



# Obesity and Female Infertility—A Review on Mechanisms (Endocrinology)

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**How to cite this paper:** Joon, T.L., Pillai, N., Yap, C.G. and Jahan, N.K. (2022) Obesity and Female Infertility—A Review on Mechanisms (Endocrinology). *Open Access Library Journal*, 9: e8817.

<https://doi.org/10.4236/oalib.1108817>

**Received:** April 30, 2022

**Accepted:** June 21, 2022

**Published:** June 24, 2022

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## Abstract

**Background:** Obesity is a state of the excess buildup of fats where it leads to chronic low-grade inflammation, lipotoxicity, deranged endocrine system and the female sex hormones. It is speculated that each of these aspects plays a contributory role to infertility in obese. So, this review aims to look into changes in the endocrine system and the hypothalamic-pituitary-ovarian (HPO) axis in obese women that affect the female reproductive system and the correlation between each mechanism leading to infertility. **Results and Discussion:** Obese women are associated with higher levels of androgens and insulin, where the latter can further potentiate levels of the former. These two changes contribute the most to infertility, where effects include poor follicular growth, premature luteinization, atresia of ovarian cells and follicles, as well as poor endometrial development. Changes are also seen in levels of growth hormones (GH), adipokines like leptin and adiponectin, inflammatory mediators and ghrelin, which altogether alter the HPO axis, either through potentiating or inhibiting one another, leading to effects like ovulatory dysfunction, irregular menstruation, increased risks of miscarriages and greater failure rates in artificial reproductive technology (ART). In terms of management, this review will be focusing mainly on non-pharmacological approaches which include weight loss, dietary modification and physical activities, as well as exploring surgical approaches to weight loss. Weight reduction is the gold standard as it can reverse the changes in the HPO axis by improving insulin sensitivity, regulating sex hormones, and restoring balances to the adipokines and inflammatory mediators. **Conclusion:** Obesity is a state of excess in metabolically active adipose tissue, which causes changes in the HPO axis and subsequently damages the female reproductive system. The correlated mechanisms only partly explain how obesity leads to female infertility. Thus, different aspects of obesity would need to be explored and correlated to fully realize how it leads to female infertility.

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## Subject Areas

Endocrinology, Gynecology & Obstetrics, Women's Health

## Keywords

Obesity, Overweight, Female Infertility, Anovulation, Mechanism, Impact, Influence, Pathophysiology

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## 1. Introduction

Based on the World Health Organization (WHO), obesity can be defined as a state of excessive fat buildup to a point that is detrimental to one's health [1]. The body reacts to the excessive fat by producing a chronic low-grade inflammation, which is through the infiltration of macrophages into adipose tissue and the release of inflammatory mediators, which in turn also alters the immune system [2]. The high circulating free fatty acids found in obesity is able to infiltrate non-adipose tissues, leading to an effect known as "lipotoxicity", which causes oxidative stresses to the endoplasmic reticulum and mitochondria of those cells, leading to apoptosis [3]. The stated effects could potentially explain how fat buildup can be linked to the many chronic conditions associated with obesity like atherosclerosis, stroke, diabetes, malignancies and even infertility [2].

In 2016, the WHO approximated that more than 1.9 billion or 39% of adults across the globe are overweight and 650 million or 13% are obese [4]. The numbers of obesity have tripled in the last couple of years whereby WHO 2016 reported that 40% of all women across the globe are overweight and 15% are obese [4]. The National Health and Morbidity Survey in 2019 estimated that 54.7% of Malaysian women are either overweight or obese [5].

Based on the body mass index (BMI) classification by WHO, overweight is classified as BMI ranging from 25 - 29.9 kg/m<sup>2</sup> whereas obesity is classified as having a BMI  $\geq$  30 kg/m<sup>2</sup>. Obesity can be further classified into class I (30 - 34.9 kg/m<sup>2</sup>), class II (35 - 39.9 kg/m<sup>2</sup>) and class III ( $\geq$ 40 kg/m<sup>2</sup>). However, in the Asian population, overweight is classified as BMI ranging from 23 - 24.9 kg/m<sup>2</sup> and obesity with BMI  $\geq$  25 kg/m<sup>2</sup> [6].

Infertility is defined as the failure to conceive or achieve a clinical pregnancy despite regular unprotected sexual intercourse and therapeutic donor insemination for a period of one year in women aged less than 35 years, and for a period of 6 months in women aged 35 years and above [7]. The WHO has stated that infertility influences approximately 50 - 80 million women across the globe and the incidence is estimated to be around 10% - 20% and up to 50% in developing countries [8] [9]. Surprisingly, many infertile women have a higher BMI as compared to their fertile counterparts and approximately 20% of all infertile women have extreme BMIs, either being underweight or overweight [10].

Since both the rates of obesity and female infertility are on the rise, many studies have been carried out to delineate the correlation between the two, with varying results. Some common findings from previous research show that infertile obese and overweight women have reduced levels of female sex hormones (estrogens and progesterone), reduced levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), and increased levels of androgens [11] [12] [13] [14]. Even though these parameters may yield importance in the rise of infertility, there may still be other causes that can better explain the linkage between obesity and infertility. With that being said, previous studies have only listed the possible mechanisms of how obesity leads to female infertility without correlating or linking the mechanisms to one another. Thus, the aim of this review is to correlate and summarize the numerous mechanisms, where each of these mechanisms may potentiate and inhibit one another to cause the changes listed above, as well as to explore effective treatment options targeted for the mechanisms. Since this is a big topic, the paper will mainly focus on the hormonal and endocrinological aspects of female infertility in the obese.

