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Obesity-Related Hypogonadism in Women

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Review

Obesity-Related Hypogonadism in Women

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Agenda

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- Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

Background

Obesity: significant burden to public health across the globe, with its prevalence having almost trebled over the past 40 years.

According to WHO, in 2016.

- > 1.9 billion adults are overweight (39% men and 40% women)
- 13% of the adult population (11% men and 15% women) had obesity

The global prevalence of obesity is projected to increase by at least a further 10% by 2030.

Background

Excess body weight is an established risk factor for comorbidities including a high prevalence of hypogonadism.

Male obesity-related secondary hypogonadism (MOSH) is relatively well-characterized (with the prevalence **~40%**).

The pathophysiology of secondary hypogonadism in men involves a complex interplay between

- Visceral adiposity
- leptin
- Insulin resistance (IR)

resulting in hypothalamic dysfunction.

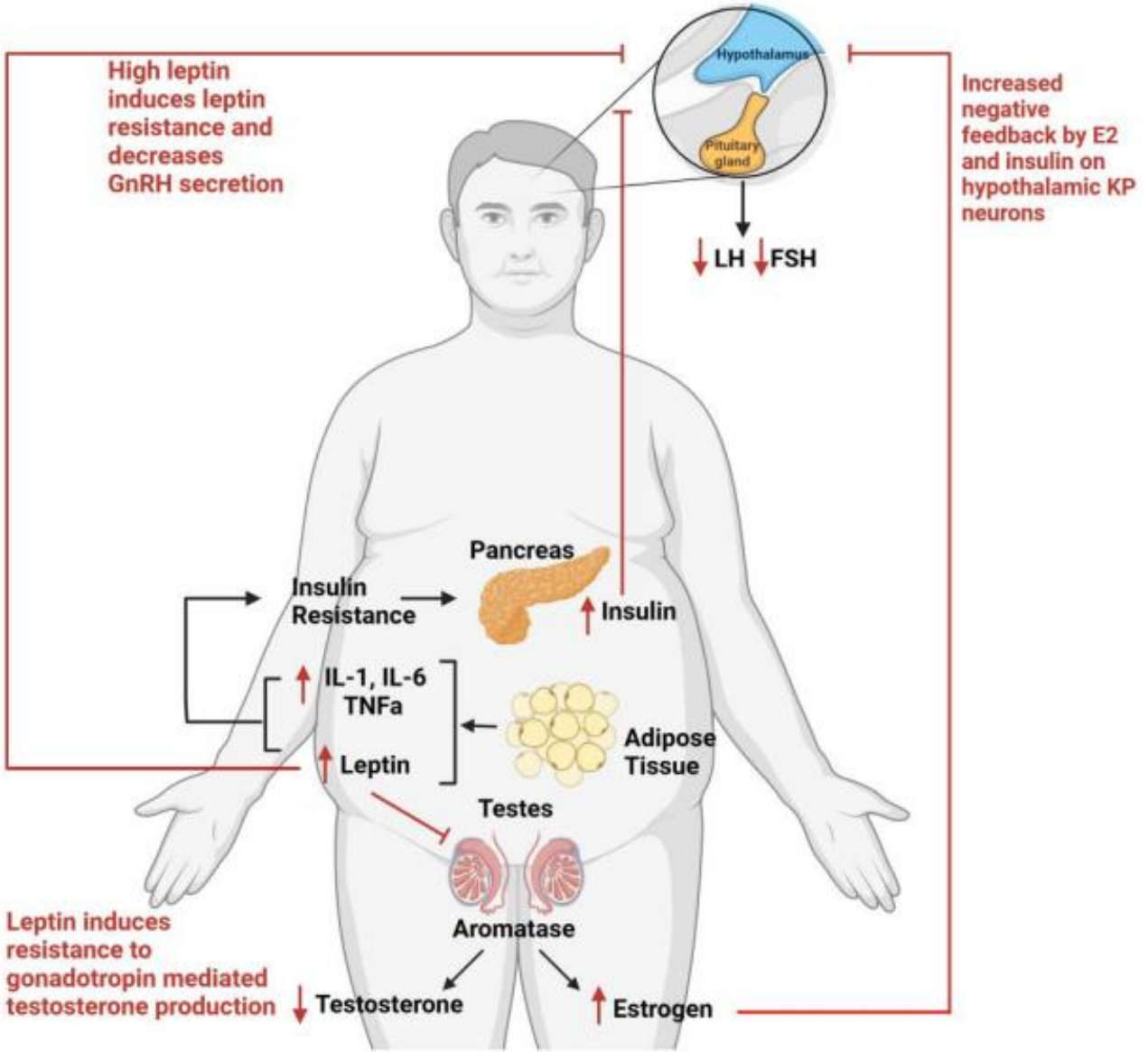

Figure 1. Mechanisms of hypogonadism in male obesity-related secondary hypogonadism (MOSH). Abbreviations: GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; SHBG, sex hormone binding globulin; NEFA, Non-esterified fatty acids; IL, interleukin; TNF-α, tumor necrosis factor.

Male obesity-related secondary hypogonadism (MOSH)

Estradiol is also increased in proportion to body weight as a consequence of greater aromatase activity in adipose tissue, which is proposed to further inhibit (GnRH)/ (LH) secretion from the hypothalamus and pituitary gland via negative feedback.

Furthermore, high leptin levels are proposed to lead to hypothalamic leptin resistance and reduced GnRH secretion, with a resultant decrease in LH levels.

