

# Insulin resistance/hyperinsulinemia and reproductive disorders in infertile women

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**Abstract** Obesity, which disturbs lipid and glucose metabolism, is a recent medical concern. It threatens human health and also has adverse effects on reproductive functions by causing insulin resistance/hyperinsulinemia, especially in women with polycystic ovary syndrome (PCOS). For PCOS patients to prevent these adverse effects, it is important to take into account improving their lifestyles by exercise and proper diets. The relationship between insulin resistance/hyperinsulinemia and reproductive disorders should be understood as fully as possible in order to provide effective treatment. It is well known that insulin resistance and compensatory hyperinsulinemia can be triggered by obesity with visceral fat accumulation. Hyperinsulinemia affects granulosa cells in small follicles and theca cells. This condition induces early response to luteinizing hormones on granulosa cells of small follicles and causes premature differentiation of these cells, which eventually results in anovulation. For improvement of anovulation because of hyperinsulinemia, insulin-sensitizing agents (biguanide and thiazolidinedione derivatives) are useful. Hyperinsulinemia may adversely affect the

endometrial functions and environment, and evoke implantation disturbance. Treatment with an insulin-sensitizing agent (metformin) improves the levels of glyco-delin, insulin-like growth factor binding protein 1, and blood flow in spiral arteries during the peri-implantation period. It supports endometrial function, improves the endometrial environment, and facilitates embryo implantation. The rate of early pregnancy loss during the first trimester is 30–50% in women with PCOS, which is threefold higher than for normal women. Metformin treatment improves the levels of insulin, the homeostasis model assessment for insulin resistance, and plasminogen activator inhibitor activity, and decreases early pregnancy loss. It goes without saying that lifestyle change is fundamental for improving reproductive performance in addition to treatment with insulin-sensitizing agents.

**Keywords** Hyperinsulinemia · Insulin resistance · Insulin sensitizer · Lifestyle · Reproductive disorders

## Introduction

There is great concern about the high prevalence of obesity and overweight worldwide, especially in Western countries. A high obesity rate is prevalent in Okinawa prefecture, Japan [1]. Obesity is known to cause disturbances of lipid and glucose metabolism. The serious health threats of diabetes, cardiovascular disease, cancers, and anovulation are the principle manifestations of obesity [2–5].

As for obesity and reproduction, weight increase is correlated with a higher frequency of menstrual disorders, infertility, gestational diabetes, and other significant sequelae [6]. Infertile women with polycystic ovary syndrome (PCOS) were first described by Stein and Leventhal

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[7]. PCOS is characterized by chronic anovulation, infertility, and a typical sonographic appearance of the ovaries. Thus, an important cause of infertility in women with PCOS is anovulation [8]. Of the women with PCOS, 40–50% frequently experience insulin resistance/hyperinsulinemia, especially obese women [9]. Obesity or overweight is usually more prevalent in infertile/subfertile women with PCOS. Although the importance of obesity/overweight and PCOS status is yet to be fully understood, recent evidence suggests that body mass index (BMI) contributes significantly to the severity of many problems, such as the risk of miscarriage [10, 11]. Furthermore, weight reduction has been reported to improve reproductive function in overweight and obese infertile women, and an insulin-sensitizing drug such as biguanide (metformin) also improves the menstrual cycle and ovulation in women with PCOS [12–14]. Thus, understanding the relationship between insulin resistance/hyperinsulinemia and reproductive disorders in infertile women living a modern lifestyle is important.

#### **Insulin resistance/hyperinsulinemia and visceral adipose tissue**

Insulin resistance is defined as the decreased ability of insulin to stimulate glucose disposal into target tissues or a reduced glucose response to a given amount of insulin. Hyperinsulinemia is a compensatory response to this target tissue resistance. It is well known that insulin resistance and compensatory hyperinsulinemia are triggered by obesity. There are two types of fat distribution in obese subjects: subcutaneous fat and intra-abdominal visceral fat. A number of clinical studies demonstrate the contribution of visceral fat accumulation to the development of metabolic disorders, including glucose intolerance and hyperlipidemia [15–19]. Kissenbah et al. [20] and Matsuzawa [21] clearly demonstrate that visceral fat obesity has greater insulin resistance than subcutaneous fat obesity.