## 2. Results and Discussion

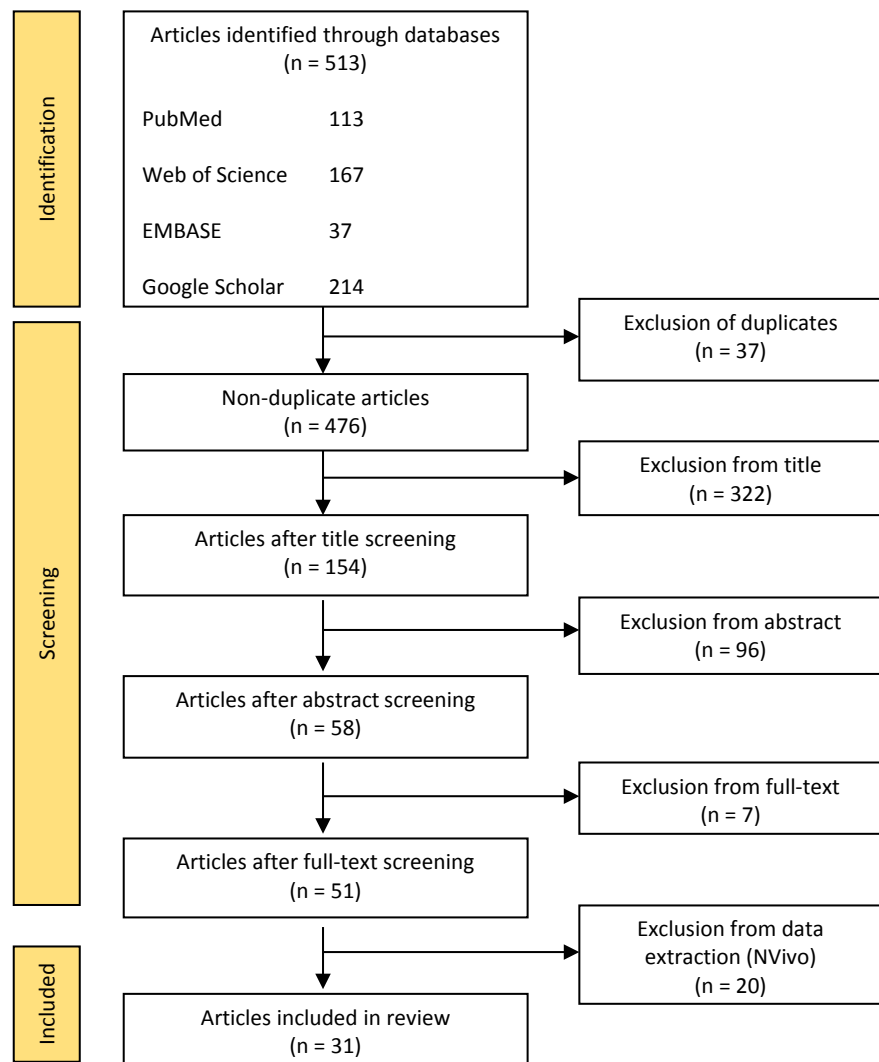
A literature search pertaining to obesity and female infertility was conducted through electronic databases—PubMed, Web of Science, EMBASE, and Google Scholar. The terms used for the search include: obesity, overweight, female infertility, anovulation, mechanism, pathophysiology, influence, and impact. Boolean operators “OR” and “AND” were used to specify the search list. The search articles were then limited to “the published year of 2010-2021”, female, English. A further limitation was performed on the article type, which includes: review, systematic review, review articles, meta-analysis and randomized controlled trials.

The search identified a total of 513 articles, with 113, 167, 37 and 214 articles from PubMed, Web of Science, EMBASE, and Google Scholar respectively, as shown in **Figure 1**. All citations and articles were included and processed through “EndNote”. After removal of duplicates, there were a total of 476 articles left. The articles then underwent inclusion and exclusion criteria of the title, abstract and full-text screen. Inclusion criteria include: the HPO axis, hormonal and endocrine system. Exclusion criteria include: male reproductive system, male infertility and polycystic ovarian syndrome (PCOS). The process excluded 322, 96 and 7 articles from title, abstract and full text screen respectively.

The remaining 51 articles were then included into the software “NVivo” and were processed for data extraction. Through the process, only 31 articles were reviewed and extracted for the use of this study.

### 2.1. Association of Obesity and Female Infertility

Obese women are nearly three times more likely to develop infertility [15]. A Danish study suggested that the odds of subfecundity are 27% and 78% higher in overweight and obese women, respectively [16]. Furthermore, the likelihood of



**Figure 1.** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for the selection of included studies in the review.

spontaneous pregnancy is estimated to drop by 5% for every increment in unit BMI when exceeding 29 kg/m<sup>2</sup> [17]. In terms of waist-to-hip ratio (WHR), the probability of conception per cycle will drop by 30% for every 0.1 unit increment [18].