Male obesity-related secondary hypogonadism (MOSH)

secondary to ⍰ free fatty acid delivery to the liver and ⍰ levels of inflammatory markers (eg, tumor necrosis factor [TNF]-α and interleukin [IL]-6) from adipose tissue ⍰ Hyperinsulinemia ⍰ further impair hypothalamic kisspeptin neuronal function and downstream testosterone production.

Androgen deficiency ⍰⍰ visceral fat accumulation/IR creating a self-perpetuating cycle inhibiting GnRH secretion and exacerbating hypogonadism.

Background

In women, obesity is associated with a dramatic increase in the frequency of menstrual irregularity.

Women with obesity at the age of 23 years have a 1.97-fold increased odds of menstrual disturbance, independent of their previous BMI during childhood.

The prevalence of menstrual disturbance increased from 23% if BMI <29.9 kg/m2 to 27% if BMI >30 kg/m2. *(Clin Endocrinol Metab*. 2004;89(6):2622-2631.)

Menstrual irregularity/BMI/ Waist circumference

Menstrual irregularity

- is 18% at a nadir BMI of ~22 kg/m2
- ~14% in women with BMI of 20 to 24.9 kg/m2.
- 26% of women with BMI >30 kg/ m2

increases linearly with BMI to reach over 60% in women with a BMI of 60 kg/m2.

The risk of menstrual disturbance increases linearly beyond a waist circumference of 70 cm.

Evidence for Secondary Hypogonadism in Women (ie, Reduced LH Levels) With Obesity

Although women with obesity and lower LH levels had similar estradiol levels during the follicular phase, the amplitude of the midcycle LH surge was reduced, resulting in lower levels of a urinary metabolite of progesterone in the midluteal phase (BMI 21 kg/m2 : urinary progesterone 181 µg/mg Cr vs BMI 49 kg/m2 : urinary progesterone 38 µg/kg Cr).

However, no change in LH pulse frequency was observed in women with obesity compared with controls (controls: LH pulse frequency 3.0 ± 0.3 vs obese: LH pulse frequency 3.2 ± 0.3 pulses per 12 hours.

Evidence for Secondary Hypogonadism in Women (ie, Reduced LH Levels) With Obesity

The impact of obesity on GnRH/ LH pulsatility in women has been studied by several research groups including those of Janet Hall and Jeffrey Chang. Overall, obesity negatively impacts on LH pulse amplitude rather than pulse frequency, indicating that the increased pulse frequency often detected in women with polycystic ovary syndrome (PCOS) is still expected to be present in women who also have obesity.

Evidence for Secondary Hypogonadism in Women (ie, Reduced LH Levels) With Obesity

Moreover, the tonic estradiol-induced negative feedback on the hypothalamic-pituitary–gonadal (HPG) axis is greater in women with obesity, as evidenced by an aromatase inhibitor doubling LH pulse amplitude by 2.54-fold in women with obesity, but not in lean women.

In summary, obesity is associated with impaired LH pulse amplitude and LH levels, resulting in reduced stimulation of corpora lutea, and lower luteal progesterone levels, with increased tonic estradiol-induced negative feedback.

Impact of Obesity on Diagnosis of PCOS

PCOS is the commonest endocrine disorder affecting between 8% to 13% of women of reproductive age. Approximately half of women with PCOS have obesity, though the reported prevalence of obesity in women with PCOS varies across countries from 38% to 88%.

Impact of Obesity on Diagnosis of PCOS

In lean women, PCOS is typically associated with increased GnRH pulsatility and high LH levels; however, mean LH levels and LH pulse amplitude are reduce women with obesity, suggesting the additional presence of a distinct pathophysiological mechanism exacerbating the occurrence of hypogonadism in women with obesity.

Impact of Obesity on Diagnosis of PCOS

Moreover, increased LH levels in PCOS promote ovarian hyperandrogenism and ovulatory dysregulation, but hyperandrogenism can occur in women with obesity even in the absence of PCOS. Furthermore, lean women with PCOS are more likely to have an increase in adrenal androgens, and obesity can also result in an increase in androgens produced through nonclassical pathways.

Importantly, polycystic ovarian morphology is harder to assess in women with obesity for technical reasons. Thus, it is conceivable that menstrual disturbance in women with obesity often could be inaccurately attributed to PCOS.

Impact of Obesity on Diagnosis of PCOS

Obesity negatively impacts on gonadotropin secretion in women with PCOS. Morales and colleagues showed that LH pulse amplitude in lean women with PCOS is over 2.5-fold greater than that in lean controls (lean PCOS: 13.3 vs lean controls: 5.0 IU/L). By contrast, this increase in LH pulse amplitude is tempered in women with obesity and PCOS who display relatively normal LH pulse amplitude (obese PCOS: 6.4 IU/L vs lean PCOS: 13.3 IU/L).

Mean serum LH was also lower in women with obesity and PCOS (lean PCOS 31.5 vs lean controls 10.4 IU/L; obese PCOS: 20.8 vs obese controls: 10.7 IU/L) and mean LH and LH pulse amplitude were inversely correlated with BMI in eumenorrheic women and anovulatory women with PCOS.

Impact of Obesity on Diagnosis of PCOS

However, LH pulse frequency remains increased in women with PCOS even if obesity is present (number of LH pulses per 24 hours: obese PCOS 23.9; lean PCOS 21.9; obese controls 15.9; lean controls 15.9).

