Ovarian stimulation 2.0

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Ovarian stimulation (OS) has been the single most effective measure ever taken for enhancing assisted reproductive technology outcomes. In the past decade, we have seen a flurry of various new protocols used for OS in assisted reproductive technology In light of the important differences that characterize these new approaches for OS, we felt it was timely to review the relative merits of each and every new protocol. (Fertil Steril® 2025;123:8–9. ©2024 by American Society for Reproductive Medicine.)
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The first assisted reproductive technology (ART) birth over four decades ago conducted by Steptoe and Edwards resulted from the in vitro fertilization of a single oocyte retrieved in the natural cycle. Soon after, however, it became obvious to everyone that ART outcomes could be improved by retrieving several rather than one single oocyte. It did not take long for results to be available and validate the strategy of conducting ART after ovarian stimulation (OS). Years later, we can confirm that the introduction of OS was the single most effective measure ever taken for improving ART outcomes.

Remarkably, the past decade has seen a proliferation of new protocols and practices for conducting OS, all more diverse than others. Certain of these new OS protocols are drastically different from what had been used for years. We, therefore, thought that it was appropriate to review the novelties of modern-day OS and see how the new options easily imbricate and ultimately assess their respective values.

OS PROTOCOLS: OOCYTE AND ENDOMETRIAL QUALITY

The primary objective of OS is to harvest a multiple oocyte cohort. The fundamental principle of OS is to override the system that normally controls the ovulatory quota set at one in humans. Practically, the process of OS ends up rescuing follicles, which were normally bound for atresia. Hence, it is appropriate to question ourselves as to whether OS—notably, all the new protocols—have any deleterious effect on oocyte quality.

In this series on OS, Harvey et al. undertake an extensive and thorough assessment of the possible impact of OS on different markers of oocyte quality (this issue of FS). As reviewed in detail, OS alters some markers of follicular fluid, but several studies indicate embryo euploidy rate is not affected by gonadotropin doses. A seminal study, albeit small in size, indicated that euploidy rate is not different between a natural cycle and OS-primed ART.

The investigators also reviewed the impact of OS on the quality of the endometrium. Looking at the impact of OS on the histological dating of the endometrium, differences have been reported with menstrual cycle findings. Interestingly, these morphological differences may not necessarily impact implantation rates. The recent advent of embryo cryopreservation by vitrification has truly upended the issue of OS and endometrial receptivity. Indeed, Harvey et al. review the evidence that favors opting for a freeze-all and deferred embryo transfer protocol each time the ovarian response is intense. Indeed, the shift toward an increasing reliance on vitrification has lowered our concern about the impact of OS protocols on the endometrium.

PROGRAMMING THE ONSET OF OS: FROM EARLY FOLLICULAR PHASE START TO ORAL CONTRACEPTIVE PILL, LUTEAL PHASE ESTRADIOL LEVELS, DUO-STIM, AND RANDOM START OS PROTOCOLS

Originally, OS protocols were initiated on menstrual cycle days 2–4 to increase the normal follicular signal occurring in the early follicular phase. Rapidly, however, gonadotropin-releasing hormone agonists became available and nearly routinely used in OS for ART. This practice was seen as convenient for doctors who enjoyed the flexibility of programming the onset of ART treatments and thereby, better plan their activity. The advent of antagonist protocols changed the picture because these protocols are started on menstrual cycle days 2–4. It thus reinitiated the issue of using various pretreatment for programming ART activity.

In an in-depth analysis, Sean et al. (this issue of FS) do a systematic review of the relative benefits and drawbacks of all options available for programming OS for ART. These investigators notably address the respective value of OS initiated in the luteal phase or even randomly, as well as the two back-to-back—DuoStim—options. Finally, Sean

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et al. reviewed the merit of the new progestin-primed protocols in which several different progestins are used to prevent premature ovulation. The latter, of course, implies that all embryos are frozen and their transfer deferred. In these cases, however, progestin regimens provide a significant cost advantage.

LEUTENIZING HORMONE EFFECTS IN OS: ONCE FEARED, NOW TACTFULLY DESIRED

The original regimens used during the early days of ART–then called in vitro fertilization used human menopausal gonadotropins (hMGs) preparations developed years before for inducing ovulation in women with hypothalamic amenorrhea. These hMG preparations were designed to contain equal quantities of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) bioactivity.

Toner and Pirtea remind us that in the early days of hMG use in ART, the LH bioactivity of hMG was seen as a contaminant rather than a beneficial component of the preparation. In those days, the LH effects of hMG were seen as susceptible to compromising OS outcomes (this issue of FS).

Subsequently, FSH-only preparations became available, notably those obtained by genetic recombination techniques. As Toner and Pirtea reviewed the topic of LH needs in OS in detail, it soon became evident that FSH-only preparations were not the true panacea. This was first revealed in women affected by hypothalamic amenorrhea. In these women, recombinant FSH induces follicular growth, but there is no estradiol production, and oocytes are unusable. Toner and Pirtea notably review in detail the arguments suggesting that LH effects exert positive and crucial effects on oocyte quality.

THE ROLE OF AROMATASE INHIBITOR COTREATMENT IN ART: NEW REMEDY OR OLD MIRAGE

A relative newcomer in the realm of OS for ART is letrozole, a nonsteroidal aromatase inhibitor. Letrozole reduces circulating levels of estrogen and has been used instead of clomiphene citrate for inducing ovulation in oligo-anovulation for nearly two decades.

In this series of reviews on OS, Bülow and Macklon look at the novel applications that are arising for using aromatase inhibitors in ART (this issue of FS). Letrozole inhibits the cytochrome P450 family 19 aromatase enzyme, thereby potentially blocking the conversion of androstenedione to estrone and testosterone to estradiol. This results in an elevation of circulating FSH and LH levels. Letrozole also increases intraovarian androgen levels by inhibiting the aromatization of testosterone and androstenedione. Together with elevated LH levels, letrozole therefore stimulates androgen production from pregnenolone in theca cells. This is believed to enhance FSH receptor expression, which likely promotes earlier follicular recruitment and therefore possibly enhances the response to OS. Bülow and Macklon review the results of their own and other recent systematic reviews and present evidence that supports this notion. The effects of letrozole added in OS protocols for ART are discussed, including a possible benefit on live birth rates in poor responders.

CONCLUSION

Ovarian stimulation, the crucial step of ART, has seen the development of a tremendous number of innovations over the past decade. These changes were examined in the present series of reviews on OS.

CRediT Authorship Contribution Statement

Dominique de Ziegler: Conceptualization, Writing – original draft, Writing – review & editing. **Sean Sokteang:** Writing – original draft, Writing – review & editing.

Declaration of Interests

D.d.Z. has nothing to disclose. S.S. has nothing to disclose.