Several mechanisms of insulin resistance are hypothesized, such as deficient insulin action [22],  $\beta$ -cell dysfunction [23], increased insulin secretion in response to dietary stimuli [24, 25], and decreased hepatic clearance of insulin [26]. Matsuzawa [27] postulates that insulin resistance in visceral fat obesity is exacerbated by an increased supply of free fatty acid (FFA). He also states that adipose tissues directly secrete multiple bioactive molecules (adipocytokines), such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), leptin, and plasminogen activator inhibitor 1 (PAI-1), which plays an important role in the development of metabolic disorders. Namely, visceral fat accumulation causes an increase in FFA and adipocytokines (probably TNF- $\alpha$ ), resulting in insulin resistance.

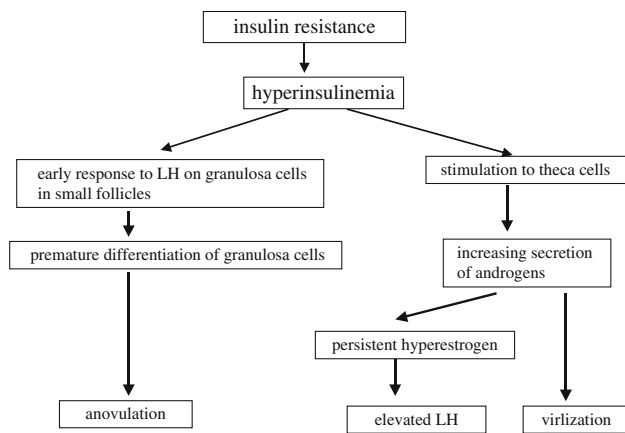
#### **Insulin resistance/hyperinsulinemia and hyperandrogenism**

Hyperinsulinemia correlates positively with the presence of hyperandrogenism in lean and obese women with PCOS [28–31]. Hyperandrogenism is understood to result from both increased adrenal and ovarian androgen production [23, 32–34]. Insulin, by acting via its receptor, appears to promote ovarian and adrenal androgen biosynthesis [35, 36], amplifying luteinizing hormone (LH)-induced androgen production by theca cells and resulting in hyperandrogenemia [37, 38]. Amelioration of hyperinsulinemia leads to a marked decline in circulating androgens to a normal level [39]. Hyperinsulinemia may also upregulate insulin-like growth factor-1 (IGF-1) receptors, which are potent stimulators of LH-induced androgen synthesis and suppression of IGF-binding protein 1 (IGF-BP1) production by the liver [40, 41]. Additionally, insulin may have an inhibitory effect on hepatic sex hormone-binding globulin (SHBG) production [42], thereby increasing the bioactive androgen, which produces virilization.

#### **Insulin resistance/hyperinsulinemia and ovulatory disorder**

The characteristic sonography of the ovary in PCOS shows the growth arrest of the antral follicles after reaching a diameter between 5 and 8 mm. Franks et al. [43] reported that the arrest of small follicles may be caused by premature activation of LH-mediated terminal differentiation of granulosa cells. In the a normal menstrual cycle, granulosa cells of the dominant follicle become responsive to LH in the mid-follicular phase at a follicular diameter of 10 mm [44]. In the preovulatory phase, LH enhances steroidogenesis and triggers terminal differentiation of granulosa cells so that the growth of follicles is arrested. On the other hand, granulosa cells from follicles as small as 4 mm in diameter of anovulatory PCOSs are responsive to LH. This response to LH is remarkably amplified by insulin [43]. The premature activation of granulosa cells by LH induces terminal differentiation, resulting in the arrest of follicle growth [9].

The relationship between insulin resistance/hyperinsulinemia and PCOS is summarized in Fig. 1. Hyperinsulinemia may amplify the production of androgen on theca cells, resulting in virilization. Also, an excess amount of androgen converts to estrogen. Converted estrogen increases LH secretion via GnRH and by a direct effect on the pituitary gland. Insulin also acts on granulosa cells of small follicles and amplifies premature responsiveness to LH. Increasing LH leads to the terminal differentiation of granulosa cells in small follicles and causes early arrest of



**Fig. 1** The relationship between insulin resistance/hyperinsulinemia and PCOS

follicular growth, which results in anovulation. Hyperinsulinemia affects two types of cells. In theca cells, hyperinsulinemia increases the secretion of androgens and results in virilization. An excess amount of androgen converts to estrogen, resulting in elevation of LH. Hyperinsulinemia initiates the response of granulosa cells to LH during the premature stage and leads to premature differentiation of granulosa cells. It results in anovulation.

