



Published in final edited form as:

Fertil Steril. 2008 July ; 90(1): 14–16.

Metformin in the Treatment of Infertility in PCOS: An Alternative Perspective

John E. Nestler, M.D.

Departments of Internal Medicine, Obstetrics and Gynecology, and Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA 23298

Narrative Abstract

This editorial discusses the recent ESHRE/ASRM recommendations on the treatment of infertility in PCOS. Evidence is provided for the use of metformin in selected patients.

In 2007, the European Society for Human Reproduction and Embryology (EHSRE) and the American Society for Reproductive Medicine (ASRM) sponsored a workshop to discuss the therapeutic challenges of infertility and the polycystic ovary syndrome (PCOS), out of which a consensus paper emerged (1). The consensus statement offered a bleak view of the use of metformin in infertility, recommending that “metformin use in PCOS should be restricted to women with glucose intolerance.”

In this editorial, I offer a perspective on the use of metformin for the treatment of infertility in PCOS that differs significantly from the consensus statement. My aim is to provide a strategy that addresses the needs not only of the reproductive endocrinologist, whose patients often desire pregnancy immediately, but also the gynecologist, medical endocrinologist and others, whose patients' time lines for achieving pregnancy may lie in the distant future. Taking into consideration the different needs of these patient populations, a rationale for individualized treatments can be formulated, in keeping with the consensus statement that “more patient-tailored approaches should be developed for ovulation induction” (1).

Metformin versus Clomiphene for Induction of Ovulation

The ESHRE/ASRM consensus statement (1) bases its recommendation that use of metformin in PCOS should be restricted to women with glucose intolerance primarily on the findings of two randomized controlled trials that indicated that metformin does not increase live-birth rates above those observed with clomiphene alone (2,3).

To understand these studies and place the role of metformin for the treatment of infertility in PCOS in perspective, it is critical to note the distinctly different pharmacologic characteristics of metformin versus clomiphene, the standard drug for ovulation induction. Clomiphene is specifically a fertility drug that acts directly to induce ovulation by blocking negative feedback on the hypothalamic-pituitary axis and carries up to a 10% chance of multiparity; its onset of

Address all correspondence and reprint requests to: John E. Nestler, M.D., Division of Endocrinology and Metabolism, Medical College of Virginia, P.O. Box 980111, Richmond, VA 23298-0111.

Capsule: Metformin remains an important option for the treatment of infertility in PCOS

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

action is rapid. In contrast, metformin is a drug that affects metabolism and acts indirectly to induce ovulation by reducing the circulating concentration of insulin. Metformin's onset of action is slower and gradual: up to 6 months of treatment with metformin may be needed to clinically improve ovulation (4-7). Given the differences in action and pharmacodynamic properties, clomiphene would be expected to be more effective than metformin in *rapidly* inducing an ovulation in a woman with PCOS, as has been borne out in several studies (2,6, 7).

Does this mean that clomiphene “remains the treatment of first choice for induction of ovulation in anovulatory women with PCOS,” as stated in the ESHRE/ASRM consensus statement (1)? No, because the consensus statement does not include the *type* of infertile woman with PCOS as a critical component of the decision process. Many infertile patients with PCOS who present to reproductive endocrinologists desire pregnancy immediately, and for them time is of the essence. In such women, I concur with the ESHRE/ASRM recommendation that a rapidly acting induction agent such as clomiphene would be most appropriate.

In contrast, medical endocrinologists and many gynecologists often see young patients with PCOS whose time-line for achieving pregnancy differs substantively. These women often present with concerns unrelated to immediate fertility (8) and might seek to postpone pregnancy for one, two, or more years; these women may be quite accepting of a pregnancy when it comes. Such women with longer time lines for achieving pregnancy constitute at least one “well defined subset” for whom metformin, with its gradual onset of action minus the potential risk of multiparity, may be the drug of choice to reestablish ovulatory menses and fertility.