One of the chief causes of infertility in obese women is anovulation. However, a large number of those with anovulation have coexisting conditions like PCOS [19]. Even without PCOS, obese women are still prone to anovulation, especially those with high central adiposity [20]. In a study of 2292 women, those with BMI  $\geq$  27 kg/m<sup>2</sup> are found to be 3.1 times more likely to have ovulatory dysfunction as compared to their normal BMI counterparts whereas another case-control study shows that overweight women without PCOS are 1.8 times more likely to develop anovulation [21] [22]. Moreover, the incidence of anovulatory cycles in overweight women increases from 2.6% to 8.4% when the amount of overweight increases from less than 20% of body weight to more than 74% of body weight,

which shows that increasing BMI increases the probability of anovulation [20]. Despite that, many obese women do have normal ovulation, albeit are still prone to subfertility [23]. So, anovulation may not be the only cause of infertility in obese women, where the causes are said to be multifactorial instead.

In addition, obese women are twice as likely to develop menstrual irregularities and have higher rates of spontaneous miscarriages where this can be demonstrated in a study that shows the miscarriage rates in obese women to be 38.1% as compared to the rate of 13.3% in women of normal BMIs [24] [25]. Obesity is also associated with a higher likelihood of failure in artificial reproductive technology (ART) and lower live birth rates following ART. Each increment in unit BMI is linked to a reduction of 0.84 factors in pregnancy following in vitro fertilization (IVF) and a reduction of 2% in live birth rates [26] [27].

In short, obese women are predisposed to anovulatory cycles, irregular menstruation, elevated risk of miscarriages, greater difficulties with ARTs and decreased live birth rates.

## **2.2. Mechanisms of Obesity on Female Infertility**

### **2.2.1. Adipose Tissue**

The adipose tissue is the biggest endocrine organ in the body where it is associated with glucose homeostasis, steroid production and metabolism, regulation of immune system and reproduction [20]. It is able to produce androgens, store sex hormones and act as a conversion site for androgens, estradiol and dihydroepiandrosterone to be converted to estrogens, estrone, and androstenediol, respectively [28].

With the excess of adipose tissue in obesity, the peripheral production of androgens is raised leading to increased production of estrogens as well through peripheral aromatization. Resultant increase in production of estrogen may cause disruptions to the endometrial receptivity as well as produce an inhibitory feedback to the HPO axis, which disrupts gonadotropin secretion and pituitary LH pulse amplitude [29]. This leads to poor oocyte recruitment and poor follicular growth [30].

### **2.2.2. Insulin**

Insulin resistance is a condition found in many obese women. Excess adipose tissues can stimulate insulin secretion from pancreatic beta cells [31]. Furthermore, the excess circulating fatty acids may amplify hepatic lipid production and disrupt hepatic function, which leads to insulin resistance and its compensatory mechanism of hyperinsulinemia [19].

Interestingly, the ovaries are still sensitive to the effects of insulin, where insulin acts directly on the theca and granulosa cells by upregulating CYP17A1 enzymes to enhance steroidogenesis [32] [33]. Insulin is also able to enhance the effects of LH on steroidogenesis by increasing LH receptors and improving ovarian LH-binding capacity [34]. Moreover, insulin enhances the effects of FSH which results in greater production of androgen substrates and thus elevates es-

trogen levels in the developing follicles [30].

The pituitary gland also remains its sensitivity to insulin, where insulin can amplify the sensitivity of gonadotroph cells to gonadotropin-releasing hormones (GnRH), which then increases LH production and further stimulating ovarian steroidogenesis [34]. As consequences of elevated steroidogenesis and hyperandrogenemia, follicular growth is arrested, differentiation and mitosis of granulosa cells are restricted, premature luteinization occurs, which is followed by premature follicular atresia [30].

Besides that, insulin inhibits the production of insulin-like growth factor (IGF) binding protein-1 in the liver and ovaries [34]. Its reduction leads to elevated levels of free circulating IGF-1, which promotes androgen production by acting on theca interstitial and stromal cells of the ovaries, where its receptors are found [35]. The increased circulating levels of IGF-1 may also explain the reduction of serum growth hormones found in obese women, possibly through potentiating the negative feedback signals [36]. Since GH aids folliculogenesis, a reduction in GH levels would indicate poor follicular growth and poor late stage development of follicles and luteinization. Low GH levels are also linked to uninhibited follicular atresia, reduced secretions of progesterone and estrogens and poor uterine environment for implantation, which are all necessary for a successful pregnancy [32].

### **2.2.3. Sex Hormone-Binding Globulin**

The serum levels of sex hormone-binding globulin (SHBG) tend to be lower in obese women, especially those with central obesity, and are inversely proportional to WHR [37]. It can be elevated by estrogens, iodothyronines and growth hormones whereas insulin and androgens reduces it [38]. The hyperinsulinemic state associated with obesity may be the leading cause in reduced levels of SHBG, through the reduction in hepatic synthesis. This leads to more free circulating sex steroids, which have a higher tendency to get metabolically cleared [37]. With increased clearance, the body produces more androgens as compensation, resulting in a state of relative functional hyperandrogenism [37]. Similarly, hyperandrogenism would then lead to poor ovarian function through premature luteinization and apoptosis of granulosa cells and follicles [37].

