Can ovulation induction be accelerated in women who have PCOS-related infertility?

Yes This study describes a "stair-step" protocol that incorporates early ultrasonography to determine whether clomiphene (Clomid) has been effective at stimulating ovulation in infertile women who have polycystic ovary syndrome (PCOS). If it has not been effective, the dosage of clomiphene is immediately increased, bypassing progestin administration and a withdrawal bleed.

Among women treated with this protocol, 74% ovulated at a clomiphene dosage of 100 or 150 mg, compared with the 35.5% ovulation rate associated with these dosages using the traditional progestin-withdrawal protocol.

Hurst BS, Hickman JM, Matthews ML, Usadi RS, Marshburn PB. Novel clomiphene "stair-step" protocol reduces time to ovulation in women with polycystic ovarian syndrome. Am J Obstet Gynecol. 2009;200:510.e1–510.e4.

FAST TRACK

A 28-day clomiphene dosage-escalation method in a series of 31 women with PCOS produced a 74% ovulation rate, compared with 34% among women using the traditional 89-day protocol

EXPERT COMMENTARY

Richard S. Legro, MD, Professor of Obstetrics and Gynecology, Penn State College of Medicine, Hershey, Pa.

Polycystic ovary syndrome is the most common cause of anovulatory infertility, and expert consensus points to clomiphene as first-line therapy.[1]

Under the conventional protocol, clomiphene is given early in the follicular phase, with midluteal monitoring for ovulation. If ovulation is not detected, progestin is administered to induce a withdrawal bleed, and the dosage of clomiphene is increased in the next cycle. Under this protocol, the clomiphene regimen can last as long as 90 days.

Hurst and colleagues propose a 28-day dosage-escalation method, relying on earlier ultrasonography to document follicular development and, in its absence, immediately "rechallenging" the patient with a higher dosage of clomiphene (**FIGURE**, page 22). They present intriguing data from a small, preliminary case series of 31 subjects who used this stair-step protocol. Seventy-four percent of these women ovulated by the end of the 28-day monitoring period, compared with 34% in 89 days among a historical control group using the traditional protocol.

Although a single stair-step cycle was more expensive than a traditional cycle, it has the potential to be less expensive when the rate of ovulation is taken into account.

Accelerated regimen may have a number of negatives

At first glance, what's not to like about a protocol that increases the likelihood of ovulation with significant savings in time and cost for the patient?

First, there are methodologic concerns when a control group is not studied by means of a randomized, controlled trial—or even at the same center as the treatment arm—but is merely created from published data from a textbook.

Second, the goal of infertility therapy is live birth, not ovulation. Our studies have demonstrated significant differences in fecundity for each successful ovulation using different medications, suggesting that not

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Before we rush to adopt this accelerated regimen, we need studies that better address the maternal–fetal risk–benefit ratio. However, this study does provide evidence that a progestin withdrawal bleed is not mandatory in the nonresponder.

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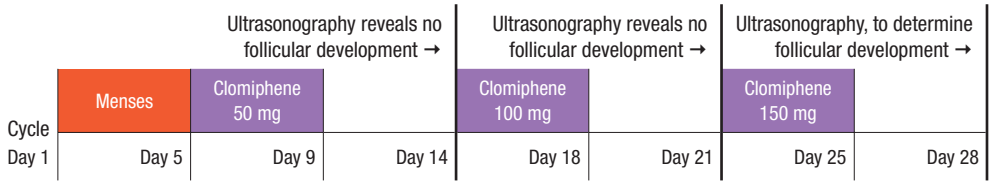
FIGURE Stair-step clomiphene protocol skips progestin administration



every ovulation is the same.[2] In the study by Hurst and colleagues, fecundity (live birth by ovulation rate) was 13%, compared with 10% using clomiphene in our large, multicenter trial—not much of an improvement, although, admittedly, the study by Hurst and colleagues was underpowered to address this question.[2]

Third, there are concerns about potential adverse effects of the accelerated clomiphene regimen on the patient or fetus. Clomiphene has a prolonged half-life of 5 to 7 days, with some metabolites persisting for months. What are the cumulative effects of such aggressive dosage escalation over such a short period of time?

The current Clomid package insert recommends a maximum dosage of 500 mg/cycle. A nonresponder in the stair-step protocol could consume 1,500 mg of clomiphene over a 20-day period.

Hurst and colleagues do not mention side effects, but it would be reasonable to expect an increased rate of hot flashes or mood changes. And what about more concerning signs such as visual changes?

Although clomiphene has no known human teratogenic effects (it is listed as pregnancy category "X"), the stair-step protocol could theoretically produce higher levels of fetal metabolites during the period of organogenesis, with unknown effects.

References

1. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril. 2008;89:505–522.

2. Legro RS, Barnhart HX, Schlaff WD, 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.

FAST TRACK

The Clomid package insert recommends a maximum dosage of 500 mg/cycle, but a nonresponder in the accelerated protocol could consume 1,500 mg over 20 days

Does US measurement of cervical length to determine the need for cerclage reduce preterm delivery?

