

—Mini Review—

# Insulin Resistance and Metformin Treatment in Women with Polycystic Ovary Syndrome

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**Abstract:** Insulin resistance is one of the key factors in the pathogenesis of polycystic ovary syndrome (PCOS). Obesity, visceral fat accumulation and excessive serine phosphorylation of the insulin receptor are factors responsible for insulin resistance in PCOS. Insulin resistance induces compensatory hyperinsulinemia, which stimulates androgen synthesis in the theca cells of the PCOS ovary. Therefore, hyperinsulinemia results in hyperandrogenemia in PCOS patients who tend to have androgen-producing ovaries. In Japanese PCOS, 25% of patients are obese and 30% of patients have insulin resistance. Improvement of insulin resistance by weight loss, exercise and insulin sensitizing drugs such as metformin can recover reproductive function. Metformin has the potential to induce ovulation in PCOS, and 58% of clomiphene resistant Japanese PCOS patients resume ovulation after combined clomiphene metformin treatment. Clomiphene-metformin therapy is simple and has low risks of multiple pregnancy and ovarian hyperstimulation syndrome. Metformin use should be considered fertility treatment, especially as a second line therapy for the clomiphene resistant PCOS.

**Key words:** pCOS, Insulin resistance, Hyperinsulinemia, Metformin

## Introduction

Polycystic ovary syndrome (PCOS) is a common menstrual disorder in women of reproductive age, with reported prevalence of 6–10% [1, 2]. The principal features of PCOS are menstrual disorder, androgen excess and

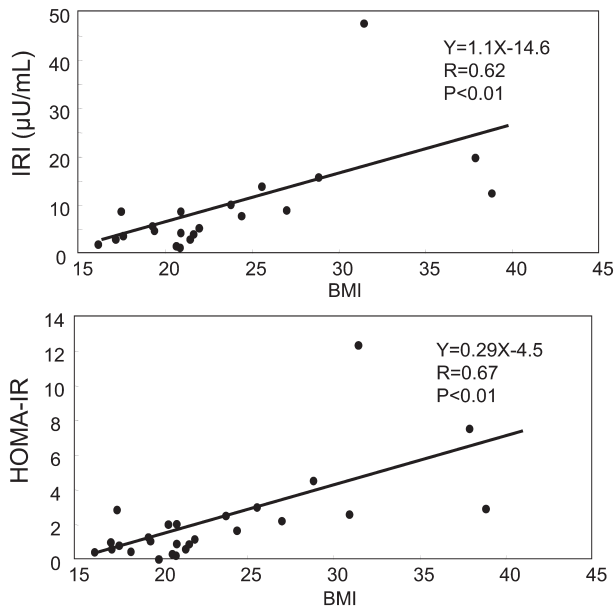
polycystic ovary morphology. Other common features are obesity and insulin resistance.

Clinical and biochemical hyperandrogenism and obesity are less prevalent in Japanese patients than in Western populations [3–7]. However, recent total testosterone measurements have revealed a higher prevalence of high serum total testosterone level in Japanese PCOS patients than was previously estimated [8–11]. The major role of insulin is to make it possible for glucose to enter the body's cells and maintain the blood glucose level in the normal range. Additionally, insulin acts on the ovary to stimulate androgen synthesis in theca cells. This action in the ovary seems to be elevated in PCOS patients who have insulin resistance mediated by compensatory hyperinsulinemia. Therefore, the estimation and control of insulin resistance is important in the treatment of PCOS.