### **2.2.4. Adipokines, Inflammatory Mediators and Enterokines**

Adipokines are cell-signalling molecules produced by adipose tissues, which includes leptin, adiponectin, tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), resistin, visfastin and so on. These adipokines are associated with adipocyte differentiation, energy metabolism and insulin resistance [39]. The production of adipokines is dependent on one's BMI, where the obese produces more pro-inflammatory adipokines like leptin, TNF- $\alpha$ , IL-6, visfastin and resistin whereas leaner individuals produces more anti-inflammatory adipokines like adiponectin, transforming growth factor-beta, interleukin-4, 10 and 11 [40].

The adipokines are able to interact with one another whereby both TNF- $\alpha$  and

IL-6 are able to inhibit adiponectin production and vice versa [41]. So, in obesity, the production of TNF- $\alpha$  is raised by macrophages infiltrating the adipose tissue [42]. The excess TNF- $\alpha$  would then suppress adiponectin mRNA expression and multimerization through the disruption of disulphide bond modification in the endoplasmic reticulum, resulting in reduced circulating adiponectin [43].

Below are the mechanisms on how each adipokine relates to female infertility:

### **Leptin**

Leptin acts primarily on the central nervous system (CNS) to regulate appetite and energy consumption [44]. In physiological levels, leptin plays a stimulatory role on the HPO axis but it takes on an inhibitory role, specifically on follicular growth, when its level rises [44]. With that being said, obese women have higher levels of leptin and are prone to develop leptin resistance, possibly through the downregulation of its receptors in the CNS as a consequence of prolonged hyperleptinemia [45]. Hyperleptinemia can also affect the hypothalamus and pituitary gland, where its receptors are found, which disrupts the GnRH and LH production indirectly through GABA and kisspeptin neurons, leading to poor follicular growth and poor oocyte recruitment [31] [44] [46]. As mentioned, high levels of leptin is inhibitory to the CNS, whereby the negative feedback mechanism of insulin may be inhibited as well. Therefore, this would then result in uncontrolled insulin production and worsening of insulin resistance, which contributes to the effects of hyperinsulinemia leading to infertility [32] [47].

Leptin also acts on the ovaries where its receptors can be found in the oocytes, granulosa and theca cells [37]. Unlike the CNS, the ovaries remain sensitive to leptin, whereby raised serum leptin corresponds to raised leptin levels in the follicular fluid [37]. Prolonged hyperleptinemia is found to inhibit ovarian steroidogenesis, suppress the actions of FSH and IGF-1 on estradiol production, and reduce 8-bromo cAMP-induced progesterone production and cAMP-induced steroidogenic acute regulatory (StAR) protein, which is a rate limiting agent in progesterone production [48] [49] [50]. Aromatase production and activities are also attenuated with hyperleptinemia, leading to reduced conversion of androgens to estrogens [47] [51]. These processes will subsequently produce the outcomes of poor growth of dominant follicles, poor oocyte maturation and poor endometrial receptivity [32]. The various mechanisms seen with prolonged hyperleptinemia may partly explain the overall reduction in levels of female sex hormones found in the obese.

Despite the various findings and hypotheses on leptin, the exact mechanisms on how it leads to female infertility are still unconfirmed as most studies are done on animal models.

### **Adiponectin**

Adiponectin is an insulin sensitizer, which works through promoting the uptake of glucose into the liver and muscles, reducing glucose production from the liver and stimulating  $\beta$ -oxidation of fatty acids in skeletal muscles [52]. As stated above, obese women have diminished levels of serum adiponectin due to rising

inflammatory mediators, which makes them more prone to develop insulin resistance. This effect contributes to the negative downplay of hyperinsulinemia on ovarian function and infertility [53]. In addition, adiponectin enhances the effects of IGF-1 on the ovaries [54]. Therefore, IGF-1 function declines as a result of low adiponectin levels, which leads to poor production of androgens, estradiol and progesterone.

#### **Tumor Necrosis Factor Alpha**

In physiological levels, TNF- $\alpha$  is able to suppress the proliferation of adipose tissues but resistance develop and TNF- $\alpha$  levels accumulate after prolonged fat accumulation, which is a phenomenon seen in obese women [55]. The levels of TNF- $\alpha$  may also directly be linked to the amount of infiltrating macrophages [42]. High levels of TNF- $\alpha$  will then induce insulin resistance through the suppression of insulin-sensitizing adiponectin as well as the downregulation of tyrosine kinase activity from insulin receptors and reduction in the production of GLUT-4 glucose transporters [43] [56]. Studies have also found that TNF- $\alpha$  regulates leptin levels where raised levels of TNF- $\alpha$  is associated with obesity-related hyperleptinemia [57]. Moreover, TNF- $\alpha$  is involved in many reproductive functions such as the regulation on ovulation and androgen production, suppression of the production of gonadotropin and LH, as well as regulation in corpus luteal regression and the growth of endometrium [58] [59] [60] [61] [62]. Thus, prolonged elevation in TNF- $\alpha$  will negatively disrupt the aforementioned functions, which decreases the chances of conception.

