates the distinct pathophysiological features characterizing these three clinical phenotypes. In Lean PCOS (left panel), the primary driver is a marked neuroendocrine dysfunction, characterized by increased GnRH pulsatility leading to high LH pulse frequency and amplitude; this hormonal profile drives significant ovarian hyperandrogenism and is typically associated with markedly elevated Anti-Müllerian Hormone (AMH) levels. Notably, even in lean subjects, a moderate increase in insulin levels can be observed, reflecting a state of intrinsic insulin resistance independent of adiposity. In Obese PCOS (middle panel), the hormonal milieu is further complicated by adipose tissue dysfunction (elevated leptin, cytokines, and NEFAs) and severe hyperinsulinemia, which synergistically exacerbate androgen production while partially suppressing the LH/FSH ratio compared to lean counterparts. Conversely, FOSH (right panel) represents a state of secondary hypogonadism induced purely by obesity; it is characterized by the most severe metabolic derangement, where chronic inflammation and hyperleptinemia exert a suppressive effect on the HPG axis, resulting in relatively lower LH and FSH levels, alongside modest androgen elevation and lower AMH levels compared to PCOS phenotypes. This figure was created with biorender.com. Abbreviations: AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; HPG, hypothalamic-pituitary-gonadal; LH, luteinizing hormone; NEFAs, non-esterified fatty acids; PCOS, polycystic ovary syndrome.

the body roundness index, there was a 19% increase in the risk of infertility (OR = 1.2, 95% CI 1.0-1.3).[89] On the one hand, metabolic dysregulation is independently associated with longer time to pregnancy and increased infertility risk.[87] On the other hand, the profound impact that obesity has on fertility is also true for metabolically healthy obese women.[90] Interestingly, Oldfield et al. demonstrated that eumenorrheic women with obesity also demonstrated altered ovarian antral follicle and endocrine dynamics compared to their counterparts without obesity.[91] In this observational study, obesity was associated with an impairment of ovarian antral follicle dynamics, including reduced recruitment events, fewer selectable follicles, and lower anti-Mullerian hormone, as well as luteal phase defects.[91] Obesity may also alter the endometrium and uterine receptivity,[92] which could explain why miscarriage risk is increased in obese women who conceive spontaneously.[93]

Not surprisingly, obesity negatively impacts assisted reproductive technology (ART) as well.[87] For instance, obese women undergoing ART require higher gonadotropin doses and longer stimulations; treatments result in fewer retrieved oocytes and lower embryo yields, as well as increased miscarriage rates,[94-98] and implantation failure rates.[92,99] Consistent with these data, Veleva et al. reported a reduction in live birth rates and increased miscarriage risks in obese women undergoing ART.[100]

Weight loss interventions, the use of GLP-1RAs and reproductive outcomes

Weight loss remains the cornerstone of treatment for restoring fertility in obese women. Among medical interventions, GLP-1RAs have recently emerged as highly effective tools for achieving significant weight reduction and improving reproductive parameters. For instance, liraglutide (3 mg) for 32 weeks reduced body weight by −5.7%, the free androgen index, and improved cardiometabolic parameters in women with PCOS and obesity.[101] In line with these changes, a few studies have shown that GLP-1RAs improve fertility. In particular, in a 24-week open-label study, 176 overweight/obese women with

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PCOS were randomized to receive either exenatide or metformin for the first 12 weeks and then metformin for the second 12 weeks. After the first 12 weeks, women treated with exenatide exhibited greater body weight and HOMA index reduction and an increased menstrual frequency ratio, while in the second part of the study, the rate of natural pregnancies was significantly higher than that of metformin-treated patients (43.6% vs 18.7%).[102] In a prospective study on 28 obese women with PCOS and infertility, patients were randomized to metformin or metformin combined with low-dose liraglutide (1.2 mg) for 12 weeks. The ovarian stimulation protocol was started after a 4-week medication-free period. The in vitro fertilization pregnancy rate (PR) per embryo transfer (ET) was significantly higher in the combination (liraglutide + metformin) group.

Before the introduction of GLP-1RAs and dual agonists, bariatric surgery had long represented the most effective strategy for substantial weight loss. This has a favorable impact on reproductive function, as shown in a recent RCT, where 80 women aged on average 31 years, with PCOS and BMI $\geq$35 kg/m^2, were randomly assigned at a 1:1 ratio to either vertical sleeve gastrectomy or behavioral interventions and medical therapy (metformin or orlistat).[103] In the end, women in the surgical group had a 2.5-fold increase in spontaneous ovulations compared with the group receiving medical therapy, correlating with a significantly greater weight loss (−29 Kg vs +3 Kg at 52 weeks).[103]

Conclusion

Metabolism and reproductive function are intrinsically linked through a complex neuroendocrine network involving leptin, kisspeptin, GnRH, LH, and FSH. While obesity is associated with earlier puberty, it paradoxically increases the risk of infertility, particularly in females, affecting both male and female reproductive health through hormonal imbalances, metabolic dysfunction, and inflammatory pathways. Men are at risk of developing MOSH (male obesity secondary hypogonadism), which is characterized by impaired sperm count and motility, and low levels of androgens. Women are at risk of developing PCOS and/or FOSH—(female obesity secondary hypogonadism), which is characterized by anovulation, menstrual irregularities, reduced oocyte quality, and higher levels of androgens. Although there is a sexual dimorphism in the hormonal response, weight loss ameliorates infertility in both sexes.

GLP-1 receptor agonists, originally developed for type 2 diabetes and obesity management, have emerged as promising agents in the treatment of obesity-related infertility. These drugs not only facilitate significant weight loss but also improve insulin sensitivity and reduce systemic inflammation, thereby restoring reproductive function, particularly in patients with PCOS and FOSH. Nevertheless, further longitudinal studies are essential to establish long-term safety profiles and optimize treatment protocols for reproductive-age individuals. Ultimately, it is of paramount importance to provide proactive counseling to patients regarding the potential increase in fertility associated with weight loss—whether achieved through lifestyle interventions, pharmacological therapy, or bariatric surgery. This ensures that patients can make informed decisions aligned with their reproductive goals.

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Conflicts of interest

The Authors declare no conflicts of interest.

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N/A

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