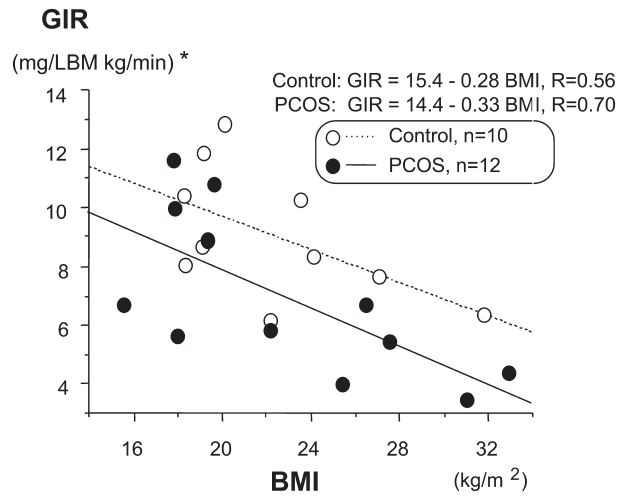
## Insulin Resistance in PCOS

Burghen et al. first reported PCOS patients showed hyperinsulinemia in the oral glucose tolerance test [12], indicating that the patients had insulin resistance. Thereafter, insulin resistance and hyperinsulinemia have been recognized as common features of PCOS [4, 13]. Obesity enhances insulin resistance, which results in compensatory hyperinsulinemia (Fig. 1) [14]. In PCOS patients, especially those with obesity or insulin resistance, androgen synthesis in the ovary is stimulated by insulin [15], and the parameters of insulin resistance correlate positively with serum total and free testosterone (Fig. 2) [14].

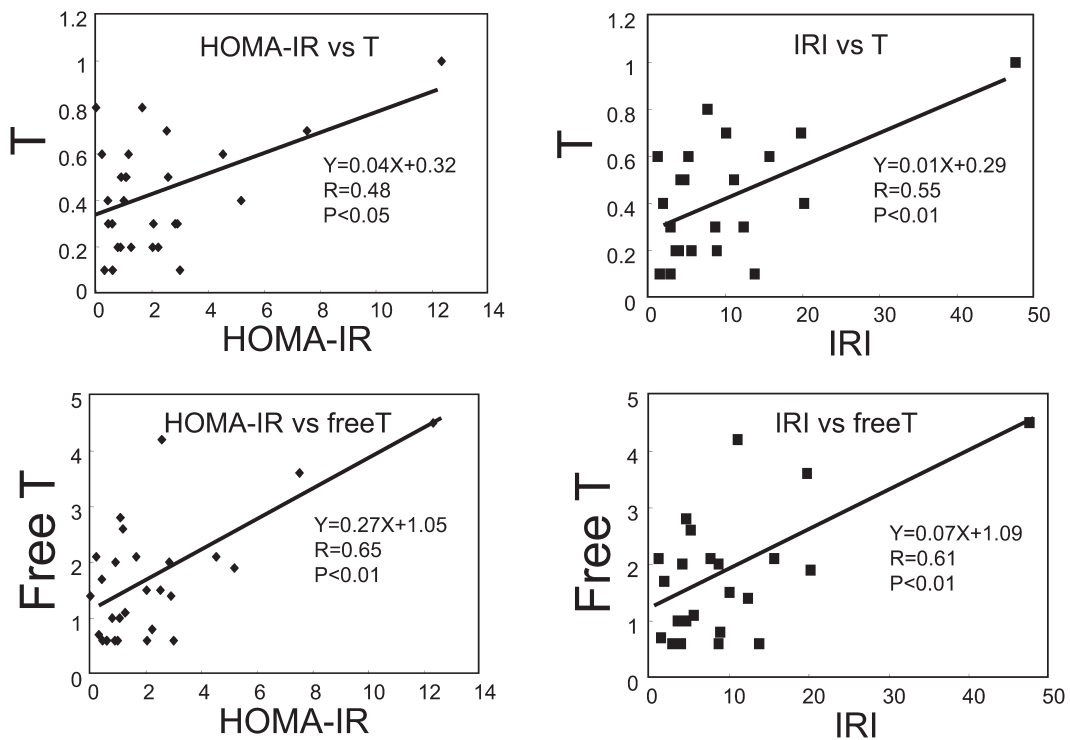
Obesity is one of the reasons for insulin resistance in PCOS, because obesity is common in PCOS patients, and obesity itself enhances insulin resistance. In Japan, the prevalence of obesity was 25.9% in PCOS patients of reproductive age in according to a survey conducted in



**Fig. 1.** Fasting insulin and HOMA-IR positively correlate with BMI in Japanese PCOS patients [14].  
 IRI: fasting immunoreactive insulin, HOMA-IR: homeostatic model of insulin resistance = insulin (μU/ml) × glucose (mg/dL)/ 405.