As documented in a recent meta-analysis (9) of 17 rigorously conducted studies performed between 1996 and 2007 that included 1,639 subjects, ovulation is improved in many women with PCOS when treated with metformin. Clinical experience from an academic center suggests that menstrual cyclicality and ovulation improve in approximately 69% of women with PCOS treated with metformin, with 88% of responders achieving normal menstrual cyclicality (5). If that is the case, why expose a woman with PCOS with a longer time line for pregnancy to the risk of multiparity associated with clomiphene, when institution of regular ovulation with metformin might improve fertility and result in a singleton pregnancy? After all, if after 6 or more months of treatment with metformin ovulation has not improved, treatment with clomiphene remains an option.

Addition of Metformin to Clomiphene for Ovulation Induction

In women with PCOS who desire a pregnancy in short order, more problematic is the question of whether metformin should be added to clomiphene. The ESHRE/ASRM consensus report states that “there is now clear evidence that the addition of metformin...to clomiphene citrate as primary therapy for induction of ovulation has no beneficial effect” (1), again based on two randomized controlled trials (2,3). I would question this assertion. It is noteworthy that a meta-analysis (9) published after the consensus paper, which includes the studies cited in the consensus paper as well as other well-designed studies, reported that the addition of metformin to clomiphene significantly increased both the ovulation rate and pregnancy rate in women with PCOS, and “showed a favorable effect of the combination therapy over clomiphene alone for live births” that was not statistically significant.

Since the main evidence cited by the consensus paper to support its negative position on the addition of metformin to clomiphene are the results of the recent Pregnancy in Polycystic Ovary Syndrome (PPCOS) Trial (2), a few comments are in order. In the PPCOS Trial, adding metformin to clomiphene increased the cumulative ovulation rate from 49.0% to 60.4% (clomiphene alone versus the combination of the two drugs, respectively; $P=0.003$), thus *confirming* the beneficial effect of metformin on ovulation induction with clomiphene

originally reported in 1998 (10). The improvement in ovulation rate was not associated with a statistically significant increase in the live birth rate (22.5% with clomiphene alone versus 26.8% with a combination of the two drugs; $P=0.31$). However, the PPCOS Trial was powered to detect an absolute difference in live birth rate of 15% between the clomiphene alone and combination groups; therefore, the 4.3% higher live birth rate in the combination group may have represented a true benefit of metformin that the study was underpowered to detect.

One is compelled to ask: why would the addition of metformin to clomiphene increase the cumulative ovulation rate but not the live birth rate? While there are several possibilities, a straightforward explanation is the fact that not every cycle of ovulation induction is equivalent. Induction with clomiphene often results in the recruitment and ovulation of multiple follicles per cycle, whereas induction with metformin typically results in ovulation of a single follicle per cycle. Ovulation of multiple follicles per cycle increases the odds of conception, but at the risk of multiparity. This idea is supported by the observation that in the PPCOS Trial the multiparity rate was 6% (including one set of triplets) in the clomiphene alone group compared with a rate of 0% in the metformin group. Interestingly, the multiparity rate in the combination group was intermediate at 3%, suggesting that the addition of metformin to clomiphene may have reduced the number of follicles recruited per cycle, without adversely affecting the live birth rate because of the increase in cumulative ovulations. Unfortunately, ultrasounds were not obtained in the study, and the possible utility of adding metformin to clomiphene to decrease multiple births remains untested and speculative.

Pre-treatment with Metformin prior to Ovulation Induction with Clomiphene

Finally, for those women with a short-term but not immediate desire for pregnancy, consideration should be given to *pre-treatment* with metformin prior to adding clomiphene as appropriate (10). This scenario was not described in the consensus paper but warrants discussion and indeed study given the absence of data on metformin pre-treatment (11).

This approach may offer two advantages. First, since the onset of action of metformin is gradual, pre-treatment with metformin for 2 or more months prior to adding clomiphene may be associated with higher rates of ovulation and live birth than when metformin and clomiphene are instituted simultaneously.

Second, a major problem of pregnancy in PCOS is that the women are frequently obese, decreasing the efficacy of clomiphene (12) and increasing the risks of pregnancy-related complications, such as gestational diabetes and preeclampsia. While controversial (13), metformin may facilitate weight loss in some women (14,15), especially when coupled with diet and exercise (16,17). Pre-treatment for several months with the combination of metformin, calorie-restricted diet, and exercise may result in thinner patients in whom induction of ovulation with clomiphene is likely to be more successful and in whom the risk for pregnancy-related complications has been reduced (18).

