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ORIGINAL ARTICLE

Ovulation induction by metformin among obese versus non-obese women with polycystic ovary syndrome

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KEYWORDS

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Abstract *Objectives:* There is some evidence that the efficacy of metformin as an ovulation stimulation agent depends on the body mass index (BMI) of the treated anovulatory women with polycystic ovary syndrome (PCOS). The aim of this study was to examine the likelihood of successful ovulation among obese (BMI $\geqslant 30$ kg/m^2) versus non-obese (BMI < 30 kg/m^2) women with PCOS.

Methods: A total of 243 medical charts of women with PCOS who visited King Khaled University Hospital (KKUH) in Riyadh, Saudi Arabia, between 2006 and 2012 were reviewed. Patients' sociodemographic, laboratory, and medical data were collected. Descriptive statistics and multiple logistic regression analyses were performed to compare the patients' baseline data and successful ovulation among the obese and non-obese anovulatory women with PCOS, respectively.

Results: One hundred and nine women with PCOS who were prescribed metformin for $\geqslant 3$ months were included in the study. Almost 60% of the women who were included in the study were obese. The likelihood of ovulation among obese women with PCOS was 77.9% (odds ratio = 0.221, 95% CI 0.052–0.947, $P = 0.042$) less than that in their non-obese counterparts.

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Conclusion: The findings of this study suggest that metformin is more effective as an ovulation stimulation agent when administered to non-obese women with PCOS. Lifestyle modifications such as diet and exercise should be emphasized upon as an integral part of any treatment plan for PCOS.

1. Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive disorder affecting 6–10% women of childbearing age (Norman et al., 2007). Furthermore, it is believed to be one of the leading causes of infertility worldwide (Barthelmess and Naz, 2014). PCOS is characterized by hyperandrogenism, polycystic ovaries, and ovulatory dysfunction (Carmina et al., 2010; Gambineri et al., 2002). Moreover, multiple features of metabolic syndrome such as obesity, insulin resistance, and hyperinsulinemia are usually present in a majority of women with PCOS (Gambineri et al., 2002). Although the pathogenesis of PCOS is not well understood, insulin resistance is considered one of its main underlying causes, especially among obese people (Barber et al., 2015; Kahn and Flier, 2000). Therefore, it is important to assess the abdominal adiposity or upper body fat distribution in women as they correlate with insulin resistance (Moran et al., 2012). Insulin resistance increases the level of serum insulin, which interacts synergistically with the luteinizing hormone (LH) within the ovarian theca cells, causing a significant increase in the cholesterol level, a reduction in glucose transport, an increased production and release of androgens, and ultimately infertility (Barber et al., 2015). In a systematic review and meta-analysis that included 35 studies to determine the prevalence of overweight, obesity, and central obesity in women with or without PCOS, the prevalence of overweight, obesity, and central obesity was significantly higher among women with PCOS than in their counterparts without PCOS (Lim et al., 2012). Furthermore, women with upper-body adiposity are at a higher risk of insulin-related metabolic and reproductive disorders such as hyperandrogenemia, anovulation, and dyslipidemia compared to those with lower-body adiposity (Moran et al., 2012; Lim et al., 2012).

It is important to consider the link between insulin resistance and obesity in the diagnosis of PCOS since obesity management plays a vital role in the treatment of this syndrome (Lim et al., 2012). Hence, lifestyle modification (e.g., diet and exercise) is considered the first-line therapy as it reduces the abnormal high plasma androgen level, improves hirsutism symptoms, reduces weight and waist circumference, and lowers the level of insulin resistance among PCOS women (Lim et al., 2012). Apart from the lifestyle modifications, practicing gynecologists usually start their PCOS patients with oral pharmacological agents such as metformin and clomiphene, which lower the level of insulin resistance and induce ovulation (Badawy and Elnashar, 2011). Metformin has been widely used in the management of PCOS and has been showed to be safe and effective (Johnson, 2014). In addition to its efficacy in inducing ovulation among PCOS women, metformin has shown a positive effect when accompanied with an exercise program on body weight, as measured by the waist to hip ratio (WHR) Fux Otta et al. (2010). Furthermore, metformin has been shown to reduce fasting plasma glucose and free testosterone levels, resulting in a significant improvement in the clinical manifestations of hyperandrogenism (Kazerooni and Dehghan-Kooshkghazi, 2003; Farimani Sanoee et al., 2011). The mechanism by which metformin exerts its ovulation stimulatory effect is believed to be through its insulin-sensitizing effect (Katsiki and Hatzitolios, 2010; Franks, 2011). The elevated plasma level of insulin results in a decrease in the synthesis of sex hormone binding globulin (SHBG) and insulin-like growth factor binding protein-1 (IGFBP-1), and an increase in the plasma level of insulin growth factor 1 (IGF-1) (Tock et al., 2014). Both insulin and IGF-1 have a negative effect on the ovaries, resulting in an increase in androgen hormone synthesis as well as the production of immature small ovarian follicles (Tock et al., 2014). Insulin sensitizers such as pioglitazone and metformin enhance the utilization of glucose by improving the peripheral insulin sensitivity, inhibiting the hepatic production of glucose, and increasing skeletal muscles uptake of glucose (Pasquali and Gambineri, 2006).

Interestingly, the efficacy of metformin in improving the metabolic parameters such as the plasma insulin level and in ovulation induction is variable based on the patients' BMI (Badawy and Elnashar, 2011; Johnson, 2014, 2011; Genazzani et al., 2007). In a randomized, double-blind, placebo-controlled, cross-over study that was conducted in Denmark, metformin lowered the testosterone level and increased the insulin sensitivity in only obese women (e.g., BMI $\geqslant 30$ kg/m^2) with PCOS (Trolle et al., 2007). On the other hand, metformin has been shown to be more effective in inducing ovulation among non-obese women in comparison with their obese counterparts in a post hoc analysis of a randomized, multicenter, double-blind, clinical trial that was conducted in the United States (Legro et al., 2007). Moreover, in a study that was conducted in Russia to examine the efficacy of metformin in ovulation induction among anovulatory lean and obese women with PCOS, the lean women had significantly higher rates of menstrual restoration and ovulation in comparison with their obese counterparts (Popova et al., 2011). Whether ovulation induction by metformin is more successful among obese or non-obese women with PCOS in Saudi Arabia, a country where $>30\%$ of women are obese (Memish et al., 2014), remains to be seen. The objective of this study was to compare the rate of ovulation among anovulatory obese and non-obese women with PCOS, who were treated with metformin.

2. Methods

2.1. Study design

This was a retrospective cohort chart review study conducted in the department of obstetrics and gynecology at King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia. The