**Fig. 3.** Assessment of insulin resistance of PCOS patients by hyperinsulinemic normoglycemic clamp [16]. Lower GIR means stronger insulin resistance. GIR shows negative correlations with BMI in both groups. The PCOS group shows lower GIR than the Control group irrespective of BMI ( $P<0.05$  ANCOVA). \*GIR (glucose infusion rate), calculated using lean body mass.



**Fig. 2.** Parameters of insulin resistance positively correlate with serum total testosterone and free testosterone in Japanese PCOS patients [14].  
 IRI: fasting immunoreactive insulin, HOMA-IR: homeostatic model of insulin resistance, T: testosterone.

2006 [6]. Comparable figures for the general population were 7.7% in 20–29 y.o. women, and 11.8% in 30–39 y.o. women according to the national census of 2009. Insulin resistance can be properly measured in PCOS patients irrespective of body mass index, using hyperinsulinemic normoglycemic clamp (Fig. 3) [16]. Additionally, the oral glucose tolerance test shows a clearly higher insulin response in PCOS patients than normal women in both the non-obese and obese populations [17]. Therefore, reasons for insulin resistance other than obesity exist in PCOS. Yucel et al. evaluated the body fat distribution in PCOS patients and healthy women who are generally overweight using dual X-ray absorptiometry (DEXA). They reported that the ratio of fat mass in the trunk to fat mass in the legs was significantly higher in patients with PCOS [18]. Kirchengast et al. reported similar results for non-obese PCOS patients [19]. They examined body composition and fat distribution characteristics in lean PCOS patients and weight-matched lean controls using DEXA, and reported that lean PCOS patients showed a significantly higher amount of body fat, and that the majority of PCOS patients showed an intermediate or android kind of fat distribution. These reports indicate that PCOS patients have more visceral fat than normal women. Visceral fat accumulation could explain the insulin resistance peculiar to PCOS. Furthermore, Dunaif et al. reported an abnormality in the molecular mechanism controlling insulin receptor signaling which is peculiar to PCOS [13]. Insulin resistance is related to excessive serine phosphorylation of the insulin receptor in some PCOS patients. Serine/threonine kinase might cause this abnormality, resulting in both insulin resistance and hyperandrogenism.

About 50 to 70% of women with PCOS demonstrate insulin resistance *in vivo* in Western countries [4]. However, only 32.8% of PCOS patients (129 out of 393) were estimated to have insulin resistance by a value  $\geq 2.5$  in the homeostatic model of insulin resistance (HOMA-IR) in Japan [6]. The relatively low rate of insulin resistance in Japanese PCOS might be explained by the low prevalence of obesity [4]. Obese PCOS is less common in Japan (25.0%) than in Western countries (41%) [5, 6]. Although the prevalence of insulin resistance as well as obesity is lower in Japan than in Western countries, insulin resistance should also be taken into consideration in the treatment of PCOS in Japan.

### Metformin Treatment in PCOS

Ovarian theca cells secrete androgen and are hyper-responsive to insulin in PCOS patients [15]. Compensatory

hyperinsulinemia seen in PCOS patients with insulin resistance also enhances androgen synthesis. Insulin-sensitizing agents, principally metformin, have been found to improve the features of PCOS including anovulation in meta-analyses [20–24]. Metformin decreases hepatic glucose production, thus reducing the need for insulin secretion; it also decreases intestinal absorption of glucose and modestly improves insulin sensitivity [25]. Metformin is a drug used in the treatment of type 2 diabetes, and it is also used in the treatment of PCOS.