Similarly, in another cross-sectional study in women with PCOS by Arroyo and colleagues, spontaneous LH pulse frequency was increased (women with PCOS: 22.8 per 24 hours vs normal cycling women: 16.5 per 24 hours), but 24-hour mean LH levels were negatively correlated with BMI ($n = 33$, $r = -0.63$), attributed to a fall in LH pulse amplitude ($r = -0.53$) (36). Stimulated LH levels after GnRH (dose 75 µg/kg) ($r = -0.42$) in women with PCOS, or GnRH agonist in women with polycystic ovaries ($r = -0.386$) , were inversely related to BMI, indicating an impaired pituitary response in women with obesity.

Impact of Obesity on Diagnosis of PCOS

In summary, LH pulse amplitude, but not the increased pulse frequency, is reduced with obesity in women with PCOS. Likewise, obesity is associated with a decrease in LH pulse amplitude even in the absence of PCOS. Thus, obesity can reduce LH levels both in women with PCOS as well as those without, suggesting that it induces a pathophysiological process that can affect reproductive hormones in all women with obesity.

Sexual dimorphism in the effect of obesity on hypogonadism

In this section, we consider how endocrine dysfunction due to obesity affects the HPG axis differentially in men (Fig. 1) and women (Figs. 2 and 3). Sexual dimorphism impacts on the effect of obesity on gonadal status, for instance with respect to androgen levels.

While MOSH is manifested by androgen deficiency, androgen concentrations are increased in women with obesity, both in the presence or absence of PCOS. Body fat composition with different distributions of adiposity can additionally influence androgen production and metabolism.

Sexual dimorphism in the effect of obesity on hypogonadism

Women with a shift in fat distribution from a gynoid to android pattern typically have lower sex hormone–binding globulin (SHBG) concentrations, higher testosterone production, with higher aromatization to estradiol. Consequently, relative hyperandrogenism occurs in women with obesity, predisposing them to IR and metabolic dysfunction, whereas obesity results in reduced androgen levels in men.

Impact of Bariatric Surgery on Gonadotropin Secretion in Women With Hypogonadism

Bariatric surgery is an effective long-term therapy for obesity. As obesity influences the regulation of the HPG axis through multiple mechanisms, weight loss is hypothesized to have a favorable impact on menstrual cycle regularity and subfertility in women with obesity.

Several studies have evaluated the effect of bariatric surgery on the restoration of menstrual cyclicity in women with obesity. A cross-sectional study of 515 women with obesity (BMI 42.2 ± 7.5 kg/m2) who underwent sleeve gastrectomy or Roux-en-Y gastric bypass surgery and lost 35.3 ± 17.9 kg of bodyweight (postsurgery BMI 29.8 ± 6.3 kg/m2) had a reduction in the proportion of women with irregular cycles (>35 days) from 38% to 25%.

Impact of Bariatric Surgery on Gonadotropin Secretion in Women With Hypogonadism

A number of studies have looked at sex hormone profiles before and after weight loss achieved through bariatric surgery. Sarwer et al examined sexual function and reproductive hormones in 106 women aged 25-60 years old at 1 and 2 years after bariatric surgery .

The average weight loss was 32.7% at 1 year and 33.5% at 2 years after surgery. LH levels increased from 9.4 IU/L to 13.3 at 1 year, and to 15.9 IU/L at 2 years, whereas FSH increased from 15.3 to 22.0 IU/L at 1 year, and 29.9 IU/L at 2 years.

The timing of blood-sampling with regards to the menstrual cycle was unclear, and some women may have become peri/postmenopausal during the follow-up period to explain the marked increase in gonadotropin levels.