#### **Interleukin-6**

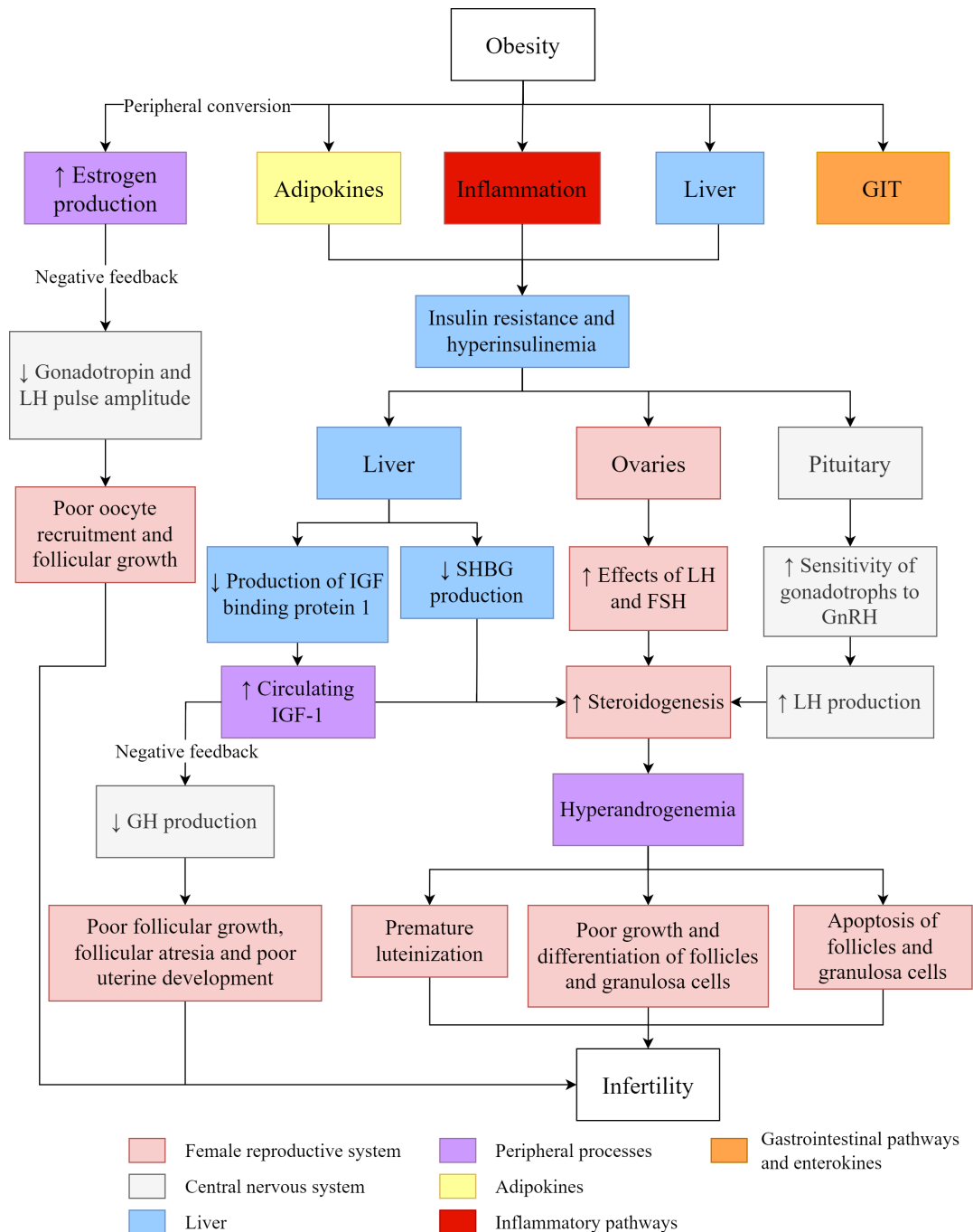
IL-6 is a pro-inflammatory adipokine that also plays a role in the deregulation of the HPO axis. Circulating levels of IL-6 are raised in obesity and it is associated with insulin resistance through the suppression of adiponectin [62]. High levels of serum IL-6 is able to inhibit estrogen production through the suppression of FSH and LH actions, aromatase activities as well as direct inhibition on granulosa cells. Additionally, prolonged raised levels of IL-6 can also suppress LH-induced ovulation [63] [64]. These effects are similar to those of its adipokine counterparts, which further contribute to infertility and the changes depicted in the obese.

#### **Ghrelin**

Ghrelin is a hormone mainly produced by the gut cells and acts on the CNS to stimulate appetite and food intake [62]. Ghrelin also has a role in the reproductive function where it is able to stimulate the production of GH, enhance aromatase activity, and promote folliculogenesis by enhancing cell proliferation and preventing follicular atresia [65] [66]. However, ghrelin levels are reduced in obese women, which may result in poor follicular growth and premature follicular atresia, ultimately leading to poor ovarian function [67].

