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# Does Insulin Resistance (IR) Have an Impact on The Reproductive and Fertility Potential in Polycystic Ovary Syndrome (PCOS) Women? : Review Article

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## Cover Page Footnote

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ORIGINAL STUDY

# Does Insulin Resistance (IR) Have an Impact on the Reproductive and Fertility Potential in Polycystic Ovary Syndrome (PCOS) Women?: Review Article

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**Abstract**

*Backgrounds*: **Polycystic ovary syndrome is the most common endocrine and reproductive disorder in the reproductive-age women. Among the pathological changes that are responsible for the development of polycystic ovary syndrome (PCOS), hyperinsulinemia due to increased insulin resistance (IR) is common and usually associated with a higher rate of ovulatory dysfunction and sub-fertility. In addition, those women have poor quality oocytes with low fertilization capability and poor quality embryos. So, insulin has a role in the reproductive function and fertility potential of reproductive age women.**

*Conclusion*: **Females with PCOS usually exhibit an extreme difficulty in achieving either a successful spontaneous or assisted pregnancy. Hyperinsulinemia/insulin resistance and reproductive dysfunction should be well understood as can as possible in order to achieve an effective treatment plan to increase the chance of a successful uncomplicated pregnancy.**

*Keywords:* Insulin resistance, Hyperinsulinemia, PCOS, Sub-fertility

## 1. Introduction

The ovarian theca and granulose cells exhibit insulin receptors. Insulin primarily acts on its own receptor to stimulate ovarian steroid-genesis [1]. Hyperinsulinemia impairs the developmental competence of oocyte and has an adverse effect on embryonic development [2,3,4]. Hyperinsulinemia also negatively affects endometrial function with a higher rate of implantation failure [5]. During controlled ovarian stimulation (COS)/assisted reproduction, the response to gonadotropin stimulation is highly affected by insulin resistance. Hyperinsulinemia is frequently associated with a multi-follicular development and women suffering from IR are more susceptible to develop ovarian hyper stimulation syndrome (OHSS) and at a higher risk of cycle cancelation [6].

### *1.1. The physiology of insulin*

Insulin is a peptide hormone secreted by pancreatic β-cells in response to high blood glucose level. Its' action mediated by binding to specific cell surface receptor to activate a cascade of signals that end with sugar uptake [7]. Appropriate processing of the signals is an important key factor and the blood glucose fails to normalize despite excess amount of insulin produced by the pancreatic tissues [8].

Another hormonal pathway known as insulin−like growth factor (IGF-1) is involved in the regulation of blood glucose level. Impaired ovulation and failure of development of appropriate endometrial lining are developed when insulin and IGF-1 levels in the blood are high [9]. High insulin and IGF-1 also disturb the cellular metabolism and

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physiological androgen level leading to the development of excessive male-like hair growth and androgenic alopecia.Abnormal level of both affects the storage of fat in the adipose tissues. Studies reported that hyperinsulinemia predisposes to central obesity which increases the risk of insulin resistance. Both central and peripheral obesity have an adverse effect on the female reproduction and decrease the fertility potential of the females [10].

### *1.2. Insulin resistance*

Insulin resistance implies a disorder characterized by impaired ability of the tissues to respond to the action of insulin resulted in elevated blood insulin level (hyperinsulinemia). Insulin resistance and diabetes mellitus are not synonymous [11]. In diabetes, the pancreas can no longer produce adequate amounts of insulin to control blood glucose, while insulin resistance, the pancreas has the ability to produce excessive amounts of insulin to maintain normal blood glucose level. Different mechanisms responsible for IR, genetic, insulin receptor defects and high body weight which either present alone or in combination with each other. Polycystic ovary syndrome (PCOS) usually associated with insulin resistance/hyperinsulinemia [12].

### *1.3. Insulin resistance effects on females' fertility*

The secretion of several hormones (counter regulating hormones) are impaired when insulin level is elevated [13]. IR leads to sub-optimal release of pituitary gonadotropins; follicle stimulating hormone (FSH) and luteinizing hormone (LH) hindering follicular development. Normal ovulation is impacted as a result of impaired ovarian steroids; estrogen and progesterone. When ovulation occurs normally, the quality of the oocyte is poor with a reduced chance of successful [14].

### *1.4. Polycystic ovary syndrome (PCOS)*

It is a state of reproductive and endocrine hormonal imbalances, characterized by irregular/decrease menses, high body mass index (BMI), hirsutism and sub-fertility due to androgen excess [15]. The characteristic ovarian morphology by transvaginal ultrasound was not included till 2003 when an international conference held in Rotterdam defined a diagnostic criterion including polycystic ovaries seen by trans-vaginal ultrasonography along with chronic anovulation and high androgen/testosterone level. An established PCOS diagnosed when two of the previous three criteria are present [16]. PCOS tends to affect up to twenty percent of women mainly during the third decade of life [17].