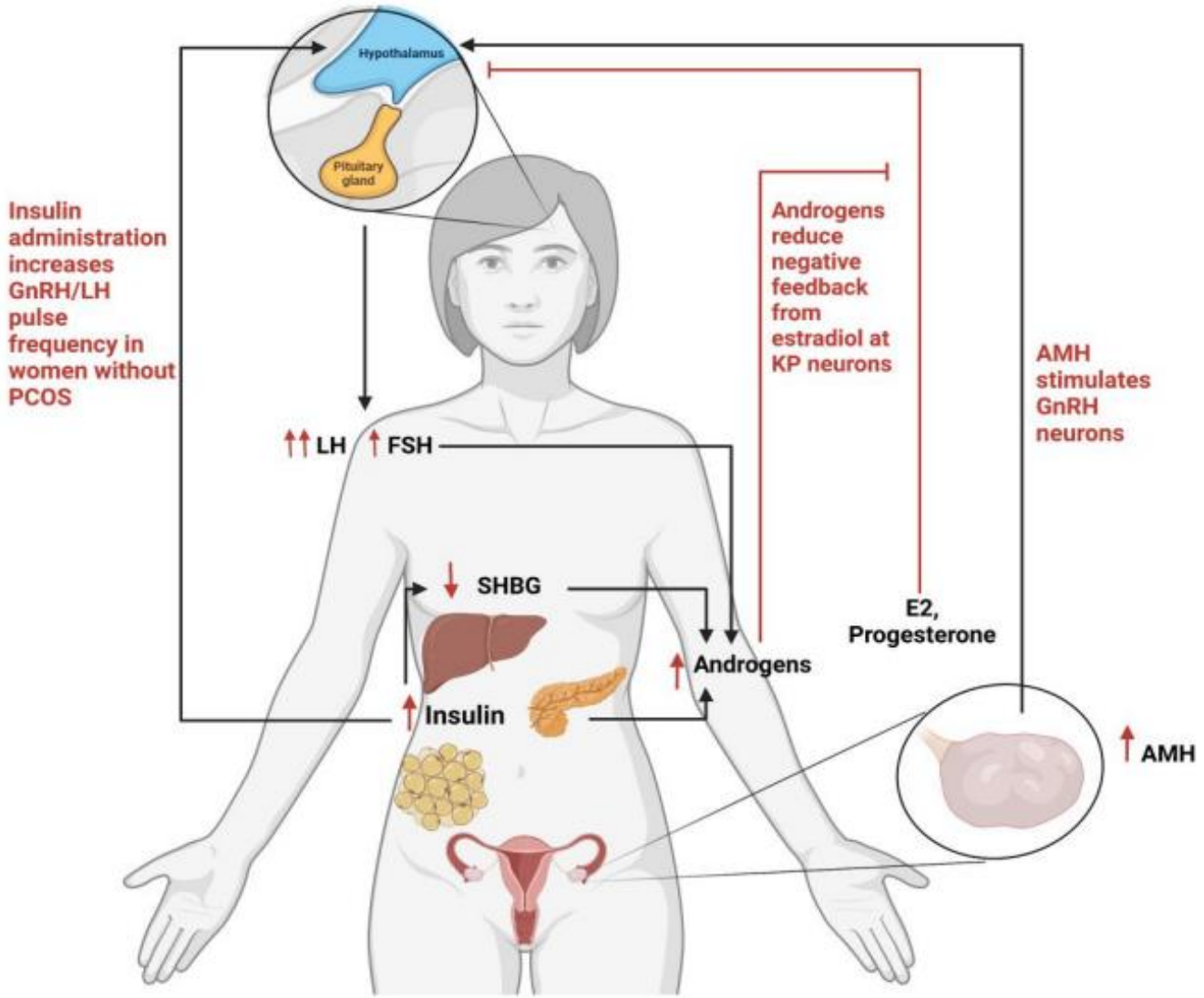

Figure 2. Mechanisms of polycystic ovary syndrome (PCOS) in lean women. Abbreviations: GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; SHBG, sex hormone–binding globulin; E2, estradiol; AMH, anti-Müllerian hormone; PCOS, polycystic ovary syndrome.

Impact of Bariatric Surgery on Gonadotropin Secretion in Women With Hypogonadism

However, total testosterone fell from 47.8 ng/dL to 30.4 ng/dL at 1 year and 23.4 ng/dL at 2 years; dehydroepiandrosterone sulfate decreased from 118.6 µg/dL to 106.1 µg/dL at 1 year, and 92.6 µg/dL at 2 years, indicating an improvement in hyperandrogenism after bariatric surgery.

Overall, this is in keeping with obesity being associated with increased androgen levels, which are reversed on weight loss.

Impact of Bariatric Surgery on Gonadotropin Secretion in Women With Hypogonadism

Interestingly, levels of urinary LH and progesterone metabolites in the luteal phase also increase with weight loss after bariatric surgery in eumenorrheic women with obesity.

Following 25% weight loss at 6 months after bariatric surgery, there was an increase in urinary LH from 27.6 ± 12.4 to 43.7 ± 10.6 mIU/mg Cr.

Impact of Bariatric Surgery on Gonadotropin Secretion in Women With Hypogonadism

Paul et al investigated the hormonal profile before and 12 months after surgery in 68 women who underwent Roux-en-Y gastric bypass. Women in the study had a median weight loss of 31% . Median SHBG increased from 33 to 71 nmol/L, and median testosterone levels reduced from 1.0 to 0.75 nmol/L ($P < .001$) (68), but there were no significant changes in serum gonadotropin, estradiol, and progesterone levels.

In summary, weight loss after bariatric surgery improved menstrual irregularity in women with obesity. Following weight loss, SHBG is increased, and androgen levels are reduced, suggesting a reduction in bioavailable androgens, although not all studies have shown consistent changes in gonadotropin levels.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Reduced Pituitary Gonadotropin Response to GnRH in Women With Obesity**

Eumenorrheic women with BMI ≥ 30 kg/m2 (n = 11) had lower baseline LH levels (with obesity 2.5 ± 0.2 IU/L, without obesity 5.2 ± 0.8 IU/L) and mean LH pulse amplitude (with obesity 1.12 ± 0.19 IU/L, without obesity 2.73 ± 0.46 IU/L) compared with women with BMI 18-25 kg/m2 (n = 10) (17).

Women with obesity had a reduced pituitary response to exogeneous GnRH. Mean LH, and maximum stimulated LH after GnRH (75 ng/kg) were all significantly lower in women with obesity.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Reduced Pituitary Gonadotropin Response to GnRH in Women With Obesity**

Serum FSH parameters (baseline FSH, and peak stimulated FSH following GnRH) were also lower in women with obesity. Transdermal estradiol treatment (0.1 mg/day) over 1 menstrual cycle length did not change mean basal LH or FSH levels; however, LH pulse amplitude was increased in women with obesity.

