

**Alternatives For Ovulation Induction and Superovulation:  
SERMs and Aromatase Inhibitors  
By David E. Tourgeman M.D., F.A.C.O.G.  
Board Certified, Reproductive Endocrinology and Infertility**

Ovulatory dysfunction is one of the most common causes for reproductive difficulty in otherwise fertile couples. Once successful ovulation is achieved, fertility is often restored. For many years, the first line of pharmacologic ovulation induction has involved the use of selective estrogen receptor modulators (SERMs), of which clomiphene citrate (CC) has been most extensively studied. The first trial of CC resulted in successful ovulation induction in approximately 80% of women, and ultimately half were able to achieve pregnancy (1). The use of CC for superovulation in patients with unexplained infertility (2), has also been the mainstay when coupled with intrauterine insemination. Yet despite advances in ultrasonographic technology, hormone assays, and urinary leutinizing hormone kits, success with CC has not changed dramatically. Therefore, it is important that we evaluate our options for ovulation induction and superovulation.



### **SERMs**

SERMs are structurally diverse non-steroidal compounds (triphenylethylene derivatives) that bind to estrogen receptors and have tissue-dependent agonistic and antagonistic effects. CC is characterized by agonistic properties when endogenous estrogen levels are low, and as a competitive antagonist when levels are high. In anovulatory women, depletion of estrogen receptors in the hypothalamus results in normalization of gonadotropin releasing hormone (GnRH) secretion and hence, secretion of pituitary follicle stimulating hormone (FSH) levels are optimized. This in turn will drive ovarian follicular development, resulting in ovulation.

The goal in anovulatory women is mono-ovulation, whereas with superovulation multiple follicle development is desired. However, even in anovulatory women, the use of CC can result in the development of multiple follicles as the result of prolonged clearance of its isomers. Thus, the risk of multiple gestation is increased to 8% (3). Other side effects also limit the usefulness of CC. Namely, CC exerts undesirable anti-estrogenic effects in the periphery (endocervix, endometrium, and ovary) that helps explain the discrepancy between ovulation and conception rates. Additionally, vasomotor flushes may occur as frequently as in 10% of cycles. Other side effects include mood swings, visual disturbances, breast tenderness, pelvic discomfort, and nausea.

The use of tamoxifen (TMX), another SERM, for ovulation induction has been the subject of clinical investigation since the early 1970s (4-5). A recent prospective randomized controlled trial compared the efficacy of TMX with CC in anovulatory women

(6). The overall rates of ovulation and pregnancy were similar in both groups. Other studies have suggested that TMX may be superior to CC in that there does not appear to have an adverse impact on the endometrium (7). TMX has been shown to be effective in the treatment of ovulation induction even when CC has failed (8), but has yet to be tested for superovulation.

Raloxifene, a structurally related compound, also appears to increase follicular phase FSH, with resultant elevation in estradiol levels. However, it has not been evaluated as a potential ovulation induction agent. In addition, raloxifene may act primarily as an antagonist at the level of the endometrium (9).

Other novel uses of the SERMs have included the combination of CC and TMX. Their combined effects in the treatment of anovulation appears to result in increased ovulation rates and pregnancy (10). Although the combination of CC and human menopausal gonadotropins induces ovulation in anovulatory (11), patients undergoing in-vitro fertilization (12), and those who have had a poor response to gonadotropins alone (13), the combination of the newer SERMs and human menopausal gonadotropins remains largely uninvestigated.

### **Aromatase Inhibitors**

Aromatase inhibitors are unique pharmacologic agents whose main mode of action is to decrease peripheral estradiol production by the ovary. This is in contrast to the SERMs that act centrally, nonetheless the end result is similar; namely, a decrease in central estrogen feedback that stimulates a compensatory increase in pituitary gonadotropin release.

By reducing circulating estradiol levels, aromatase inhibitors have been used to treat endometriosis, estrogen responsive cancers, leiomyomata uteri, as well as to induce ovulation. Primate studies have demonstrated that administration of aromatase inhibitors during the follicular phase results in the development of mature follicles which, when coupled with hCG could be shown to ovulate (14).

Recent studies used this rationale to compare letrozole with CC in patients who failed to ovulate with CC alone or ovulated with CC but had inadequate endometrial development (15,16). When administered in a 5-day regimen similar to CC, letrozole resulted in ovulation in 77% of patients and a pregnancy rate of 33%. Interestingly, fewer follicles tend to develop with the administration of aromatase inhibitors, which may be the result of normal intact feedback mechanisms. This would seem particularly appealing for those undergoing ovulation induction for anovulation, but may limit its usefulness for superovulation.

Furthermore, there tends to be an enhanced uterine environment with the use of letrozole (17), which may be relevant especially in those that have not been able to conceive with CC. Adding to our experience, yet another group demonstrated that when coupled with human menopausal gonadotropins, letrozole decreased the requirement of human menopausal gonadotropins to achieve follicular maturity (18). Currently, there are ongoing trials to evaluate the efficacy of a newer aromatase inhibitor, anastrozole, which may further our experience with this alternative.

## Summary

In women with anovulatory infertility, the treatment of first choice for induction of ovulation is most commonly CC. However, not all women will ovulate with CC alone or may have impaired endometrial development. Yet others may have severe side effects limiting the use of CC. In these patients, the use of other SERMs such as tamoxifen may allow the achievement of our goals. Yet, the impact of multiple gestation continues to reduce the appeal of these medications. With our growing experience, aromatase inhibitors may help accomplish mono-ovulation in this group of patients. In couples with unexplained infertility that are undergoing superovulation and intrauterine insemination, it appears that the SERMs are most effective in provoking the development of multiple follicles, and thus remain our primary treatment modality.

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