As a summary, obese women are depicted to have large quantities of androgens and insulin, where these hormones are major contributors to infertility found in this review paper, as shown in **Figure 2**. Androgens, in high amounts, will lead to poor ovarian function through a series of poor follicular growth and





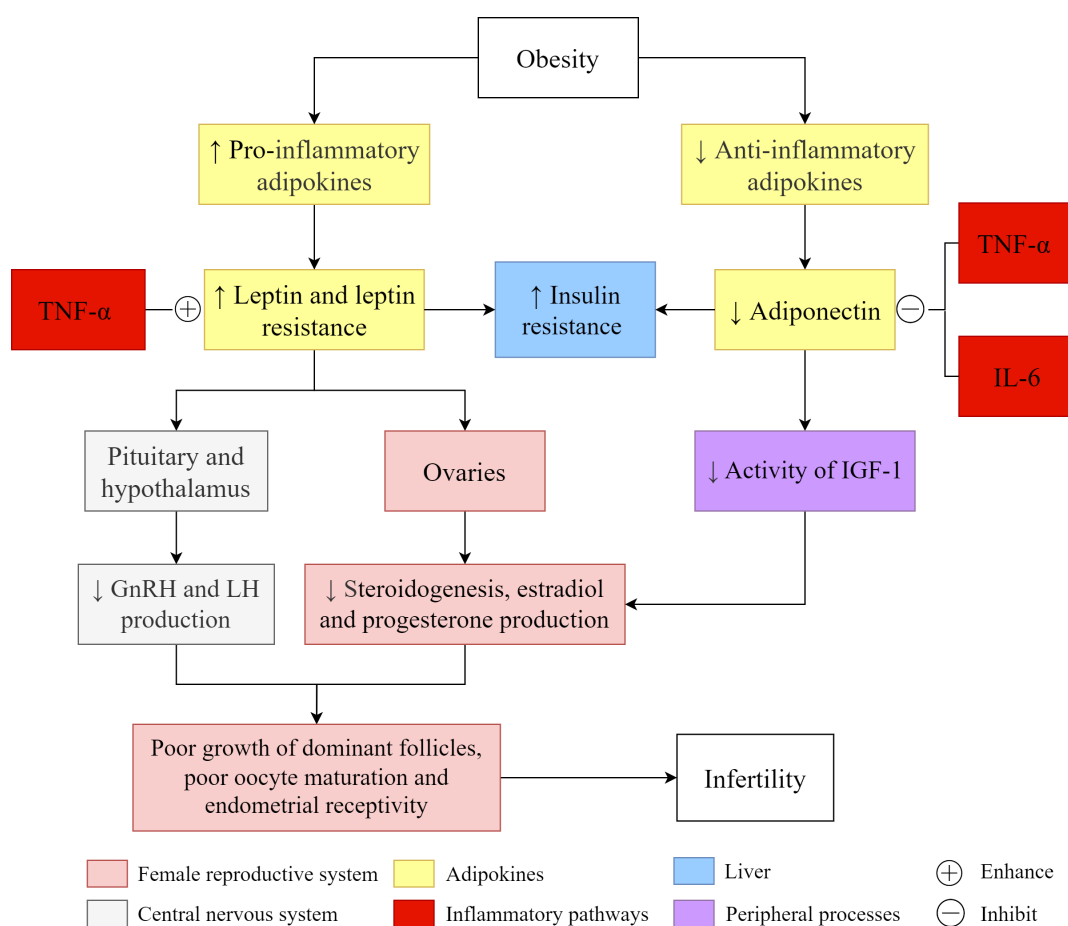
**Figure 2.** Correlating the hormonal changes from excess adipose tissue to the HPO axis and female reproductive system. GIT = Gastrointestinal tract; LH = Luteinizing hormone; IGF = Insulin-like growth factor; GH = Growth hormone; FSH = Folicle stimulating hormone; GnRH = Gonadotropin-releasing hormone; SHBG = Sex hormone-binding globulin; ↑ = Increase; ↓ = Decrease.

differentiation, premature luteinization, which then leads to apoptosis of ovarian cells and follicles. Furthermore, insulin acts as a potentiator that promotes the negative effects brought on by hyperandrogenemia through increasing its serum levels, either through the process of enhancing LH and its function, promoting ovarian steroidogenesis or tricking the body into releasing more androgens by

