

FERTILITY

- Metformin as frontline treatment for ovulation induction and other PCOS-related disorders
- New PCOS diagnostic criteria

It seems that most advances in the field of infertility entail high-tech, high-risk therapies and expensive diagnostics that are the domain of subspecialists. But this year brought compelling evidence of a better “low-tech” treatment for a common dilemma that has challenged generalists and subspecialists alike for decades: PCOS-related infertility.

A more effective primary-care based strategy is all the more welcome because the difficulties encountered in helping women with PCOS achieve pregnancy have prompted many generalists to routinely refer these patients to subspecialty care.

Try metformin first for PCOS-related infertility

Palomba S, Orio F Jr, Falbo A, 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;90:4068–4074.

This study heralds a shift away from our typical approach. It argues that a trial of metformin for up to 6 months prior to an alternative strategy is very reasonable, and easily managed by any ObGyn.

There’s more: The same new findings that generalists can apply to management of infertility also apply to other PCOS-caused problems: abnormal bleeding, obesity, and cosmetic concerns.

The new research on PCOS also points out our need to stay up-to-date on the current definition and diagnostic criteria for PCOS—both have changed within the past 2 years.

In addition, as a follow-up to my comments in this column a year ago: new and exciting information on oogonial stem cells, though not of immediate clinical utility, may nevertheless be of interest for patients who desire to preserve their fertility.

Metformin has been utilized increasingly over the past decade to improve ovulation and conception rates in women with PCOS who wish to conceive. Traditionally, primary therapy has involved ovulation induction, initially with

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clomiphene citrate, frequently followed by gonadotropins due to failure of the initial therapy. Palomba and colleagues conducted the first well-designed, well-controlled head-to-head trial of metformin versus clomiphene citrate as frontline therapy to induce ovulation.

A total of 100 women with nonobese PCOS were randomly assigned to metformin (850 mg twice a day) or clomiphene citrate (150 mg on days 3–7 of each cycle) for 6 months. The main outcome measures were ovulation, pregnancy, abortion, and live-birth rates. More than 200 potential conception cycles were studied in each group.

Although metformin and clomiphene resulted in statistically similar rates of ovulation in the treatment groups (about 2 out of 3 cycles), there was a big difference in the pregnancy rates. The per-cycle pregnancy rate was twice as high in the metformin group (15.1% vs 7.2%, $P=.009$). The cumulative pregnancy rate was also far higher in the metformin group (68.9% vs 34.0%, $P<.001$), and the abortion rate was much lower (9.7% vs 37.5%).

Metformin's benefits increase over time

Equally interesting was the progressive increase in both ovulation and conception rates in the metformin group during the course of the 6-month trial, compared with a progressive decrease in both the ovulation and conception rates in the clomiphene group—suggesting a cumulative benefit with ongoing metformin therapy. Although the trial was conducted in nonobese PCOS patients, it is reasonable to extrapolate the approach to the larger subgroup of women with PCOS who are obese.

Side effects. Metformin is relatively safe and well tolerated, except for a small percentage of women with intractable gastrointestinal (GI) side effects. The risk of multiple gestations does not increase.

■ Metformin for hirsutism and abnormal bleeding

While the Palomba study deals specifically with treatment of PCOS to induce pregnancy, the metabolic implications of inducing normal ovulation make this strategy applicable to the treatment of PCOS in women who are not attempting conception. It now appears reasonable to consider the use of metformin to help manage other issues such as hirsutism and abnormal bleeding, particularly when more conventional therapies have been insufficient.

■ Treatment tips

I now use metformin as first-line therapy in all patients with a confirmed diagnosis of PCOS regardless of the reason for therapy.

- Minimal pretreatment screening is appropriate to rule out thyroid or pituitary disorders, unsuspected renal disease, or actual diabetes mellitus.
- I titrate the dose over several weeks from an initial 500 mg daily with food to a target of 1,500 mg daily to help reduce GI symptoms.
- I prefer the extended-release preparation for its ease of use and (anecdotal-ly) fewer side effects.

When to start additional therapy. If regular menses do not occur within 3 months on metformin alone, I add additional therapy as indicated.

A new way to define PCOS

Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril.* 2004;81:19-25.

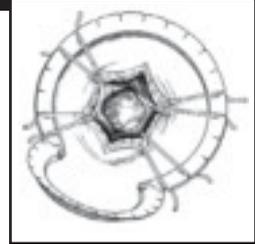
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The addition of ultrasonographic criteria for the diagnosis has effectively nearly doubled the prevalence of PCOS in the United States—and justifies the use of ultrasound to make the diagnosis.

In conjunction with the shift toward metformin as first-line therapy for ovulation induction in women with PCOS, it is important that ObGyns incorporate the latest clinical criteria for the diagnosis of PCOS.

■ 3 clinical indicators

The “Rotterdam Criteria” from the 2003 Consensus Conference require 2 out of 3 clinical indicators to make the diagnosis:

1. **Oligo- or anovulation,**
2. **Clinical and/or biochemical signs of hyperandrogenism, and**
3. **Polycystic ovaries as evidenced on ultrasound or histology.** Ultrasound criteria for polycystic ovaries are specific: increased stroma-to-follicle ratio with multiple subcapsular early antral follicles.

It is also important to note that the diagnosis is primarily clinical, not biochemical, thereby shifting the emphasis to history, physical examination and ultrasound. It also requires the exclusion of other endocrinologic diseases such as thyroid or prolactin disorders, Cushing’s syndrome, or adult onset congenital adrenal hyperplasia.

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■ When to use ultrasound in the diagnosis of PCOS

If you suspect PCOS but the patient has only oligo/anovulation or evidence of hyperandrogenism, it is quite reasonable to use vaginal ultrasound to establish the diagnosis, if the strict sonographic criteria are met.

If she has both oligo/anovulation and evidence of hyperandrogenism, however, the diagnosis is established and ultrasound is not necessary.

More promise for fertility preservation

Johnson J, Bagley J, Skaznik-Wikiel M, et al. Oocyte generation in adult mammalian ovaries by putative germ cells in bone marrow and peripheral blood. Cell. 2005;122:303–315.

For women interested in preserving their fertility, this finding suggests the possibility of harvesting and storing oogonial stem cells from a simple blood draw.

In a follow-up from Jonathan Tilly’s lab as reported in this column last year, this paper describes the latest advance in the oogonial stem cell story. The authors report that both bone marrow transplantation and peripheral blood transplantation restored oocytes in the ovaries of mice sterilized with chemotherapy. While

the reproductive competence of the restored oocytes has not yet been determined, these findings suggest that germ line stem cells may reside in bone marrow and circulate in the blood stream.

Although a great deal of work is required to verify these findings and demonstrate them in humans, they highlight the astounding progress in the field of stem cell biology and emphasize the promise for fertility preservation in the future. ■

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If a patient has oligo/anovulation, or evidence of hyperandrogenism, it is reasonable to use ultrasound to identify PCOS