Studies reported an association with metabolic syndrome, type 2 diabetes mellitus, endometrial and cardiovascular morbidity. There is a belief that insulin resistance is a key responsible factor for the development of these associates. Insulin resistance is considered in the pathogenesis, clinical and para clinical features of PCOS together with secondary hyperinsulinemia [18].

### *1.5. The development of insulin resistance in PCOS*

The most probable mechanism that support IR in PCOS is a defect at the post-receptor level. Glucose and carbohydrate metabolism are abnormal. Auto phosphorylation of the insulin receptor (IR), inhibited insulin receptors' intrinsic tyrosine kinase activity and decrease in the insulin mediated phosphatidylinositol 3(PI3) kinase activity which is associated to insulin receptor substrate 1(IRS1) are common [18,19]. Ovarian theca cells' androgen synthesis is directly stimulated luteinizing hormone (LH) and insulin. Impaired insulin-gonadotropic function contributes to high serum level of androgens in PCOS [20]. Furthermore, insulin increased free testosterone by reducing hepatic synthesis of the sex hormone binding globulin (SHBG). Insulin augments ovarian androgen production by increasing biodisponibility of IGF1 in the ovaries and by its inhibitory effects on hepatic synthesis of IGFBP1(18). Adrenal androgen is an important contributor in the appearance of hyper androgenemia in about half of the cases, hyperinsulinemia leads to altered adrenal steroidogenesis [21]. Insulin also may act on the ovarian cells by a pathway other than tyrosine kinase that is mediated by inositol glycan at the post receptor level which can be a best explanation why the insulin resistance in other tissues fails to impede the insulin effects in the ovaries [17].

### *1.6. Insulin resistance (IR) and excess body weight*

When the insulins' ability to stimulate target tissues' glucose disposal is reduced or the response of glucose to a given amount of insulin is decreased, a state on insulin resistance is the result [5]. A compensatory mechanism to this target tissue resistance, is an increased insulin level in the blood (hyperinsulinemia). Obesity can be triggered by both insulin resistance and compensatory hyperinsulinemia [20].

The development of metabolic syndrome as a result of visceral fat accumulation leads to hyperlipidemia and glucose intolerance [11].

The exact mechanism of insulin resistance is clearly understood. Theories suggested; β-cell dysfunction, abnormal insulin action, excess insulin as a response to dietary stimuli and reduced hepatic clearance of insulin. Insulin resistance is exacerbated by an increased supply of free fatty acid (FFA) in obese patients. Adipose tissues secrete multiple bioactive molecules directly into the blood named as adipocytokines for e.g. leptin, tumor necrosis factor α (TNF-α) and plasminogen activator inhibitor 1 (PAI-1). Adipocytokines play important role in the development of metabolic syndrome. Visceral fat accumulation causes an increase in free fatty acid and adipocytokines and enhance insulin resistance [22].

### *1.7. Insulin resistance (IR) and hyperandrogenism*

Both hyperinsulinemia and hyperandrogenism are associated with each other and could be observed in non-obese and obese women with PCOS [20]. Both ovarian and adrenal tissues contributed to hyperandrogenemia in those women [21], also, insulin receptor promotes the biosynthesis of ovarian and adrenal androgen and amplifies LH-induced androgen secretion by theca cells [23].

Amelioration of hyperinsulinemia results in a marked decline in circulating androgen levels reaching a normal level at some conditions [5]. The production of both insulin like growth factor 1 (IGF-1) and IGF-binding protein 1 are affected by hyperinsulinemic state, there is an upregulation of the receptors of the former (a potent stimulator of LH-induced androgen synthesis) and suppression of the later synthesis in the liver [8]. Insulin exhibits an inhibitory effect on hepatic SHBG production with an increase the bioactive androgen level, which manifested as virilization [10].

### *1.8. Insulin resistance (IR) causes ovulatory dysfunction*

The characteristic sonographic feature (peripherally located small follicles; necklace appearance and thick ovarian struma) of the polycystic ovaries during trans-vaginal ultrasound is usually as a result of antral follicles growth arrest at a diameter of 5–8 mm [24]. Premature activation of LH-mediated terminal differentiation of ovarian granulose cells is usually the responsible factor. At the mid-follicular phase of ovulatory menstrual cycle, the dominant follicle granulosa cells acquire high responsiveness to LH when the follicle reaches 10 mm diameter [25]. While at the pre-ovulatory phase, LH supports ovarian steroid-genesis and triggers granulose cells' terminal differentiation, so follicular growth is suppressed with the resultant of follicular arrest. In the anovulatorey cycle, like PCOS, small follicles' granulose cells responsiveness to LH is markedly amplified by insulin [17,24].

