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Decline of clomiphene for PCOS-related infertility

Metformin and aromatase inhibitors may promise fewer spontaneous abortions and multiple gestations

FAST TRACK

A randomized trial found a higher pregnancy rate and lower abortion rate with metformin

For decades clomiphene citrate has been the first-line agent for ovulation induction in women with PCOS, but evidence is accumulating that metformin and aromatase inhibitors are superior.

Metformin effective as first-line agent

Based on consistent clinical trial results, many specialists now use metformin as the first-line agent for anovulatory infertility in women with PCOS.

Metformin is a biguanide antihyperglycemic approved for management of diabetes mellitus. It is an insulin sensitizer that suppresses hepatic glucose output, decreases intestinal absorption of glucose, and increases insulin-mediated glucose utilization in peripheral tissues. Metformin reduces circulating testosterone and insulin, and is often associated with resumption of ovulation in oligomenorrheic women with PCOS.[1] Major side effects include diarrhea, nausea or vomiting, flatulence, indigestion, and abdominal discomfort. About 10% to 20% of patients discontinue metformin because they cannot tolerate these effects.

A meta-analysis of more than a dozen randomized clinical trials found metformin superior to placebo, and metformin plus clomiphene superior to clomiphene plus placebo for ovulation induction.[2]

A recent randomized trial found a higher pregnancy rate and lower abortion rate with metformin than with clomiphene.[3] Nonobese women with PCOS, defined by the presence of oligomenorrhea and hyperandrogenism, were randomized to metformin 850 mg twice daily for 6 months or clomiphene 150 mg for cycle days 3 to 7 each month for 6 months. After 6 months, the cumulative pregnancy rate was 69% (31/45) in the metformin group and 34% (16/47) in the clomiphene group. The rate of spontaneous abortion was significantly greater with clomiphene than with metformin (38% vs 10%, $P<.05$). The authors concluded that 6 months of metformin was more effective than 6 cycles of clomiphene. Others have also reported fewer spontaneous abortions with metformin than with clomiphene.[4,5] Many experts suggest that women who become pregnant while taking metformin should continue the metformin through the first trimester to reduce risk of spontaneous abortion, and then discontinue the medication so that they can be tested for gestational diabetes.

Aromatase inhibitors promising

If randomized trials confirm that aromatase inhibitors induce ovulation in these patients, and are associated with fewer multiple gestations and spontaneous abortions than clomiphene, the use of clomiphene is likely to decline.

Aromatase inhibitors are approved for treatment of hormone-sensitive breast cancer. Aromatase inhibitors block conversion of androstenedione to estrone and reduce circulating estradiol levels. When given to women with PCOS for cycle days 3 to 7, the reduction of circulating estradiol causes an increase in pituitary secretion of follicle-stimulating hormone, resulting in follicular growth in many women. The agents often

used in breast cancer treatment include letrozole 2.5 mg daily, anastrozole 1 mg daily, and exemestane 25 mg daily.

Although few randomized trials have been reported on the efficacy of aromatase inhibitors for the treatment of PCOS, cohort studies and clinical experience clearly indicate that, when given for cycle days 3 to 7 after a progestin-induced withdrawal bleed, they often cause ovulation in oligomenorrheic women with PCOS.

One randomized trial found both letrozole and anastrozole effective in women with PCOS who had not become pregnant with clomiphene.[6] The women were randomized to either letrozole 2.5 mg daily or anastrozole 1 mg daily, for cycle days 3 to 7. The ovulation rate was significantly higher in the letrozole group (84% vs 60%, $P<.05$) and the pregnancy rate was also higher in the letrozole group (27% vs 17%).

To date, no randomized clinical trial has reported on the efficacy of clomiphene versus aromatase inhibitors for ovulation induction in women with anovulatory infertility caused by PCOS. Cohort studies report that multiple gestation occurs less in pregnancy induced by aromatase inhibitors compared to clomiphene,[7] and spontaneous abortion may occur less often in pregnancy resulting from aromatase inhibitors compared with clomiphene.[8]

Newborn and childhood outcomes

A major deficit in the literature on ovulation induction with metformin and aromatase inhibitors is the relatively small number of studies on newborn and childhood outcomes. However, from the limited data available, clomiphene treatment appears to be associated with a higher rate of multiple gestation than either metformin or aromatase inhibitors.

If this finding is accepted as true, and given the strong relationship between multiple gestation and adverse pregnancy outcome, it is likely that metformin and aromatase inhibitors will be associated with better overall newborn and childhood outcomes than clomiphene.

Stepwise treatment options

For the treatment of anovulatory infertility caused by PCOS, lifestyle changes that normalize body mass index are clearly preferable to pharmacologic therapy because weight loss is associated with many health benefits. For example, pregnancy in women with normal body mass index is associated with better outcomes than pregnancy in obese women.

If pharmacologic therapy is chosen:

- Metformin is probably the agent of choice.
- If metformin is not effective as a single agent, an aromatase inhibitor might be considered.
- Alternatively, clinicians might continue to use clomiphene as a first-line agent if they prefer to utilize an FDA-approved medication for ovulation induction.

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FAST TRACK

For PCOS-related anovulatory infertility

- Try metformin
- If not effective, consider an aromatase inhibitor
- Alternatively, use clomiphene first

REFERENCES

1. Barbieri RL. Metformin for the treatment of polycystic ovary syndrome. Obstet Gynecol. 2003;101:785–793.
2. Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database Syst Rev. 2003;(3):CD003053.
3. 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.
4. Glueck CJ, Phillips H, Cameron D, Sieve-Smith L, Wang P. Continuing metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first-trimester spontaneous abortion: a pilot study. Fertil Steril. 2001;75:46–52.
5. Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. J Clin Endocrinol Metab. 2002;87:524–529.
6. Al-Omari WR, Sulaiman WR, Al-Hadithi N. Comparison of two aromatase inhibitors in women with clomiphene-resistant polycystic ovary syndrome. Int J Gynaecol Obstet. 2004;85:289–291.
7. Mitwally MF, Biljan MM, Casper RF. Pregnancy outcome after the use of an aromatase inhibitor for ovarian stimulation. Am J Obstet Gynecol. 2005;192:381–386.
8. Al-Fozan H, Al-Khadouri M, Tan SL, Tulandi T. A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. Fertil Steril. 2004;82:1561–1563.