### Ovulatory disorder and insulin-sensitizing agents

In general, treatment for ovulatory disorders attributed to obesity and/or insulin resistance is by lifestyle changes such as dietary changes and increased physical activities [45]. At the same time, other approaches to treat these patients include the use of insulin-sensitizing agents, namely, biguanide (metformin) and thiazolidinedione derivative (troglitazone). Metformin has been used for anovulatory patients with PCOS. This treatment has been highly successful, with ovulation rates as high as 46% [46]. Thiazolidinedione derivative (troglitazone) is also used for ovulation induction in PCOS. Thiazolidinedione derivative (troglitazone) improves the ovulation rate by 57% in PCOS patients compared with 12% in placebo-treated patients [47]. The functional mechanisms of the two agents are known to be different. Metformin is an oral biguanide, category B drug for pregnant women that has been approved for treatment of type 2 diabetes mellitus. It is thought to affect multiple metabolic pathways, decreasing glucose absorption, suppressing hepatic glucose output and gluconeogenesis, and also decreasing the BMI [48–50]. In addition, metformin directly inhibits androgen production in human thecal cells [51]. Side effects are rare, and gastrointestinal disturbances, such as abdominal pain and nausea, rarely cause discontinuation

of treatment. On the other hand, troglitazone is a thiazolidinedione derivative used for the treatment of type 2 diabetes mellitus. It has a more potent glucose-lowering effect and favorable effects on abdominal lipid levels, including the decrease of circulating triglyceride and FFA levels. Troglitazone may affect and differentiate adipocytes via peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ). As a result, differentiated adipocytes regulate insulin sensitivity and improve insulin resistance [52]. The reported side effects are hepatic disturbance and edema, but these are tolerable. At present, there is uncertainty about which types of insulin-sensitizing agents to select for specific patients. Therefore, high molecular weight (HMW) adiponectin is the focus because HMW adiponectin is secreted from adipocytes and acts on increasing insulin sensitivity in target organs [53]. Decreased HMW adiponectin has been found to play a crucial and causal role in obesity-linked insulin resistance [54]. Namely, HMW adiponectin reflects the pathophysiological condition of insulin resistance. Recently, based on the properties of biguanide and thiazolidinedione derivative and also levels of HMW adiponectin, anovulatory patients with PCOS have been treated. The obtained results showed a high ovulatory rate, a high pregnancy rate, and a low abortion rate (unpublished data). However, further precise investigations are necessary concerning the choice of insulin-sensitizing agents.

### Insulin resistance/hyperinsulinemia and implantation disorder

Recently, it has been reported that hyperinsulinemia may adversely affect the endometrial functions and environment, and evoke implantation disturbance and/or early pregnancy loss [55]. Jakubowicz et al. [56] studied glycodelin, IGF-BP1, and uterine vascularity and blood flow in PCOS patients with metformin and placebo treatment. Glycodelin is a specific protein synthesized by secretary/decidualized endometrial glands. Circulating glycodelin may reflect endometrial function, such as endometrial maturation and inhibition of the endometrial immune response to the embryo [57–61]. IGF-BP1 is a protein that appears to facilitate adhesion processes at the fetomaternal interface and may play an important role in the peri-implantation period [62, 63]. The concentration of glycodelin and IGF-BP1 in the luteal phase is highly increased by three- to fourfold by metformin treatment compared with placebo. Also, metformin treatment increases vascular penetration and decreases the blood flow of spiral arteries, demonstrating a 20% decrease in the resistance index. These results indicate that improvement of hyperinsulinemia may support endometrial function and amelioration of

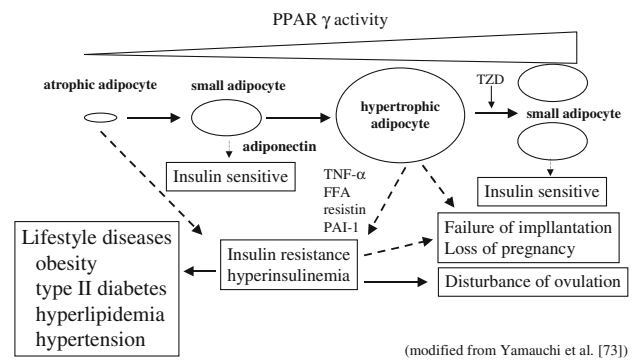
the endometrial environment, resulting in facilitation of embryo implantation.

