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EDITORIAL

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Metformin – Rise and Fall

Oral agents to induce ovulation are the first line therapy for infertile women with polycystic ovarian syndrome (PCOS). The most commonly used drug, clomiphene citrate, leaves us with room for improvement. Ovulation rates of 80% are achieved, but pregnancy rates are close to 40% with clomiphene [1]. The need for an alternative oral ovulation induction agent is robust. It is nearly 30 years since the link between abnormal insulin action in PCOS has been demonstrated [2]. Though peripheral insulin resistance is most evident in obese patients, it is prevalent in lean women with PCOS. The mechanism(s) underlying insulin resistance and reproductive abnormalities in women with PCOS remain unclear [3]. Metformin, a biguanide used as an oral hypoglycemic agent in overweight individuals with diabetes reduces peripheral insulin resistance. This property made it a subject of study and much controversy in women with PCOS.

Basis of metformin use

Metformin acts mainly by decreasing hepatic glucose production. Metformin also improves glucose utilization in the periphery, reduces intestinal glucose uptake, and decreases lipolysis reducing the substrate for gluconeogenesis. Additionally, some evidence has suggested that metformin may act directly to attenuate ovarian steroidogenesis [4]. The role of metformin has been extended to the lowering of ovarian hypersensitivity to insulin. It has also been proposed that metformin may modify some of the defects in the adipose tissue lipolytic cascades or inflammatory mediators (IGF-1, SHBG) which induce peripheral insulin resistance.

Clinical use of metformin

The most physiological approach to lowering insulin resistance and inducing ovulation in women with PCOS is weight loss. This should be an integral part of any treatment program. Metformin is available in both short and long-acting formulations. The short acting formulation comes in 500, 850 and 1000mg tablets and the extended release formulation in 500 and 750 mg tablets. It is recommended to start at a dose of 500 mg with the largest meal and titrate up to the maximum dose over several weeks depending upon patient tolerance. The slow increase in dosage will prevent or minimize the gastrointestinal side effects such as nausea, vomiting, and bloating. In clinical practice, most women will respond to a dose between 1000 and 1500 mg. Though it is uncommon, patients should be given instructions to watch for hypoglycemia. Ideally, renal and liver function should be checked since impairment predisposes to lactic acidosis. For the same reason, women with cardiac failure and pulmonary failure, and those who are alcoholic should be excluded. Therapy has to be continued for 6 to 8 weeks before evaluating results. In case pregnancy has not occurred at the end of this time, additional agents such as clomiphene or letrozole are added to induce ovulation.

Metformin in the literature

The pioneering work of Nestler et al [5] opened the doors for the investigations on metformin as an ovulation induction agent in women with PCOS. In an early study of a small group of women with PCOS who had failed to ovulate in response to 150 mg/day clomiphene, 8 of 11 women ovulated on a regimen of metformin (500 mg 3 times daily) plus clomiphene, whereas only 3 of 14 ovulated on a regimen of placebo plus clomiphene [6]. Subsequently, there have been at least 13 randomized controlled trials involving metformin for ovulation induction in women with PCOS. A metaanalysis of these trials by Lord et al [7] concluded that metformin improved the ovulation rate by about four fold in women with PCOS: the estimated pooled odds ratio was 3.88 (95% CI =2.25 to 6.69) for metformin versus placebo. This has established the superiority of metformin over placebo. When metformin plus clomiphene were compared to clomiphene alone the combination was superior to clomiphene alone (OR 4.41; 95% CI 2.37 to 8.22). The authors of this review further state that metformin should be the agent of first choice for ovulation induction in women with PCOS. This comes as a surprising conclusion especially when the lack of data on long term use, side effects, and longer duration of therapy of metformin are considered.

All clinical trials, including the ongoing ones, must be registered with Clinical Trial Registry of India on www.ctri.in

Until recently, metformin had never been compared with CC in a head-to-head trial of ovulation induction. Such a trial was published recently by Legro et al [8] for the NIH Reproductive Medicine Network. The study divided women to follow three ovulation induction strategies: clomiphene alone, metformin alone, and clomiphene plus metformin. The live birth rates were 22.5%, 7.2% and 26.8% respectively. Metformin did not have a protective effect on miscarriages as the rates of first trimester loss were equal in all groups. Women who ovulated with clomiphene were more likely to have a pregnancy as compared to those who ovulated with metformin. The only result in favor of metformin use was the lower rate of multiple pregnancies in this group.

Metformin - present status

As matters stand today, clomiphene, with its long track record, seems to be superior to metformin for the induction of ovulation in women with polycystic ovaries. It should be the drug of first choice. Metformin may be used as an adjunct in women who are clomiphene resistant. The long term impact of metformin on ovulation is open for investigation since the present trials focus on a short term (4 to 6 months) use. Metformin may also be useful in reducing the risk of ovarian hyperstimulation in PCOS women undergoing IVF [9]. This is an important development since these women are at the highest risk of this problem. It also affords insights into the role of insulin in early follicular recruitment, growth, and vascular development of follicles. In the fertility arena, metformin may prove to be of some benefit, but mainly in association with other forms of treatment.

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