No This randomized, controlled trial of cervical ultrasonographic (US) scanning versus history to determine the need for cerclage found no reduction in the rate of preterm delivery (i.e., delivery before 34 weeks' gestation) among high-risk women who underwent US imaging. Women who were offered US surveillance were more likely to receive a cerclage and to spend more time in the hospital than women who had a cerclage placed on the basis of history alone. However, there was no improvement in gestational age at delivery in the group that underwent US scanning.

Simcox R, Seed PT, Bennett P, Teoh TG, Poston L, Shennan AH. A randomized controlled trial of cervical scanning vs history to determine cerclage in women at high risk of preterm birth (CIRCLE trial). Am J Obstet Gynecol. 2009;200:623.e1–623.e6.

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FAST TRACK

Women who underwent cervical-length measurement via ultrasonography were more likely to receive a cerclage, but had no improvement in the preterm delivery rate

▸ **EXPERT COMMENTARY**

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This methodologically rigorous trial explored the utility of US imaging versus history in establishing the "need" for cervical cerclage. I have deliberately placed the word "need" in quotations because, as yet, the efficacy of cerclage under any circumstances has yet to be definitively established.

In their discussion of the findings, Simcox and colleagues assert that a trial to settle the questions frequently raised in the cerclage debate would require thousands of patients and may not be feasible.

Rigorous trial is impressive, but doesn't settle key questions

The authors performed an excellent randomized, controlled trial, and their intention-to-treat analysis is laudable. They are also to be congratulated for remaining focused on the primary outcome of delivery before 34 weeks' gestation. It is notable that the primary outcome was essentially the same in each group, regardless of the treatment, be it **1)** US screening and cerclage for cervical length <20 mm or **2)** no screening and cerclage for historical indications. I recall a conference on prematurity from the mid-1980s that included, as one of its conclusions, the observation that as many as 70% of patients who have historical "indications" for cerclage will deliver at term in their next pregnancy if left untreated.

Unresolved questions in regard to cervical cerclage include:

- What is the best way to determine who is a candidate?
- What is the best type of cerclage?
- What is the most appropriate outcome to be measured?
- Is there a place in practice for "universal" screening of cervical length?
- What is the true cost (in terms of both dollars and morbidity) of intervention versus no intervention?
- What are the medicolegal implications of each approach?

This study by Simcox and colleagues settles none of these questions.

High-risk women may benefit from US imaging, but the data from this study do not support that conclusion. Nor is the best type of cerclage defined, though there is ample opinion on this topic.

Is 34 weeks' gestation the appropriate primary outcome? More and more, we read about late preterm or so-called near-term outcomes being less optimal than they once were thought to be—though delivery at 34 to 37 weeks would seem to be preferable to delivery at less than 34 weeks.

The cost of each approach is unclear. How many "unnecessary" cerclages would be needed to prevent one very-low-birth-weight delivery? And how "risky" is elective cerclage placement in skilled hands?

Finally, not many patients or physicians are likely to want to embrace a wait-and-see approach if they have already had one or more adverse outcomes, and the risk of doing nothing may be considerably greater in medicolegal terms than the risk of proceeding with what may be an unnecessary intervention that ends in a term or near-term delivery.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

On the basis of these results, I think the practitioner should rely on history to make a clinical judgment about the need for cerclage. Ultrasonographic imaging may not only be of little help, but it may lead to greater intervention than would otherwise be needed. Perhaps a return to clinical basics, such as detailed history taking and physical examination, is a good message for these economic times.

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Infertility: Women with PCOS have irregular menstrual cycles. They also may not release an egg (ovulate) with each menstrual cycle. Combined, these factors can lead to a woman with PCOS having difficulty falling pregnant. Obesity and insulin resistance: Approximately 50% of women with PCOS suffer from obesity.Â This risk is particularly high in women who have a first degree relative with diabetes. There is a genetic link between PCOS and diabetes. Other possible clinical manifestations of PCOSÂ Infertility: In most patients with PCOS, infertility is due to ovulatory failure (failure of the ovary to release an egg each month). Treatment is therefore directed at inducing regular ovulation. In most cases, fertility problems in women with polycystic ovary syndrome (PCOS) result from the absence of ovulation (anovulation), but anovulation may not be the only reason for these problems.Â If you have PCOS-related infertility, your health care provider may prescribe one of the following medications to help you get pregnant. Clomiphene (pronounced KLOM-uh-feen), or clomiphene citrate.Â Women who conceive with the aid of clomiphene are slightly more likely to have multiples, most commonly twins.7. Metformin (pronounced met-FAWR-min). Although this insulin-sensitizing drug is normally used to treat diabetes, it may also be used as an adjunct to increase or regulate ovulation in women with PCOS. Ovulation induction is the process of using medications to stimulate ovulation in women who have irregular or absent ovulation (anovulation). According to the National Institutes of Health, 25 to 30 percent of women with infertility have problems with ovulation.Â Ovulation induction is usually one of the first treatments used for infertility because it is noninvasive and relatively low cost compared with other fertility treatments, such as IVF that includes costs of tests, medications, minor procedures and lab work. For more severe cases of anovulation or other causes of infertility, ovulation induction can also be an effective treatment in conjunction with IVF, intrauterine insemination (IUI) and other holistic treatments. Side nav 1. Treatment & Testing.