### Insulin resistance/hyperinsulinemia and early pregnancy loss

The rates of early pregnancy loss, defined as miscarriage during the first trimester, have been reported to be 30–50% in women with PCOS, which is threefold higher than in normal women [64, 65]. In addition, 36–82% of women with recurrent early pregnancy loss have PCOS [66]. According to Jakubowicz et al. [67], the rate of early pregnancy loss with metformin treatment was 8.8% compared to 41.9% in the control group with PCOS. Glueck reports that metformin treatment decreases early pregnancy loss in current (on metformin) and previous (no metformin) pregnancy with PCOS [68]. Additionally, metformin treatment improves the levels of insulin, homeostasis model assessment for insulin resistance (HOMA-IR), and PAI-Fx. This insulin-lowering effect of metformin treatment might result in protection from early pregnancy loss. Furthermore, metformin treatment during pregnancy in women with PCOS is safely associated with a reduction of first-trimester spontaneous abortions and is not teratogenic, having no adverse effects on the biological and physical conditions of baby.

### Conclusion

Recently, the obesity rate has been a great concern in Okinawa, Japan, as Western dietary habits are becoming more popular [69]. Moreover, as signs of metabolic syndrome, insulin resistance and hyperinsulinemia are among the major issues. These conditions are highly related to lifestyle-related diseases such as diabetes, cardiovascular disease, and cancer in middle-aged people [2]. For young women, these conditions also threaten their reproductive systems. Concerning metabolic syndrome, properly obtaining a nutritional and metabolic balance in daily life becomes increasingly crucial not only for middle-aged and older women, but also for young adults in order to increase their fecundity. In fact, some studies showed that the usage of insulin-sensitizing agents alone is not sufficient for treating infertility associated with PCOS [70]. Furthermore, according to Mathur et al. [71], there are no clear data showing that using metformin alone reduces pregnancy loss or improves the pregnancy rate. Thus, it is possible to suggest that combining insulin-sensitizing agent therapy with an improved lifestyle may greatly support women with PCOS and improve their pregnancy outcomes. In addition, exercise and diet have been reported to improve



**Fig. 2** The relationship between differentiation of visceral adipocytes and reproductive processes. Small adipocyte secretes adiponectin, which facilitates insulin sensitivity. Hypertrophic adipocyte secretes FFA, TNF- $\alpha$ , resistin and PAI-1, which suppress insulin sensitivity and result in insulin resistance and hyperinsulinemia. This status may evoke disorders such as disturbance of ovulation, failure of implantation and loss of pregnancy. If insulin resistance and/or hyperinsulinemia become advanced, it may eventually cause lifestyle diseases such as obesity, type II diabetes, hyperlipidemia and hypertension. TZD differentiates adipocytes and improves insulin sensitivity. Likewise, metformin and/or improved lifestyle are also able to facilitate insulin sensitivity. Atrophic adipocyte has inadequate secretion of adiponectin and initiates insulin resistance and hyperinsulinemia. This figure was originally published in the *Journal of Biological Chemistry* and referred with permission from [73]. FFA free fatty acid, PAI-1 plasminogen activator inhibitor 1, PPAR- $\gamma$  peroxisome proliferator-activated receptor gamma, TNF- $\alpha$  tumor necrosis factor alpha, TZD thiazolidinedione

insulin resistance and reproductive performance [72]. Some are of the opinion that PCOS is one of the primary symptoms of lifestyle diseases among women. Regarding the present report, gynecologists should emphasize healthy lifestyles for women as part of their medical care.

The relationship between differentiation of visceral adipocytes and reproductive processes is shown in Fig. 2 [73].

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