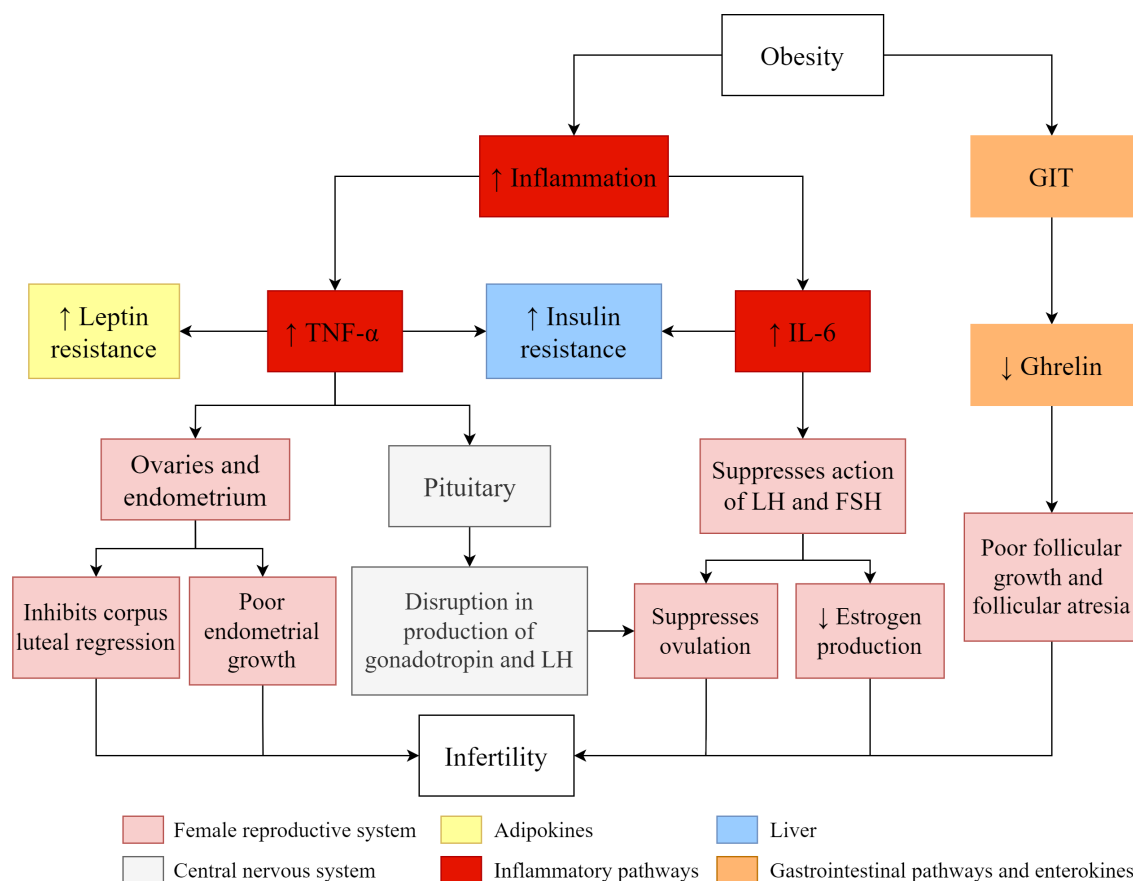
reducing SHBG levels. To make it worse, leptin and inflammatory mediators like  $\text{TNF-}\alpha$  and IL-6 are capable of promoting insulin resistance and subsequently potentiating the effects of hyperinsulinemia on the ovarian function, as shown in **Figure 3** and **Figure 4**.

Despite the large amount of evidences on androgens and insulin, there are still many changes that occur along with obesity that can affect the HPO axis, which contributes to changes on the female reproductive system. A few recent discoveries that provide a clearer picture on how obesity affects female infertility are the correlation on GH, leptin, adiponectin, inflammatory mediators and ghrelin, with the HPO axis and how they directly or indirectly affect the ovarian function. To summarize, they work through inhibiting the levels of female sex hormones, which is contradictory to the effects of insulin, disrupting follicular growth and ovulation, inhibiting endometrial development and implantation, or a combination of all the effects.

Collectively, the various mechanisms will ultimately present themselves as ovulatory dysfunction, irregular menstruation, miscarriages and failures in ARTs, which correlates to the statistics found in obese and overweight women.



**Figure 3.** Correlating the changes in adipokines to the HPO axis and the female reproductive system.  $\text{TNF-}\alpha$  = tumor necrosis factor alpha, IL-6 = Interleukin-6; IGF = Insulin-like growth factor; ↑ = Increase; ↓ = Decrease.



**Figure 4.** Correlating the changes in inflammatory mediators and enterokines to the HPO axis and the female reproductive system. TNF- $\alpha$  = tumor necrosis factor alpha, LH = Luteinizing hormone; IL-6 = Interleukin-6; FSH = Follicle stimulating hormone; GIT = Gastrointestinal tract;  $\uparrow$  = Increase;  $\downarrow$  = Decrease.

## 2.3. Treatment Options for Infertility in Obese Women

### 2.3.1. Weight Loss

Adiposity is the main culprit for infertility in obese women, so losing weight should be effective in the resumption of fertility. Weight reduction is possible through negative energy balance, where one's energy expenditure is greater than energy intake. Weight loss is associated with better ovulation and pregnancy rates, live birth rates, menstrual regularity and greater success in ART [68] [69]. Ferlitsch *et al.* [26] suggested that with each reduction of unit BMI, there is an increment in pregnancy rates by a factor of 1.19. A few studies implied that 5% reduction in weight is sufficient to improve ovulation rate, menstrual regularity and pregnancy rates [70] [71]. However, the specific amount of weight reduction needed to achieve positive fertility outcomes are not confirmed and higher amount of weight loss are not equivalent to higher pregnancy and live birth rates [68].

Based on the hormonal aspects, weight loss reduces the levels of serum glucose, insulin and androgens in obese, non-PCOS women, whereas it increases SHBG levels and insulin sensitivity in obese women with PCOS [70] [72] [73]. Weight reduction is also found to decrease leptin levels and restore leptin sensi-

tivity, increase adiponectin and ghrelin levels, and reduce IL-6 levels [62] [74] [75] [76] [77] [78]. Therefore, weight reduction is seen as one of the most effective methods in the resumption of fertility in obese women as it is capable of reversing most of the parameters that contribute to poor follicular growth, oocyte maturation, ovulation and endometrial development.

### **2.3.2. Diet**

A diet consisting of 1200 - 1500 kcal/day seems to be beneficial in terms of both weight reduction and better fertility outcomes, especially in obese PCOS women [79]. Further caloric restriction within a short timeframe may have detrimental effects on fertility and IVF treatments [69] [80].