Furthermore, 1 month of estradiol treatment resulted in an increase in the peak LH after GnRH from 6.81 IU/L to 10.6 IU/L in women with obesity, but decreased the peak LH after GnRH from 14.6 IU/L to 11.9 IU/L in women without obesity.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Reduced Pituitary Gonadotropin Response to GnRH in Women With Obesity**

Likewise, estradiol treatment resulted in the maximal change in FSH following GnRH to increase from 6.14 IU/L to 7.46 IU/L in women with obesity, but to decrease from 7.09 IU/L to 4.99 IU/L in women without obesity. These findings suggest an attenuation of pituitary response to GnRH stimulation in non-PCOS women with obesity. Thus, whilst estrogen treatment increased the gonadotropin response in women with obesity, women without obesity had a reduction in gonadotropin response. Indeed, estrogen treatment increased the urinary progesterone excretion from 17.6 to 21.8 µg/mg of creatinine in women with obesity but not in women without obesity.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Reduced Pituitary Gonadotropin Response to GnRH in Women With Obesity**

The improvement in pituitary responsiveness to GnRH with estrogen treatment suggests that feedback to estrogen is altered in women with obesity, in keeping with a differential effect to an aromatase inhibitor in women in the presence of obesity.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Increased Clearance of Endogenous LH Resulting in Reduced LH Levels in Women With Obesity**

BMI is inversely related to endogenous LH in women with PCOS, in part due to increased renal clearance of LH. In a study of 21 healthy women with PCOS who received a GnRH antagonist to suppress endogenous LH, serum LH was quantified after GnRH (75 ng/kg), and after a bolus of 300 IU of recombinant human LH. Srouji et al showed that women with higher BMI (35.4 kg/m2) displayed a blunted rise in LH after GnRH (change in serum LH of ~30 IU/L) compared with women with lower BMI (18 kg/m2 ; change in serum LH of ~160 IU/L).

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Increased Clearance of Endogenous LH Resulting in Reduced LH Levels in Women With Obesity**

The half-life of endogenous LH exhibited a significant negative correlation with BMI in women with PCOS and the estimated renal clearance of LH positively correlated with BMI.

Increased renal clearance with BMI was not observed after recombinant LH (rhLH), which was attributed to alternative isoforms of endogenous LH being present in women with obesity and PCOS.

Sulphonated isoforms of LH are cleared faster than sialylated isoforms. Wide et al collected serum samples from 71 women (12 of whom had PCOS) and used electrophoretic analysis to quantify the number of sulphonated and sialylated forms of LH and FSH.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Increased Clearance of Endogenous LH Resulting in Reduced LH Levels in Women With Obesity**

Although sialyation of LH molecules is increased in PCOS, the proportion of sulphonated LH isoforms (which are cleared faster) positively correlated with BMI .which could contribute to the reduced LH levels seen in obese vs lean women with PCOS.

This relationship was not observed in lean women during the follicular phase; however, there were only a few women without PCOS or obesity in this study. Overall, increased clearance of endogenous LH is likely to contribute to lower LH levels in women with obesity.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Insulin Resistance-impact of Raised Insulin on LH Secretion**

Insulin has a well-established role as a central metabolic regulator and may also influence reproductive function.

Obesity increases the risk of IR; however, this resistance may be tissue specific such that organs, including the ovaries, can remain sensitive to the effects of elevated insulin levels with respect to steroidogenesis.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Insulin Resistance-impact of Raised Insulin on LH Secretion**

Moreover, IR in the ovary is likely to be a postreceptor abnormality and a signaling pathwayspecific defect.

While insulin-mediated glucose uptake and lactate production were both attenuated in GCs from women with anovulatory PCOS, steroidogenic (progesterone) response to insulin remained undiminished.

The implication is that the ovaries in women with PCOS remains sensitive to the effects of insulin with respect to steroidogenesis in insulin resistant states.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Insulin Resistance-impact of Raised Insulin on LH Secretion**

IR occurs secondary to an increase in circulating nonesterified fatty acids (NEFAs), inflammatory cytokines, and abdominal fat deposits. Insulin receptors have been reported in the hypothalamus including in the arcuate nucleus, suprachiasmatic nucleus, and in the median eminence.

In overweight individuals, the brain, in particular the hypothalamus, can develop impaired insulin response, referred to as “brain insulin resistance” .

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Effect of Nonesterified Fatty Acids on LH Secretion**

NEFAs are metabolic substrates of lipolysis. In women with obesity, dysregulated lipolysis results in increased circulating NEFAs, whereas women with PCOS do not consistently show altered NEFA levels.

Elevated circulating NEFAs accumulate in the follicular fluid of developing ovarian follicles.

Exposure of murine or bovine ovarian follicles to elevated levels of NEFAs in vitro caused impaired fertilization and reduced production of estradiol.

An increase in GC estradiol levels is needed for induction of the ovulatory LH surge.

Therefore, elevated NEFAs in obesity could lead to decreased estradiol levels and contribute to anovulation.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Inflammation and its Impact on Reduced GnRH/LH Secretion**

Obesity is a chronic disease characterized by a proinflammatory state. Women with obesity are reported to have higher baseline proinflammatory cytokine levels such as IL-6 and IL-12. These cytokines may act directly through their receptors on GnRH neurons or through intermediary neurons to affect GnRH neuronal function.