According to the Cochrane Review on insulin sensitizing drugs for PCOS in 2012 [24], and its previous versions [23], metformin improves ovulation and clinical pregnancy (metformin versus placebo), but there is no evidence to improve ovulation, clinical pregnancy and live birth rates compared with clomiphene (clomiphene versus metformin or combination of them). The present consensus is that the role of metformin in improving reproductive outcomes in women with PCOS appears to be limited, and leading medical bodies do not recommend metformin as the first line of treatment [26–28].

A recent meta-analysis of metformin treatments analyzed 38 trials involving 3,495 women, however, only 7 trials involving 451 women were analyzed for an effect on the live birth rate [24]. Furthermore, clomiphene resistance was not considered in the analysis of the live birth rate. On the other hand, Moll et al. analyzed 27 randomized controlled trials (RCT) for clomiphene-resistant PCOS with respect to history of previous treatment [29]. In therapy naïve women, there was no evidence of a difference in live birth rates when comparing metformin with clomiphene, or comparing metformin plus clomiphene with clomiphene alone. However, in the clomiphene-resistant women, clomiphene plus metformin treatment resulted in higher pregnancy rates and live birth rate than clomiphene alone. The combination of clomiphene plus metformin is the preferred treatment option before commencing laparoscopic ovarian drilling (LOD) or low-dose FSH therapy [29, 30].

The combination of clomiphene plus metformin seems to be effective in Japanese PCOS patients who do not respond to clomiphene. As summary of clinical results are shown in Table 1 [14, 31–34]. The ovulation rate was calculated as 58.1% in total. The daily dose of metformin is dominantly 750 mg in Japan, which is lower than the doses used in other countries: 1,700–2,000 mg. In patients who did not respond to 750 mg of metformin, doses up to 1,500 mg have been highly effective at inducing ovulation [33], indicating that 750 mg is not the highest effective dose of this combined treatment in Ja-

**Table 1.** Ovulation Rate of combined Clomiphene-metformin Therapy for clomiphene Resistant PCOS Patients in Japan

	Metformin dose	Ovulation rate in Clomiphene + Metformin	Ovulation rate in clomiphene
Matsuzaki [14]	750 mg*	71.4% (5/7)	16.7% (1/6)
Kurabayashi [31]	500 mg	58.6% (17/29)	
Matsuura [32], Shimizu [33]	750 mg	51.1% (23/45) [33]	30.3% (10/33) [32]
	1500 mg	81.3% (13/16) [33]	
Nakamura [34]	500–750 mg	37.5% (3/8)	
Total		58.1% (61/105)	28.2% (11/39)

\*Metformin treatment period was from the 5th day of menstrual cycle to hCG injection.

**Table 2.** Treatment Outcomes of combined Clomiphene-metformin [22]

	clomiphene-metformin	clomiphene	
cycle (case)	7	6	
ovulation (%)	71.4 (5/7)	16.7 (1/6)	
pregnancy (%)	33.3 (2/6)	0 (0/6)	
multiple pregnancy (%)	0 (0/2)	–	
OHSS (%)	0 (0/6)	0 (0/6)	
other side effects(%)	14.3 (1/7) (nausea)	0 (0/6)	
number of growing follicles	1 ± 0	1	cycles with follicular growth
single follicular development (%)	100 (5/5)	(1/1)	
hCG cancellation (%)	0 (0/5)	(0/1)	
follicular development (day)*	13.5 ± 3.1 (11–17)	13	
outpatient visit (day)**	3.3 ± 0.6 (3–4)	3	

(mean ± SD)

\*from the first day of clomiphene treatment to hCG injection.

\*\*total days from start of treatment to follicular maturation.

