

Benefits of metformin in infertility of polycystic ovary syndrome origin

Mohd Ashraf Ganie, Abdul Hamid Zargar

In the pathogenesis of polycystic ovary syndrome (PCOS), insulin resistance has been considered as a characteristic feature that is present in every case be it obese or not. Considering that the obesity is present only in 50-60% of PCOS women, insulin resistance should be regarded as an important feature of this disease. Insulin is directly involved in anovulation, testosterone production and lowering of SHBG.

Metformin and thiazolidinediones which are well characterized insulin sensitizers were studied as possible therapies of clinical manifestations of PCOS including anovulation and infertility. Overall, the results of such studies have been conducted to an optimistic view.

The first study reporting metformin action in PCOS was published in *Metabolism* in 1994(1) but the first real landmark was published in the *N Engl J Med*, in 1998(2) and the results were indeed very promising (24% ovulatory rate compared to 4% in placebo treated cases). Metformin added to clomiphene was certainly even more impressive resulting in 90% ovulatory rate (in comparison to 8% in the clomiphene alone group). Many studies have been done since then and almost all demonstrated increased ovulatory rates with metformin use in PCOS. Besides, metformin effect was proven to occur quickly, i.e., less than 2 months(3,4).

These studies prompted the first review done in 2003 by J. Lord *et al*(3). They concluded as well proven that metformin had a great effectiveness in ovulation induction in PCOS cases (46% vs 24% with placebo). The ovulation attained with metformin and metformin plus clomiphene citrate was 57%. Many of these studies, however, included very few patients and were conducted for very short periods of time(2,5). Increased pregnancy rates, on the contrary, were much more difficult to demonstrate except in the cases that were resistant to clomiphene.

Palomba *et al* reported the results of the first double

blind placebo controlled trial comparing metformin and clomiphene citrate in non-obese PCOS patients, in relation not only to ovulation increment but also and specially in relation to pregnancy rates in PCOS women. Ovulation induction didn't appear to be different between the groups but metformin was superior in terms of achieved pregnancies (15.1% vs 7.2%), lower abortion rate and increased live births(6). Few recent studies demonstrating the great effectiveness of metformin in inducing ovulation concluded that clomiphene citrate was as good if not better inducing ovulation and also in terms of pregnancy rates and live birth rates.

Neveu *et al* studied 154 women with PCOS. In spite of the study period being short, ovulation was 75.4% in the metformin alone group vs 50% in the clomiphene citrate alone group. In the combination group it was 63.4%. Pregnancy rates did not differ between the groups(7). A meta-analysis done by Moll *et al* in 2007 analyzed the results of 27 studies with the primary outcome being live birth rate. There was no evidence for a significant difference in live birth rates between metformin and clomiphene citrate or metformin + clomiphene citrate vs clomiphene citrate alone. In clomiphene citrate-resistant cases, on the contrary, the addition of metformin increased live birth rate (RR=6.4). In IVF the only recognized positive effect of metformin was to reduce the number of hyperstimulation syndrome cases(8).

The PPCOS trial aimed to determine the optimal drug regimen for initiation of ovulation induction in PCOS. This study included 628 patients from 13 centers. Ovulation rate was 29% in the metformin group, 49% in the clomiphene citrate group and 60% in group with metformin + clomiphene citrate. Live birth was 7%, 22% and 26% respectively in those same groups(9).

The new study of Palomba *et al* with a duration of 6 months that demonstrated that ovulation was 55.4% with metformin and 59.8% with clomiphene citrate while

pregnancies 10.8% with metformin vs 11.2% with clomiphene citrate(10).

Patient differences are certainly the most plausible explanation (going from genotype to the presence of obesity, androgen levels, etc). But still there remain many unexplained results. Both Legro's and Palomba's group found that metformin had better results in women with lower BMI. Being an insulin-sensitizing agent wouldn't it be much more logical that it worked better in obese women where insulin resistance is much more marked? Palomba also demonstrated that metformin's positive effects leading to pregnancy occur later than with clomiphene citrate's (median 7 months vs 5 months with clomiphene citrate), in contrast to the induction of ovulation that Lord *et al* reported to be precocious during metformin treatment [2 months](3).

Beyond these controversies and all the study design errors another conclusion should be looked upon carefully: In many of these studies ovulation rates are so high that it raises a question if anovulation diagnosis has been correctly done. Is it that progesterone levels of 4 ng/ml or higher indeed indicate that an ovulation occurred? And if that is correct is it not true that levels between 4 and for instance 8 ng/ml might indicate a worst quality ovulation or a worst capacity to prepare the endometrium to nidification, either way resulting in less capacity to become pregnant?

Another important aspect concerns the diagnosis of PCOS itself. For the diagnosis of anovulation how many cycles should be studied to have a certain diagnosis of anovulation? Many authors don't even confirm anovulation with at least one progesterone level in the luteal phase of the cycle. This may indicate that the women that are being studied by different groups are indeed different from each other, thus explaining the so different results.

Diagnosing PCOS according to the Rotterdam criteria makes this problem even worst allowing the inclusion in PCOS groups, of women that are not anovulatory. In our opinion, ultrasound instead of being used for defining PCOS could become a great help if used serially, as a tool to identify developing follicles up to the point of ovulation and after.

We conclude that metformin has multiple benefits in PCOS women especially in treating fertility. More studies with higher doses may support the view

REFERENCES

1. Velasquez E, Mendoza S, Hamer T, Sosa F, Glueck C. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. *Metabolism*. 1994; 43: 647-654.
2. Nestler J, Jakubowicz D, Evans W, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med*. 1998;338 (26): 1876-1880.
3. Lord J, Flight I, Norman R. Insulin sensitizing drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. *Cochrane Database Syst* 2003; 3: CD003053.
4. Lord J, Flight I, Norman R. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 2003;327:951-953.
5. Ganie MA, Khurana ML, Eunice M, Gulati M, Dwivedi SN, Ammini AC. Comparison of efficacy of spironolactone with metformin in the management of polycystic ovary syndrome: An open label study. *J Clin Endocrinol Metab* 2004;89:2756-2762.
6. Palomba S, Orio F Jr, Falbo A, Manguso F, Russo T, Cascella T, *et al*. Prospective parallel randomized double blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first line treatment for ovulation induction in non-obese anovulatory women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2005; 90: 4068-4074.
7. Neveu N, Granger L, St-Michel P, Lavoie HB. Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction and achievement of pregnancy in 154 women with polycystic ovary syndrome. *Fertil Steril*. 2007;87(1): 113-20.
8. Moll E, van der Veen F, van Wely M. The role of metformin in polycystic ovary syndrome: a systematic review. *Hum Reprod Update* 2007;13(6): 527-37.
9. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, *et al*. Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2007; 356: 551-566.
10. Palomba S, Orio F Jr, Falbo A, Russo T, Tolino A, Zullo F. Clomiphene citrate versus metformin as first-line approach for the treatment of anovulation in infertile patients with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2007; 92(9): 3498-3503.