Summary

Given the above observations, I suggest that metformin remains an important therapeutic option in the pharmacologic treatment of infertility in PCOS, and its use should not be restricted to women with glucose intolerance, as recommended by the ESHRE/ASRM consensus statement. Taking into consideration the different time lines for achieving pregnancy among women with PCOS, I would suggest the following:

- In women with PCOS for whom time is of the essence and rapid establishment of pregnancy is desired, clomiphene should be the first-line agent. The addition of

metformin to clomiphene has been shown to increase the cumulative ovulation rate, but it remains unclear whether it increases the odds of a live birth.

- In women with PCOS for whom pregnancy is a goal at a more distant time (>6 months), initial treatment with metformin, combined with diet and exercise, is an option to induce ovulation. An advantage of achieving pregnancy with metformin versus clomiphene in this situation may be a decrease in the risk of multiparity.

Infertility treatment needs to be individualized, and these recommendations attempt to take into account the needs and preferences of patients with PCOS, who may differ with respect to the urgency of achieving pregnancy and the willingness to risk multiparity. They also recognize continuing uncertainties in the field that warrant continued investigation.

Acknowledgements

Supported by NIH grants R01HD35629, K24HD40237, U54HD034449, and D43TW007692

References

1. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. *Fertil Steril* 2008;89(3):505–522. [PubMed: 18243179]
2. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med* 2007;356(6):551–566. [PubMed: 17287476]
3. Moll E, Bossuyt PM, Korevaar JC, Lambalk CB, Van D V. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. *BMJ* 2006;332(7556):1485–1490. [PubMed: 16769748]
4. Baillargeon JP, Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Nestler JE. Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. *Fertil Steril* 2004;82:893–902. [PubMed: 15482765]
5. Essah PA, Apridonidze T, Iuorno MJ, Nestler JE. Effects of short-term and long-term metformin treatment on menstrual cyclicality in women with polycystic ovary syndrome. *Fertil Steril* 2006;86(1):230–232. [PubMed: 16716324]
6. 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. [PubMed: 17595241]
7. 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 nonobese anovulatory women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2005;90(7):4068–4074. [PubMed: 15840746]
8. Nestler JE. Metformin for the treatment of the polycystic ovary syndrome. *N Engl J Med* 2008;358(1):47–54. [PubMed: 18172174]
9. Creanga AA, Bradley HM, McCormick C, Witkop CT. Use of Metformin in Polycystic Ovary Syndrome: A Meta-Analysis. *Obstet Gynecol* 2008;111(4):959–968. [PubMed: 18378757]
10. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med* 1998;338:1876–1880. [PubMed: 9637806]
11. Sinawat S, Buppasiri P, Lumbiganon P, Pattanittum P. Long versus short course treatment with Metformin and Clomiphene Citrate for ovulation induction in women with PCOS. *Cochrane Database Syst Rev* 2008;(1):CD006226. [PubMed: 18254096]
12. Lobo RA, Gysler M, March CM, Goebelsmann U, Mishell DR. Clinical and laboratory predictors of clomiphene response. *Fertil Steril* 1982;37:168–174. [PubMed: 7199484]
13. Dunaif A. Drug insight: insulin-sensitizing drugs in the treatment of polycystic ovary syndrome--a reappraisal. *Nat Clin Pract Endocrinol Metab* 2008;4(5):272–283. [PubMed: 18364705]

14. Golay A. Metformin and body weight. *Int J Obes (Lond)* 2008;32(1):61–72. [PubMed: 17653063]
15. Harborne LR, Sattar N, Norman JE, Fleming R. Metformin and weight loss in obese women with polycystic ovary syndrome: comparison of doses. *J Clin Endocrinol Metab* 2005;90(8):4593–4598. [PubMed: 15886247]
16. Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, et al. Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2000;85(8):2767–2774. [PubMed: 10946879]
17. Gambineri A, Pelusi C, Genghini S, Morselli-Labate AM, Cacciari M, Pagotto U, et al. Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2004;60(2):241–249. [PubMed: 14725687]
18. Barbieri RL. Clomiphene versus metformin for ovulation induction in polycystic ovary syndrome: the winner is *J Clin Endocrinol Metab* 2007;92(9):3399–3401. [PubMed: 17823274]