The current role of metformin in the management of infertility

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In 1935, Drs Irving Stein and Michael Leventhal were the first to report the association of amenorrhoea, hirsutism, obesity, and infertility; a syndrome that is currently known as the polycystic ovary syndrome (PCOS). The PCOS is considered one of the commonest endocrinopathies that affect between 5 to 10 percent of women of reproductive age (1). The syndrome is also the commonest cause of infertility in women as it is estimated that between 15 to 20 percent of infertile women suffer from anovulatory infertility due to PCOS. Although this syndrome has been extensively studied for more than 70 years, its etiology, pathogenesis, clinical presentations, diagnostic criteria, hence its management, are still not clearly understood or universally approved.

Is there an accepted pathogenetic pathway?

Although intraovarian androgen excess is considered the direct cause of anovulation and the polycystic appearance of the ovary; yet the etiological and pathogenetic pathways of the PCOS are still controversial. A lot of mechanisms have been proposed as etiological factors leading to PCOS. Some old theories were ovarian congestion, ovarian dystrophy, thickened tunica albuginea and excessive secretion of androgens by the adrenal gland. More recently many other mechanisms have been implicated in the pathogenesis of PCOS such as abnormal pituitary function, abnormal ovarian steroidogenesis, obesity, and insulin resistance. However, the syndrome is currently seen as a complex genetic disorder, similar to diabetes and metabolic syndrome, in which a variety of predisposing genes interact with environmental factors to produce the disease (2). The involved genes include genes regulating gonadotropin and steroid biosynthesis and action (manifested by elevated LH), weight and energy regulation (manifested by obesity), androgen biosynthesis and action (manifested by ovarian hyperandrogenism), and insulin secretion and action (manifested by hyperinsulinemia) (2). Environmental factors such as diet and its association with obesity may also contribute to the development of the syndrome.

What are the diagnostic criteria of PCOS

The classic criteria for diagnosing PCOS described by Stein and Leventhal were the association of infertility, obesity, hirsutism, and amenorrhoea (1). However, since this classic description a myriad of symptoms and signs were attributed to the syndrome such as menstrual irregularities ranging from amenorrhoea, oligomenorrhoea, to normal cycles, and irregular menstruation, hyperandrogenic manifestations in the form of acne, hirsutism, oily skin, and alopecia, High LH/FSH ratio, obesity either generalized or central adiposity, infertility, recurrent pregnancy loss, and polycystic appearance of the ovaries by ultrasound.

In 1990 National Institutes of Health Conference on PCOS; the presence of three criteria was proposed, at minimum, to diagnose PCOS: a) oligo-ovulation or anovulation, b) clinical or biochemical evidence of hyperandrogenism, and c) exclusion of other causes of hyperandrogenism (3). These criteria also ignored the ultrasonographic appearance of the ovaries.

In 2003, The Rotterdam criteria for diagnosing PCOS have been proposed by the ESHRE/ASRM consensus workshop group (4) in which any two out of three criteria are required to make the
diagnosis: a) oligo-ovulation and/or anovulation, b) clinical and/or biochemical signs of hyperandrogenism, c) polycystic ovaries by ultrasound. This classification included two different groups of patients; patients with polycystic ovaries and hyperandrogenism but with normal ovarian function, and patients with oligo- or anovulation and polycystic ovaries but with no evidence of hyperandrogenism. The two groups might have different etiologies, and prognosis. Thus, the Rotterdam revised criteria are not universally accepted.

In 2006, the Androgen Excess Society proposed the presence of the following 3 diagnostic criteria for the diagnosis of PCOS: a) clinical and/or biochemical hyperandrogenism, b) ovarian dysfunction in the form of oligo-anovulation and/or polycystic ovary appearance), and c) exclusion of other causes of androgen excess or ovulatory disorders.

The running controversy is not settled yet and the diagnosis of PCOS remains controversial.