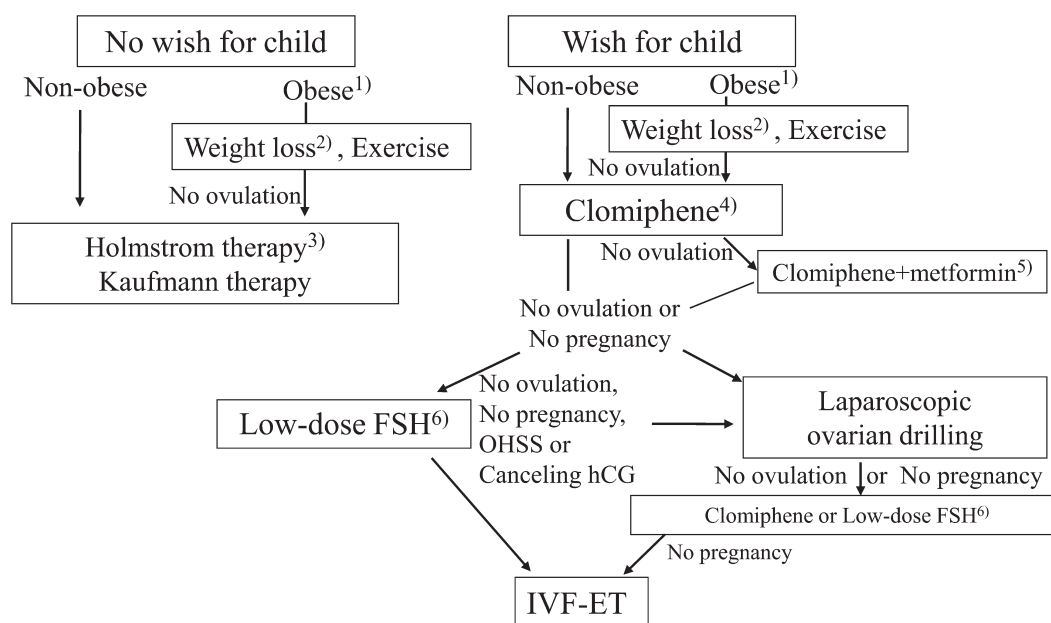
pan. Clomiphene-metformin therapy is convenient, and has low incidences of multiple pregnancy and OHSS, because the number of developing follicles is one in almost all cycles (Table 2) [14]. The major adverse effect of metformin is gastrointestinal disturbance, such as appetite loss, nausea, vomiting, constipation and diarrhea, and general fatigue. These occur mainly in the first week of medication. In the guiding principle of Japanese Society of Obstetrics and Gynecology on the treatment of PCOS, combined clomiphene-metformin therapy is described as an optional treatment before low-dose FSH or LOD for clomiphene resistant patients who are mainly obese and have insulin resistance or impaired glucose tolerance (Fig. 4) [35]. Metformin also seems to be effective in non-obese cases with normal insulin resistance parameters, but the indication for this treatment have yet to be clarified.

## Conclusion

Clomiphene is still the first choice infertility treatment for PCOS. For clomiphene resistant cases, a clomiphene-metformin combination has been proved to be effective for ovulation, pregnancy and live birth rates. This combination is simple and safe, and is therefore, a valuable option before LOD or FSH therapy.

## Conflict of interest

The authors declare that there are no conflicts of interest that would prejudice the impartiality of this scientific work.



Note.

1) BMI  $\geq 25$

2) 5~10% weight loss over 2-6 months

3) Oral contraceptive is beneficial in the case of hyperandrogenism

4) Dopamine agonist, glucocorticoid might be added in cases with elevated serum prolactin or adrenal androgen.

5) Obese, impaired glucose tolerance or insulin resistance

6) hCG injection: when follicle diameter reaches 18 mm. hCG cancel: 3 or more follicles which exceed 16 mm

**Fig. 4.** The guiding principle of Japanese Society of Obstetrics and Gynecology for the treatment of PCOS (JSOG 2009) [35].

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