Dietary modification is another promising method for improving fertility in obese women. Diets consisting of low glycemic index (GI) have generated increased pregnancy and live birth rates, better oocytes yield during ovarian stimulation, possibly through its improvements on the serum insulin levels [81]. Low GI diets are also able to reduce leptin levels, which allows better follicular and endometrial growth through the improvements on insulin sensitivity and levels of female sex hormones [81]. The addition of high-protein in low GI diets has been found to further improve insulin sensitivity and reduce androgen levels in those with PCOS [82] [83]. Furthermore, adherence to Mediterranean-diet is strongly linked to a reduction in IL-6 levels, possibly due to the high composition of fruits and vegetables in the diet which yields anti-inflammatory properties [84]. Therefore, diets consisting of low GI and high fruits and vegetables can be attempted in conjunction with weight loss prior to fertility treatments to achieve the best possible outcome.

### **2.3.3. Physical Activity**

Hakimi and Cameron [85] suggested that daily exercises of 30 - 60 minutes are able to improve ovulation and fertility rate. A meta-analysis implied that physical activity before ART can increase clinical pregnancy and live birth rates by 1.96-fold and 1.94-fold, respectively [86]. However, excessive amount of vigorous exercises (>60 minutes) are detrimental to one's fertility status with an increased risk of anovulation [85].

In addition, physical activity reduces inflammatory biomarkers, including IL-6 and TNF- $\alpha$ , and improves insulin sensitivity, through the process of reduction in metabolically active visceral fats and increase in cellular metabolism in skeletal muscles, which in turn help regulates the proteins acting on insulin signal transduction [85] [87]. With reduced inflammatory processes in the body, the negative effects on the female reproductive system can be reversed, which is evidenced by the two-fold increases in both pregnancy and live birth rates. Hence, physical activity should be recommended for obese women despite failures in targeting weight loss.

### **2.3.4. Weight-Loss Medication**

Orlistat is the most common weight-reducing pill used in obese women. It is

found to improve insulin resistance and reduce androgen levels in obese women with PCOS [37]. However, not many studies are done to prove the effectiveness of weight-reducing pills on infertility in obese women without PCOS. As data is limited, the WHO suggests that pharmacological therapy should be used in conjunction to lifestyle interventions like diet and exercise, for a better outcome [1].

### 2.3.5. Bariatric Surgery

A meta-analysis suggested that bariatric surgery reduces infertility rates in obese women with PCOS from 18.2% to 4.3% [88]. Moreover, >70% of anovulatory obese women are able to achieve menstrual regulation and a shorter follicular phase post-surgery [89] [90].

Rochester *et al.* [91] show improvements in baseline LH levels and luteal pregnanediol-3-glucuronide (PdG), a progesterone metabolite, in eumenorrheic obese women undergoing bariatric surgery. This can be interpreted where the regulation of LH levels would bring about a higher success in ovulation, which can be evidenced by the raise in progesterone, a hormone mainly produced by the corpus luteum. In addition, obese women that have undergone bariatric surgery have increased SHBG and adiponectin levels, as well as reduced leptin and IL-6 levels, as compared to those that have not [90] [92]. Specifically, restrictive procedures have been shown to improve ghrelin concentration whereas bypasses have not [62]. Again, these changes could reverse the negative effects of prolonged imbalances in endocrinological levels in the female reproductive system, which is evidenced by the reduction in infertility rates post-surgery as stated above.

## 3. Conclusions

This review has depicted how each of the underlying mechanisms of obesity leading to female infertility correlates and interacts with one another, which is shown through either potentiating or inhibiting one another to cause changes in the HPO axis, female sex hormones as well as changes in the female reproductive system. The conclusive effects are poor follicular growth, poor oocyte maturation and recruitment, premature atresia of ovarian cells and follicles, as well as poor endometrial development and implantation, which are evidence through ovulatory dysfunction, irregular menstruation, increased miscarriages and ART failure rates.

Weight reduction should be attempted first in obese women seeking fertility treatment as it seems to be the most effective when it comes to the restoration of ovarian function and changes in the female reproductive system. It works by reducing the metabolically active adipose tissues, improving insulin sensitivity, regulating sex hormones, and restoring balances to the adipokines and inflammatory mediators. Moreover, dietary modification and physical activity can be alternatives in conjunction with weight reduction as it improves insulin sensitivity and reduces the inflammatory processes in the body. Bariatric surgeries can be reserved as a last resort as it not only reduces weight in women who failed to

do so, but also restores fertility through the regulation of parameters responsible for poor ovarian function. However, every operation does come with its own risks, so it should be weighed against its benefits.

In terms of future studies, it would be great to investigate adipokines in human models and realize the gap in knowledge on how adipokines relate to the changes in the female sex hormones. Furthermore, it would be more complete to have another review to correlate mechanisms that are not yet discussed in this review, which include inflammation, lipotoxicity and cellular metabolisms, and how they all links to the changes in the female reproductive system leading to infertility. It will also be helpful to investigate the effectiveness of pharmacological agents targeting the main mechanisms leading to infertility in obese women. Alternatively, it would be great to have more research on pharmacological agents that target weight reduction with the effects of fertility resumption in obese women without PCOS, as the current literature for weight-reducing pills are mostly done on obese women with PCOS.

### Conflicts of Interest

The authors declare no conflicts of interest.

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