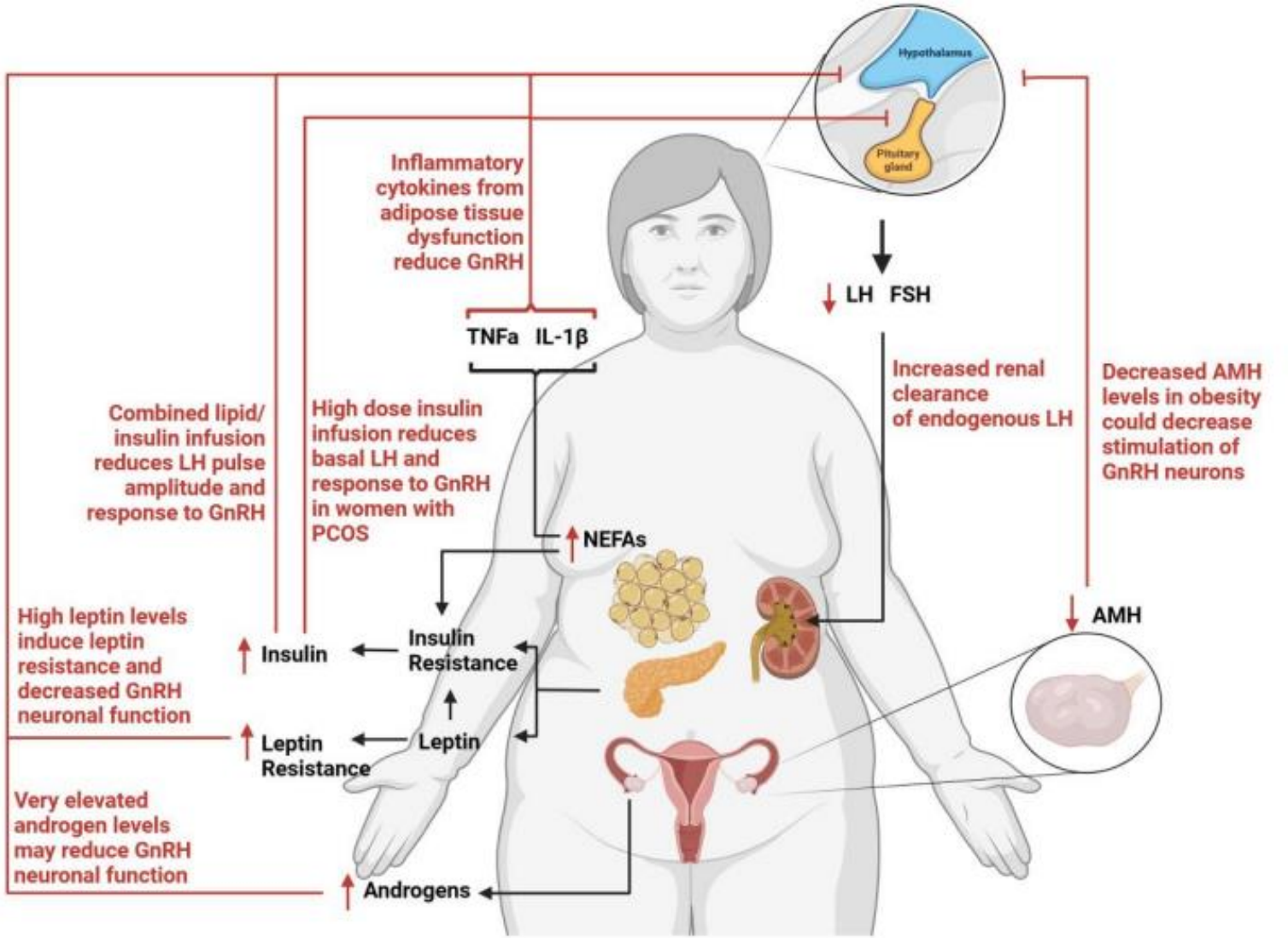

Figure 3. Putative mechanisms of female obesity-related secondary hypogonadism in women with obesity. Abbreviations: GnRH, gonadotrophin releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; SHBG, sex hormone–binding globulin; E2, estradiol; AMH, anti-Müllerian hormone; PCOS, polycystic ovarian syndrome; NEFA, nonesterified fatty acids; IL, interleukin; TNF-α, tumor necrosis factor.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Contribution of Hypothalamic Leptin Resistance to Reduced GnRH/LH Secretion**

Leptin is a satiety-signaling adipokine responsible for reducing appetite and increasing energy expenditure via its action in the hypothalamus. Circulating levels of leptin are associated with fat mass

Leptin is regarded as a permissive factor for GnRH secretion; thus low bodyweight and leptin levels are associated with decreased hypothalamic function and subfertility.

Humans with congenital leptin deficiency are hypogonadal, and healthy reproductive endocrine function can be restored via recombinant leptin administration. Likewise, women with hypothalamic amenorrhea have low leptin levels and LH pulsatility can be restored with recombinant leptin treatment.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Contribution of Hypothalamic Leptin Resistance to Reduced GnRH/LH Secretion**

Human obesity is associated with leptin resistance from either receptor downregulation or postreceptor defects.

Leptin could also impact on fertility via an action at the ovaries. Leptin enters the brain via a saturable transport system, and cerebrospinal fluid:serum leptin ratio is decreased in obesity.

In women with obesity, tissues such as the ovaries are exposed to higher concentrations of leptin.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Contribution of Hypothalamic Leptin Resistance to Reduced GnRH/LH Secretion**

In another study, an inhibitory effect of leptin on progesterone production was observed if GCs were cocultured in the presence of insulin (3-4 mg/mL) by antagonizing insulin-supported steroidogenesis.