The excess amount of androgen which is usually as a result of estrogen aromatization increases LH secretion due to its direct effect on the anterior pituitary gland. As mentioned above, the excessive LH secretion enhances the terminal differentiation of small follicles' granulose cells and follicular growth arrest, which results in anovulation. So, we can reach a conclusion that the two types of ovarian cells are affected by hyperinsulinemia; theca cells by increasing androgen secretion and granulose cells by enhancing their responsiveness to LH during the premature stage. Premature differentiation of granulose cells results in anovulation [26].

### *1.9. Hyperinsulinemia causes implantation failure*

It has been reported that hyperinsulinemia can have a negative effect on the endometrial environment. There is an altered expression of glycodelin and insulin like growth factor binding globulin 1 (IGF-BP1) which may evoke implantation disturbance and early pregnancy loss [27].

Those specific proteins that are synthesized by decidualized endometrial glands have a major role in normal endometrial function, stimulate endometrial growth and maturation and inhibit endometrial immune response against the implanted embryo [28]. They also facilitate the process of embryonic adhesion at the feto maternal level and during the peri-implantation period [29]. Improvement of hyperinsulinemia can support endometrial environment and facilitates embryo implantation.

### *1.10. Hyperinsulinemia causes early pregnancy loss*

The first trimester miscarriage has been reported in 30–50% of women with PCOS, which is threefold higher than normal women. Together, about 36–82% of cases with recurrent early pregnancy loss either have PCOS or developed it later on during their lives [28].

Since hyperandrogenism and hyperinsulinaemia are present in combination with each other in PCOS, hyperandrogenism affects insulin secretion indirectly by its effect on IGF-1 receptors. The mechanism by which pregnancy loss occur is

unclear. Elevated blood insulin level may reduce glycodelin and IGFBP-1 concentrations during the 1st trimester and can be considered as a possible candidate of pregnancy loss [30]. However, an alternative mechanisms might be responsible; placental transport of excess amounts of glucose to the fetus leading to first trimester fetal loss. Placental insufficiency is also reported with an increased risk of placental vessels thrombosis due to high plasminogen activator inhibitor-1 (PAI-1) concentrations as a result of hyperinsulinemia [31].

### *1.11. Insulin resistance affects the assisted reproduction (ICSI) outcome*

Women with PCOS who failed to ovulate following conventional fertility treatment (weight reduction with and without insulin sensitizing agents, anti-estrogen, oral and/or injectable gonadotropins and laparoscopic ovarian diathermy), assisted reproduction (ICSI) could be considered as choice with an acceptable outcomes [32]. Another indications of ICSI in PCOS with sub-fertility are presence of associated conditions such obstructed fallopian tubes and severe male factor infertility. Treatment resistance may be another candidate. Studies showed that insulin resistance adversely affects the outcome; the response to ovarian stimulation protocol, gametes and embryos quality and pregnancy rate [33].

The independent effect of insulin resistance in PCOS on fertility treatment is less well understood. Irrespective of body weight, higher doses of gonadotrophins are needed when insulin resistance is present. Together, the success rate of fertility treatment is highly compromised by insulin resistance [11].

Multi-follicular development and cycle cancellation rate is not uncommon. The oocytes of women with hyperinsulinemia usually have a low fertilization rate following ICSI and high percentage of the resulting embryos fail to implant. High incidence of miscarriage due to low release of progesterone is also reported [34].

### *1.12. Strategies of reducing insulin resistance in PCOS*

1- **Nutritional therapy:** Specific food supplements and medical nutrition therapy (MNT) in PCOS patients are usually started as first line therapy with the aim of reducing body weight, improving the syndrome signs and symptoms, by their role in regulating insulin resistance, metabolic and endocrine functions [35] Appropriate early dietary intervention for the management of obese young PCOS females is considered as a recommended approach to normalize metabolic and hormonal parameters in order to restore normal ovulation and protect their fertility [36].

2- **Using insulin-sensitizing drugs to treat infertility in women with polycystic ovary syndrome:** Studies had been showed that insulin-sensitizing drugs in PCOS have a role in improving both insulin resistance and fertility [37]. Insulin-sensitizing drugs have Food and Drug Administration (FDA) approval for use in PCOS. The most commonly used drug is metformin. Troglitazone, and myo-inositol also are used (with or without metformin) and appear to enhance spontaneous ovulation [38]. The scientific evidence about their role in PCOS is substantial and progressively mounting, and the clinicians' use of these drugs in treatment of PCOS is already established [37].

## 2. Conclusion

Polycystic ovary syndrome considered number one hormonal condition that both reproductive age women and doctors are facing today frequently. Females usually exhibit an extreme difficulty in achieving either a successful spontaneous or assisted pregnancy. Hyperinsulinemia/insulin resistance and reproductive dysfunction should be well understood as can as possible in order to achieve an effective treatment plan to increase the chance of a successful uncomplicated pregnancy.

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