Lessons from low-dose gonadotropin therapy for ovulation induction in polycystic ovary syndrome: Can prolonged letrozole therapy eliminate failure to respond to oral ovulation agents?

The initial cost-effective approach to ovulation induction in anovulatory patients with polycystic ovary syndrome (PCOS) involves oral administration of medications. Historically, clomiphene citrate was the first orally active agent used for ovulation induction. This selective estrogen receptor modulator was traditionally used for a duration of 5 days. The interval of 5 days was chosen arbitrarily but was found to be effective in most cases and continues to be used to this day. However, not all patients with PCOS achieve ovulation after 5 days, even with high doses. The concept of extending the duration of therapy was first reported more than 40 years ago (1). An extended regimen of 8 days for patients who failed to ovulate with 5 days of therapy was found to be effective in more than 50% of cases (1). However, in most cases, patients who failed to respond to clomiphene were treated with gonadotropins. Standard dosing of follicle-stimulating hormone (FSH) risked multiple gestations and ovarian hyperstimulation syndrome. Accordingly, several groups advocated a low-dose approach (2,3).

In the low-dose regimen, FSH (alone or in combination with luteinizing hormone) was administered at a low dose, typically 53.5–75 IU daily, and maintained for up to 14 days before increasing the dose by 37.5 IU (half of a 75 IU ampule) daily. The dose was increased by 37.5 IU every 7 days until a follicle of >12 mm was observed (2,3). Thereafter, the same dose was continued until the lead follicle achieved a size of 18 mm, which is when a human chorionic gonadotropin trigger was administered. This was an intentionally low dose of FSH, and its use required patience because, in many cases, no response was observed for several weeks. The low-dose approach was successful in that approximately 80% of cycles were ovulatory. Importantly, most ovulatory cycles had a monofollicular response. The low-dose approach took longer than other treatments; however, the lesson was clear: there was no harm to prolonged FSH stimulation, and the slow, low-dose approach often yielded the monofollicular response that was desired.

In the early 2000s, the aromatase inhibitor letrozole was introduced as an alternative ovulation-inducing agent. It had the advantage of not interfering with endometrial development and proved to be more effective in inducing ovulation in obese patients with PCOS (4). As a consequence, it is now in common usage. However, as with the selective estrogen receptor modulator clomiphene, not all patients respond to a 5-day regimen. Therefore, extended regimens (7–10 days) and stair-step protocols have been proposed (5). The stair-step protocol, first used with clomiphene, is also an extended regimen because higher doses of clomiphene or letrozole are administered at a time when the initial dose has arguably already had some effect on the ovaries. However, stair-step protocols still use 5-day intervals each time the dose is increased.

Is there a lesson that we can learn from the low-dose gonadotropin approach to PCOS? Would it be reasonable to administer letrozole continuously for prolonged periods, perhaps weeks? Can we simply start the aromatase inhibitor with the goal of increasing serum FSH levels and then continue the therapy while monitoring follicular development with weekly ultrasound examinations? In contrast to gonadotropins, which have a short half-life, letrozole stays in the circulation longer, with a half-life of approximately 45 hours. Therefore, letrozole administration could be stopped when the lead follicle reaches a size of 12–14 mm, in anticipation of triggering ovulation a few days later. In this paradigm, prolonged letrozole therapy would potentially be continued for several weeks. Even so, if gonadotropin injections are avoided, this approach may be cost-effective because the cost of letrozole is much lower than that of gonadotropins.

Ovulation induction is an integral part of fertility therapy. Its application to anovulatory patients with PCOS is inexpensive and cost-effective and allows patients a path to fertility that is as natural as possible. The use of aromatase inhibitors does not interfere with estrogen receptors in the endometrium or in other tissues. At low doses, letrozole allows feedback inhibition and the selection of a dominant follicle. The lessons of low-dose gonadotropin therapy may thus lead to prolonged letrozole therapy in patients who do not respond to standard doses. If this approach proves useful, it may well obviate the need for gonadotropins for ovulation induction in PCOS.

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