Together, these data highlight that leptin can impair reproductive function through both a central and peripheral effect.

However, some researchers in the field feel that leptin resistance is associative rather than causative to the decreased GnRH function observed with obesity.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Impact of Adiponectin on LH Secretion**

Adiponectin is an adipokine hormone derived from white adipose tissue that exerts its insulin sensitizing and antiinflammatory activity via actions on its 2 receptors, AdipoR1 and AdipoR2, as well as a third receptor, T-cadherin.

Adiponectin receptors are expressed in peripheral tissues including muscle, liver, bone, ovaries, as well as the hypothalamus and pituitary gland.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Impact of Adiponectin on LH Secretion**

Adiponectin levels are at least 2 to 3 times higher in females and are reduced in individuals with type 2 diabetes, IR, androgens, or high BMI. In women with PCOS, adiponectin is inversely related to BMI. Women with PCOS and BMI ≥ 25 kg/m2 had lower levels of adiponectin and higher levels of insulin than women with PCOS and BMI < 25 kg/m2 (adiponectin in women with BMI ≥ 25 kg/m2 : 3.7 mg/L; women with BMI < 25 kg/m2 : 35.5 mg/L).

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Anti-Müllerian Hormone in Women With Obesity**

Anti-Müllerian hormone (AMH) is produced by GCs of ovarian follicles and is regarded as a surrogate marker of ovarian reserve and fertility. Locally, AMH reduces follicular sensitivity to FSH and so inhibits follicular recruitment.

In women with PCOS, AMH corresponds to the number of PCOS features and the degree of severity of the PCOS phenotype. Increased AMH levels negatively correlate with serum FSH levels potentially leading to defective follicular maturation and follicular arrest.

Additionally, metformin treatment results in improvements in PCOS clinical parameters and a decrease in AMH levels.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Anti-Müllerian Hormone in Women With Obesity**

The impact of obesity on AMH remains unclear. Some studies have reported that AMH negatively correlates with BMI; however, others have showed no change. Park and colleagues found that AMH was inversely correlated with BMI, and women with obesity had 1.5 fold lower AMH levels than lean women.

A recent metaanalysis of 26 studies found that AMH was significantly reduced in obese populations by 1.08 ng/mL compared with nonobese populations .This was in contrast to Oldfield et al, who reviewed 13 studies of AMH in women and found no impact of obesity on AMH levels.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Anti-Müllerian Hormone in Women With Obesity**

IR is amplified by obesity; some studies have reported a negative correlation of serum AMH with IR in lean women with PCOS, whereas others have found no correlation, and no difference in AMH levels amongst women with different PCOS phenotypes or across different BMIs.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Anti-Müllerian Hormone in Women With Obesity**

AMH levels are correlated with fasting insulin levels in women with PCOS; women with PCOS and BMI ≥ 25 kg/m2 had higher AMH levels than lean women with PCOS. Treatment with metformin for 8 months results in a 20% reduction in AMH in women with PCOS, while BMI was also reduced from 37.1 to 35.7 kg/m2. This suggests that AMH could correlate with IR in women with PCOS and improve with treatment to reduce IR.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Anti-Müllerian Hormone in Women With Obesity**

If AMH is reduced by obesity, one could expect an increase in AMH following weight loss. However, a prospective cohort study of 183 women with obesity (BMI 39.6 kg/m2 ; AMH 2.66 ± 3.71 µg/L) and 63 women with PCOS and obesity (BMI 39.6 kg/m2 ; 5.47 ± 4.89 µg/L), found there was no change in serum AMH levels at 12 months after weight loss of 10% to 12% achieved with dietary intervention.

Further, AMH could even be reduced following more substantial weight loss after bariatric surgery. In women with obesity (BMI ~45 kg/m2), AMH was decreased in 14 women with PCOS (5.44 to 4.25 ng/mL) and in 18 non-PCOS women (1.83 to 1.36 ng/mL) at 12 months after bariatric surgery after a mean weight loss of 65%

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Anti-Müllerian Hormone in Women With Obesity**

Thus, overall AMH is either unaltered or reduced in women with PCOS and obesity and is either unchanged or could even be decreased further after weight loss intervention, potentially consistent with some resolution of the PCOS-associated raised AMH levels.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Impact of Obesity on Androgen Levels, and Their Effect on LH Secretion**

Levels of testosterone and dihydrotestosterone in women are one-fifteenth of that seen in men, yet they play an important role in regulation of the HPG axis in women.

Control of androgen secretion in women is multifaceted and occurs partly in response to stimulation by LH as well as modulation by intraovarian regulatory factors (eg, inhibin B) that coordinate thecal androgen production with conversion to estrogen in GCs.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Impact of Obesity on Androgen Levels, and Their Effect on LH Secretion**

Dysregulation of androgens is regarded as being central to the pathophysiology of PCOS, with 80% to 90% of patients having clinical or biochemical hyperandrogenism.

Androgens are hypothesized to cause a reduction in sex steroid–mediated negative feedback on GnRH neurons, contributing to the abnormally high basal levels of LH and pulsatility seen in PCOS. Androgens are also elevated in women with obesity who do not have PCOS.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Impact of Obesity on Androgen Levels, and Their Effect on LH Secretion**

In a cross-sectional study comprising 1900 premenopausal women with severe obesity, hyperandrogenemia was present in 32% (n = 616) of women with obesity without PCOS and 45% (n = 845) of women with obesity and PCOS.

