



Metformin for Reproductive Success in Polycystic Ovary Syndrome: Pros and Cons

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Metformin is a commonly used treatment in polycystic ovary syndrome (PCOS), and it is widely believed that metformin improves reproductive outcomes in patients with PCOS. Richard S. Legro, MD, Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA, discussed the pathophysiology of PCOS as well as management of PCOS-associated infertility.

Approximately 80% of women with anovulatory infertility also have PCOS. The original characterization of PCOS noted amenorrhea, hirsutism, hyperandrogenemia, sterility, and large pale polycystic ovaries. Decades later, the previous characteristics are still applicable when making a diagnosis of PCOS, regardless of which criteria is used.

PCOS can be associated with several risk factors for cardiovascular disease, including elevated body mass index, insulin resistance, and elevated lipids, as well as an increase in carotid intimal medial thickness [Talbot EO et al. *Arterio Thromb Vasc Biol* 2000].

There is evidence that treatment of insulin resistance in patients with PCOS can improve symptoms, including infertility. Although treatment with D-*chiro*-inositol and troglitazone increased the rate of ovulation, they have substantial side effects that prohibit their use [Nestler JE et al. *N Engl J Med* 1999; Azziz R et al. *J Clin Endocrinol Metab* 2001]. However, open-label treatment of 26 women with PCOS with metformin was demonstrated to reduce hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, as well as improved

menstruation and rate of pregnancy [Velazquez EM et al. *Metabolism* 1994].

Increasingly, women with PCOS who wish to conceive are referred for *in vitro* fertilization (IVF) therapy, which in turn has resulted in a high rate of multiple pregnancies. Dr. Legro discussed other methods of increasing fertility in women with PCOS. In a highly cited study, metformin plus clomiphene improved the ovulation rate to 90% compared with 8% in patients who received placebo [Nestler JE et al. *N Engl J Med* 1998]. In addition, a randomized study demonstrated that continued therapy with metformin reduced PCOS-related pregnancy complications [Vanky E et al. *Hum Reprod* 2004]. In a more recent study, women with PCOS treated with clomiphene alone had significantly increased rates of live birth compared with patients who received metformin alone ($p < 0.001$) and was not significantly different from a combination therapy with both [Legro RS et al. *N Engl J Med* 2007]. In addition, fecundity per ovulation was greater in patients who received clomiphene compared with metformin. Despite these findings, a meta-analysis found that metformin and clomiphene, as monotherapy or in combination, did not improve the number of live births [Tang T et al. *Cochrane Database Syst Rev* 2012], suggesting that metformin has a limited effect on reproductive outcomes in women with PCOS (Table 1).

Dr. Legro concluded by highlighting several reasons why metformin continues to be used in women with PCOS to improve reproductive outcomes, despite a lack of evidence supporting its use for that indication. He noted that most of the positive studies using metformin used surrogate variables such as ovulation rate, and the initial randomized trials were small and irreproducible. In addition, a safety bias occurs because metformin has a good risk-benefit ratio.

Table 1. Effect of Metformin on Live Births by Women With PCOS

Study	N	Treatments	Results
Palumba et al. <i>JCEM</i> 2006	100	Metformin vs CC	Metformin superior to CC
Moll et al. <i>BMJ</i> 2006	225	CC vs metformin/CC	No benefit of metformin/CC
Legro et al. <i>N Engl J Med</i> 2007	626*	CC vs metformin vs CC/metformin	No benefit of metformin/CC
Mohd Zain et al. <i>Fertil Steril</i> 2008	125	CC vs metformin vs CC/metformin	Clomiphene superior to metformin
Morin-Papunen et al. <i>J Clin Endocrinol Metab</i> 2012	320	Metformin/placebo and then after 3 mos, other treatments	No difference as single agent Metformin beneficial as adjuvant in obese

*Adequately powered and designed to detect differences in live birth rates.

CC=clomiphene; mos=months.

Source: Tang T et al. *Cochrane Database Syst Rev* 2012.