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EDITORIAL COMMENTARY *Infertility*

Metformin as adjuvant therapy to IVF in women with PCOS: when is intention-to-treat unintentional?

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More than 15 years have passed since metformin was hailed as a possible treatment for infertility in women with polycystic ovary syndrome (PCOS) (Velazquez *et al*., 1994). Though a recent Cochrane Systematic review examining metformin for ovulation induction concludes that 'the use of metformin in improving reproductive outcomes in women with PCOS appears to be limited' (Tang *et al*., 2010), the debate over metformin's role in infertility continues passionately. A systematic review is only as good as the studies contributing to it, and there have been multiple critiques of previous randomized trials of metformin in women with PCOS, including an over-representation of obese women, a too short pretreatment period with metformin, possible differences between immediate release and extended release preparations of metformin, and failure to recognize its benefit as an adjuvant therapy for other infertility treatments, for example, IVF/ICSI. Another Cochrane Systematic review of metformin for IVF/ICSI in women with PCOS noted no benefit of metformin on pregnancy rates, but stated 'The risk of ovarian hyperstimulation syndrome (OHSS) in women with PCOS and undergoing IVF or ICSI cycles was reduced with metformin' and recommended further multi-center trials (Costello *et al*., 2006).

In this issue of *Human Reproduction* Kjøtrød *et al.* (2011) have answered the call to provide a multi-center double-blind randomized controlled trial of the use of metformin as an adjuvant to PCOS, as well as identify a population (thin) and a treatment regimen (immediate release metformin given 3 months prior to IVF) that may further increase live birth. This is a well-designed trial, and the best of its kind to date. This tantalizing trial suggests a benefit to metformin in this adjuvant role, but the design and analysis raise as many questions as the study answers. These questions include the use of intention to treat (ITT) analysis for a multi-tiered intervention, the role of IVF in treating anovulatory infertility and the feasibility of randomized trials for a widely popular but unproven adjuvant therapy.

The study of Kjøtrød *et al.* (2011) randomized thin or mildly overweight women (BMI < 28 kg/m^2) with PCOS to either metformin or placebo for 12 weeks before or during IVF/ICSI, and focused on clinical pregnancy rate as the primary outcome. The sample size was well justified based on a pilot trial which had showed a significant benefit to metformin on clinical pregnancy rate (Kjotrod *et al*., 2004). An ITT analysis was planned; i.e. everyone is analyzed according to their initial randomized treatment assignment, whether they receive all of the intended treatment (e.g. IVF) or not. On the basis of the ITT analysis, the addition of metformin significantly improved clinical pregnancy rates. There were 62 pregnancies in 149 subjects, 37/74 (50.0%) in the metformin group and 25/75 (33.3%) in the placebo group. The clinical pregnancy rate was significantly higher in the metformin versus the placebo group, with a difference of 16.7% (95% CI: 1.1–32.3; $P = 0.0391$). At first glance, this is a stunning outcome, and one likely to change clinical practice. However, further analysis shows that the benefit accrued only in the period prior to assisted reproduction; i.e. women assigned to metformin conceived clinical pregnancies prior to assisted reproduction techniques (ART) at about twice the rate compared with placebo (65 versus 35%), whereas clinical pregnancy rates were identical in the subjects who made it to IVF/ICSI (50% in each group). Both clinicians and the tabloids could have a field day with these results depending on how they wanted to spin it.

While a spontaneous conception on metformin without a whiff of IVF in this ITT analysis may count towards an IVF benefit, does it count in the world of common sense? Certainly the *post hoc* poor man's sensitivity analysis (analyzing pregnancies with and without IVF/ICSI), suggests there was no benefit to metformin on IVF/ICSI pregnancy outcomes. The rules in real-time for determining ART pregnancies are often confusing. For example, in the USA, reporting methods for pregnancy rates are mandated by the Society of Reproductive Technology (SART) and overseen by the Centers for Disease Control and Prevention (which is required as a result of the 1992 Fertility Clinic Success Rate and Certification Act to publish the annual ART success rates at U.S. fertility clinics). According to these methods, a pregnancy that occurs in an IVF cycle after start of a GnRH agonist, but before start of gonadotrophins does not count as an ART pregnancy. However, an IVF cycle that is converted to intrauterine insemination and results in pregnancy counts as an ART success. Neither of course involved IVF. In the case of the article of Kjøtrød *et al.* (2011), I do not see the pretreatment period as a continuum to IVF/ICSI, I see it as a separate treatment.

The rationale for adding metformin for a period pre-IVF is that metformin requires some period of time to achieve its maximum benefit before proceeding with the main thrust of the intervention, i.e. IVF/ICSI. While every drug requires some time period to achieve its benefit, the ideal period for metformin to achieve its PCOS benefit is nebulous. Metformin is thought to achieve its maximum glucose lowering effect by 2 weeks, though obviously downstream benefits may take longer. Similarly uncertain is the time needed to achieve its maximum benefit on ovulation in women with PCOS, though judging from the results of this trial, it appears to be fairly quick. In the PPCOS I (Pregnancy in Polycystic Ovary Syndrome I) trial (Legro *et al.*, 2007), there was no time effect to metformin over six cycles in women with PCOS; i.e. they had the same chance of ovulation (and pregnancy) in the first month as any other month, implying that onset of action for this parameter is quick, as supported by this trial.

This trial raises questions about the suitability of IVF/ICSI for this population of lean women with PCOS; it looks like overkill if so many conceived so easily. Though PCOS was the leading indication for IVF/ICSI, more than half of the subjects had other factors, such as male factor or tubal factor to support the use of IVF (See Table 2 of the article). It is uncertain what treatment subjects received prior to participation in the trial (they all had at least 12 months of infertility), but this pundit says if they did this well on metformin alone, perhaps the next trial should look at pretreatment with clomiphene (Tang *et al.*, 2010). Secondary benefits of metformin were not clear from this trial and, in all fairness; the study lacked the power to detect differences in these outcomes. There were equal numbers of cases of OHSS in each group ($n = 5$ in each), and no difference in miscarriages (three with metformin and seven with placebo).

Finally, this trial holds important implications for randomized trials in infertility and in ART. The investigators are to be commended for designing and instituting a larger scale follow-up trial. They could have rested on the laurels of their pilot trial and just uniformly adapted metformin for all future PCOS IVF/ICSI cases. Instead they sought to validate their results. This follow-up trial was powered for 300 total subjects, but only 150 subjects were recruited into the study. The study was terminated early due to the expiration of study medication. The slow recruitment had multiple factors including perhaps too narrow inclusion/exclusion criteria, too few study sites (and difficulties getting willing study sites on board), and also eventually a growing reluctance of subjects to be randomized to metformin, since metformin had in the interim become a common adjuvant therapy for IVF, and no one wanted to miss out on the 'benefit'.

This is a disturbing trend, and a similar multi-center double-blind randomized controlled trial of metformin during pregnancy in women with PCOS was also terminated early due to similar reasons (Vanky *et al.*, 2010), including that the standard of care had switched during the trial to give all women with PCOS metformin during pregnancy. That trial too showed no benefit of metformin on preventing pregnancy complications, and like this trial was preceded by a smaller trial that showed a large treatment benefit (Vanky *et al.*, 2004). Have we come any further in the last 15 years, other than we still tend to place too much value in positive results generated from case series and small randomized trials? Beware the Ides of Metformin much more than those of March! Let us not elevate a halfway proven adjuvant treatment to the standard of care for all women with PCOS undergoing IVF until we have more convincing evidence.

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