**Insulin resistance and the PCOS**

Insulin resistance is a state in which a given concentration of insulin is associated with a subnormal glucose response (6). Resistance to endogenous insulin is characterized by a high fasting insulin levels while blood glucose levels are normal or high. There is a strong association between PCOS and insulin resistance. It was found that around 31% (7) to 40% (8) of reproductive age women with PCOS have an impaired glucose tolerance (IGT) and 7.5% (7) to 10% (8) of them have type 2 diabetes. Moreover the annual conversion rate from normal to IGT among women with PCOS was found to be 16% (9). Hyperinsulinemia acts by increasing androgen levels both directly by stimulating androgen synthesis in the ovarian theca cells and indirectly by suppressing the hepatic production of sex hormone binding globulin. Measures to reduce insulin resistance as weight loss, metformin, or thiazolidinedione use are associated with decreased androgen levels in women with PCOS. This response formed a base for the use of metformin in PCOS.

**Metformin: to be used or not to be used?**

Both insulin resistance (manifested as hyperinsulinemia) and increased LH production increase intraovarian as well as peripheral androgen secretion leading to anovulation. There is no consensus among endocrinologists on how to evaluate patients for insulin resistance. Tests to detect insulin resistance are used in scientific research but they are impractical for routine clinical use. Metformin acts by combating hyperinsulinemia leading to decreased androgen levels. The insulin lowering effect of metformin is mainly obtained by its ability to decrease glucose production by the liver and its absorption from the intestine reducing the need for insulin secretion by the pancreas (10). Metformin has also an anti-lipolytic effect reducing circulating free fatty acids and hence gluconeogenesis (11). Unlike sulfonylureas used also to treat hyperglycemia, metformin does not lower blood glucose to hypoglycemic levels either in normal or in diabetic patients.

Metformin is a rather safe drug. Its side effects are diarrhea, nausea, vomiting, flatulence, indigestion, and abdominal discomfort. Its recommended dose is 1500 – 2550 mg (500 - 850 mg bid or tds) preferably with meals to reduce its GIT side effects. Thus metformin use in the treatment of infertility is mainly empirical based on its high margin of safety. To date Metformin is FDA approved only for use in non-insulin dependant diabetes but its use in the treatment of PCOS is “off-label”.

The use of metformin either alone or combined with clomiphene citrate (CC) for the treatment of anovulatory infertility due to PCOS has been widely studied. Although many studies showed an evident benefit for the use of metformin in infertility treatment, yet many of the studies were either uncontrolled, had small numbers of participants or did not have allocation concealment. Also the controversy in the diagnostic criteria of PCOS was reflected on the selection of participants to various studies rendering these studies with heterogeneous populations, thus; combining their results to reach a conclusion is very difficult to accept if not impossible.

A Cochrane systematic review published in 2003 revised 24 randomized controlled trials that studied the effect of insulin sensitizers mainly metformin in the treatment of PCOS (12). Fifteen studies were judged valid to be included in the
review. For infertility treatment; pregnancy is the patient-oriented outcome that matters and that should be looked for. Comparing metformin alone to placebo in 5 studies showed no significant increase in the pregnancy rate in the metformin treated patients. Five trials only compared the use of metformin plus CC versus CC alone and their analysis showed a significantly higher clinical pregnancy rate in favor of adding metformin to CC (Peto OR 4.40, p=0.0003, 95% CI 1.96 to 9.85). However, 4 of the 5 studies included patients who failed to ovulate on CC alone (CC-resistant) and none of the studies considered pregnancy as the primary outcome. Also the total number of participants in the 5 studies was small (219 patients), heterogeneity in the inclusion criteria, as well as the possibility of publication bias limits confidence in this analysis.