Several studies have shown a positive association between free testosterone level with visceral adipose tissue and abdominal fat.

Increased androgen production is additionally due to increased conversion of androstenedione to testosterone via 17β-hydroxysteroid dehydrogenase 5 in subcutaneous fat, expression of which has been found to positively correlate with BMI.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Impact of Obesity on Androgen Levels, and Their Effect on LH Secretion**

Additionally, hyperinsulinemia decreases SHBG in both PCOS and non-PCOS populations by decreasing its synthesis in the liver. Decreases in SHBG increase availability of free androgens. Treatment with liraglutide 3 mg daily in women with obesity (BMI > 30 kg/m2) and PCOS (n = 55) for 32 weeks increased SHBG and decreased the free androgen index from 6.9 ± 0.6 to 5.98 ± 0.6 compared with placebo.

In another study, treatment with liraglutide 1.8 mg/day for 26 weeks reduced free testosterone by 0.005 nmol/L and free androgen index by 1.34 in women with PCOS and a BMI > 25 kg/m2. Together, these data suggest that hyperinsulinemia due to IR could also contribute to the pathophysiology of obesity-related hypogonadism by directly and indirectly increasing androgen levels.

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Impact of Obesity on Androgen Levels, and Their Effect on LH Secretion**

Hyperandrogenemia increases uric acid by inducing hepatic metabolism of purine nucleotides and increasing purine renewal in kidney. Hyperuricemia in turn induces IR through suppression of both basal and glucose-stimulated insulin secretion. Consequently, serum uric acid was positively associated with visceral obesity, dyslipidemia, and hypertension. Interestingly, uric acid to creatinine ratio strongly correlated with free androgen index ($r = 0.81$).

Women with obesity and PCOS had significantly higher uric acid to creatinine ratio than those without PCOS. The combination of uric acid to creatinine ratio and free androgen index increased the odds of PCOS in women with obesity by 4.3-fold (95% CI 3.4-7.6).

Mechanisms that Could Contribute to Secondary Hypogonadism in Women With Obesity

- **Impact of Obesity on Androgen Levels, and Their Effect on LH Secretion**

Obesity is associated with both inflammation and hyperandrogenism. Recently, inflammation has been suggested to directly increase ovarian androgen production. An inflammatory stimulus increased androstenedione production from rat ovarian theca interstitial cells, and this effect could be blocked by a nonsteroidal anti-inflammatory drug.

Furthermore, a 3-week pilot trial in women with PCOS showed that ibuprofen (400 mg twice daily in women with bodyweight 70 kg) reduced total testosterone from 0.75 ± 0.06 ng/mL to 0.59 ± 0.05 ng/mL (P = .008). These studies support the oncept of inhibiting ovarian hyperandrogenism by suppressing inflammatory pathways.

Summary of Evidence for non-PCOS Female Obesity-Related Secondary Hypogonadism

While women with obesity and hypogonadism are often labelled as having PCOS, **there are mechanistic differences causing the increased activation of hypothalamic GnRH neurons observed in lean PCOS**, as opposed to the reduction in GnRH neuronal activity in obesity-related secondary hypogonadism.

Summary of Evidence for non-PCOS Female Obesity-Related Secondary Hypogonadism

Our review highlights that the following features are more associated with obesity-related secondary hypogonadism than PCOS in lean women.:

LH pulse amplitude is reduced with obesity, both with and without PCOS, whereas raised LH levels are more typically found in lean women with PCOS.

The diagnosis of PCOS can therefore be less clearcut in women with obesity, as raised androgens can occur even in the absence of PCOS, menstrual disturbance can occur due to obesity-related secondary hypogonadism, and imaging of the ovaries to identify polycystic ovarian morphology can be more challenging.

Summary of Evidence for non-PCOS Female Obesity-Related Secondary Hypogonadism

- In this review, we have discussed the various mechanisms that can contribute to “female obesity-related secondary hypogonadism” (FOSH).
- Obesity is associated with:
- an increase in leptin levels, which can result in hypothalamic leptin resistance
- reduction in GnRH pulsatility and LH levels. Lower LH levels can occur due to increased clearance of endogenous LH in women with obesity as well as reduced pituitary response to GnRH.
- AMH levels are reduced in some women with obesity, and theoretically a reduction in AMH levels with obesity could lead to reduced stimulation of GnRH neurons and thus LH levels.
- Androgens are increased in women with obesity, and markedly elevated levels could contribute to a reduction in LH levels.
- Obesity is associated with an increase in inflammatory markers that can also contribute to the reduction in LH levels and hypogonadism observed in women with obesity.

Summary of Evidence for non-PCOS Female Obesity-Related Secondary Hypogonadism

Thus, thorough evaluation of reproduction endocrine function in women with obesity and hypogonadism is needed to differentiate those with PCOS from those with obesity-related secondary hypogonadism.

It is possible that persistence of increased LH pulse frequency can be used to identify underlying PCOS rather than obesity-related secondary hypogonadism. However, assessment of LH levels does not form a major part of current assessment of women with possible PCOS.

Conclusion

In conclusion:

we have summarized evidence in support of the concept of a distinct FOSH

that is distinct from PCOS.

Further dedicated research is needed to confirm the existence of FOSH and to specify diagnostic criteria for it, to deepen our understanding of reproductive dysfunction in women with obesity.