In 2006 and 2007, 2 large RCTs have been published that evaluated the use of metformin in the treatment of infertility due to PCOS. What characterized the two studies is that they had high validity, the number of participants in any of them was much higher than the total number of participants in the 5 studies analyzed in the 2003 systematic review, their inclusion criteria matched those of the ESHRE/ASRM 2003 consensus, all the patients were naive patients, other causes of anovulation (or hyperandrogenism) as well as male factor were excluded, and both studies reported pregnancy in their outcomes. The first study included 225 infertile women with chronic anovulation and PCO appearance by US who were randomized into 2 groups to receive either CC plus metformin or CC plus placebo for up to 6 months. The results showed a non significant difference in the pregnancy and abortion rates between the two groups (13). The second study included 626 infertile women with oligomenorrhea and hyperandrogenism who were randomized to receive CC plus placebo, extended-release metformin plus placebo, or a combination of metformin and CC for up to 6 months. The results showed that the live-birth rate was significantly higher (P<0.001) in the CC (22.5%) and the CC plus metformin (26.8%) groups (14).

In conclusion

Current evidence suggests that the use of metformin or the addition of metformin to CC therapy does not increase the chances of pregnancy in infertile women with PCOS. However, the lack of a universal agreement on the criteria of diagnosing PCOS and the lack of a screening procedure for insulin resistance may contribute to this failure. Thus, whether metformin would be helpful in a subgroup of patients who show evidence of insulin resistance or not is not clear yet and awaits further evidence.

REFERENCES

Polycystic ovary syndrome (PCOS) is associated with about 75% of all cases of anovulatory infertility. PCOS is a very heterogeneous syndrome both in its clinical presentation and laboratory manifestations. Hyperinsulinemia is the commonest contributor to the state of anovulation and its reduction, by weight loss or insulin sensitizing agents such as metformin will alone often restore ovulation or will improve results when used in combination with other agents. Insulin is of prime importance in the pathophysiology of PCOS. Women with PCOS exhibit a decrease in insulin sensitivity between 30% and 40%, a deficit similar to that seen in subjects with type 2 diabetes mellitus (1), which means that a very large proportion of cases of anovulation and infertility is associated with hyper-insulinemia and that the lowering of insulin concentration provides a new therapeutic pathway. The indications for the administration of metformin to anovulatory women with PCOS in anovulation induction program have widened, as it seems to be difficult to predict which individuals will respond well with this medication (2).

Metformin, a biguanide, an oral hypoglycemic that does not cause hypoglycemia in normoglycemic patients, is a non-steroidal compound that appears to influence ovarian function both directly and indirectly. It is metformin that has been extensively used in the management of insulin-resistant states and that has been most thoroughly investigated for the management of PCOS. The sum of total of its action is a decrease in insulin levels and, as a consequence, a lowering of circulating total and free androgen levels with a resulting improvement of the clinical sequelae of hyperandrogenism. There is evidence that metformin also has a direct effect on androstenedione and testosterone production by theca cells in vitro by inhibiting the expression of steriodogenic acute regulatory (StAR) protein and 17-alpha-hydroxylase (CYP17) (3). In the last few years a number of mostly uncontrolled short-term studies have assessed the effects of metformin on insulin sensitivity and endocrine profile in women with PCOS. Velazquez et al demonstrated that an improvement in insulin sensitivity induced by 1500 mg of metformin a day for 8 weeks, leads to a favorable change in serum concentrations of androgens, SHBG and gonadotrophins. Metformin resulted in rapid fall insulin and the insulin to glucose ratio, with a concurrent significant decrease in serum concentrations of testosterone (T), free T, DHEAS and androstenedione. As far as gonadotrophin concentrations were concerned, there was a significant decrease in LH concentrations, an increase in FSH and a normalization of the LH: FSH ratio (4). Not all the data, however, have been so encouraging. Two trials with essentially identical recruitment criteria and using slightly higher doses of metformin (850 mg twice and three times a day) over similar lengths of time, showed little or no benefit with respect to insulin metabolism, hormone concentrations or lipid variables (5,6). The reasons for these