Programming the onset of ovarian stimulation: from early follicular phase start to oral contraceptive pill, to luteal phase E2, Duostim, and random start oral contraceptive protocols

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Ovarian stimulation has been the single most efficient measure ever taken in assisted reproductive technology for improving outcomes by harvesting multiple oocytes and ultimately, embryos. Today, ovarian stimulation protocols consist of administrating exogenous gonadotropins to override the natural mechanisms that control the ovulatory quota to one in humans. For practicality issues, there have been numerous attempts to control, or "program," when ovarian stimulation is initiated to improve functionality and in turn efficacy for assisted reproductive technology programs. The different options for controlling the onset of ovarian stimulation currently available are discussed here, as well as the novel possibility of using progestins for blocking premature ovulation. (Fertil Steril® 2025;123:22–30. ©2024 by American Society for Reproductive Medicine.)

Key Words: IVF synchronizing, pre-ART E2 treatment, OC pill and ovarian stimulation (OS) for IVF, optimal ovarian stimulation (OS) protocol

Historically, the onset of menstrual cycle has been timed by reference to menses. Following this paradigm, the advancement of the follicular phase is judged in cycle days, with cycle day one being the first day of menses. This approach is anchored in practicality, as the onset of menses is an easily identifiable event typically taking place between two menstrual cycles. Physiologically speaking, however, menses constitute the last event of the prior cycle, which finishes with the onset of endometrial desquamation. Conversely, menstruation has no physiological connection with the onset of the new cycle. The functional initiation of the new cycle occurs a little before, during, or a little after the onset of menses but menstruation per se is an independent event from the onset of the next cycle.

The physiological event that initiates the menstrual cycle, the reference for follicular phase advancement, is a slight follicle-stimulating hormone (FSH) elevation or "FSH signal." This FSH signal, on average of 2.5 mIU/mL in amplitude, stimulates the FSH receptor-carrying antral follicles present in both ovaries. On average, there are 10–20 antral follicles between the two ovaries. These are characterized by their antral cavity – 2–9 mm in diameter – which allows their identification on ultrasound and the presence of FSH receptors. In principle, the whole cohort of follicles responds by increasing the production of both E2 and inhibin B. This, in turn, lowers serum FSH levels by a negative feedback effect and thereby, terminates the FSH signal. The negative feedback that turns off the FSH signal is the mechanism through which the ovulatory quota is set at one – sometimes two – in humans.

The intercycle FSH signal cannot be easily identifiable due to its small amplitude (2.5 mIU/mL, on average), short of doing multiple samplings for several days (1). As we will discuss it later, the occurrence of the intercycle FSH signal can be controlled, however, or programmed by different means.

Right from the inception of assisted reproductive technology (ART), over 4 decades ago, increasing the number of

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oocytes retrieved, and thereby embryos obtained, was seen as instrumental for improving outcomes. Today, ovarian stimulation (OS) for the purpose of increasing the number of oocytes retrieved stands as the single most effective measure ever taken for improving ART outcomes. The objective of OS was therefore to induce multiple follicular development.

PROGRAMMING OS: PROBLEM STATEMENT

The original objective of OS in ART was to override the control of the ovulatory quota, set at one in humans. This has been achieved by preventing the FSH drop occurring in the early follicular phase after the initial antral follicle response to FSH. Not knowing exactly when the FSH signal occurs, original stimulation protocols were arbitrarily initiated on cycle days 2–4.

In the early days of ART, OS – increasing the number of follicles developing and maturing – has been done using medications originally designed to induce ovulation in anovulatory women. Two options were available: increasing endogenous FSH by blocking the negative feedback loop with the anti-estrogen clomiphene citrate or now, aromatase inhibitors; or providing exogenous FSH. In the latter case – the most common approach used in ART today – exogenous FSH has been originally initiated on cycle days 2–4. This approach indeed amounts to maintain serum FSH at levels similar to those seen during the early follicular phase FSH signal throughout the whole follicular phase. Indeed, the daily administration of 150 IU of FSH – a standard stimulation dose for normal responders – elevates serum FSH levels by approximately 2.5 mIU/mL. This level is equivalent to an early follicular phase FSH signal. Hence, maintaining serum FSH at the levels of the intercycle signal throughout the entire follicular phase was the way to override the ovulatory quota set at one. Achieving multiple follicular development for harvesting multiple oocytes was called OS.

This regimen, physiological in appearance, suffered from causing programming problems, however, as it implied starting OS at the beginning of menstrual cycles. On the contrary, ART teams, as their activity increased, became eager to organize or "program" their activity to aim for having an equal number of oocyte retrievals every day, as we will discuss it. This was seen as instrumental for optimizing the practical efficiency of infertility treatments and in turn, quality control, both on the clinical side and in the laboratory. As discussed, several means have been developed for programming the onset of OS in ART. The advent of gonadotropin releasing hormone agonist (GnRH-a) used for preventing premature ovulation also allowed controlling the onset of OS, an approach that has been used for many years. Today new options are envisioned including even random start protocols, which we will review also (2).

METHODS

The most common databases, Embase, PubMed, and Cochrane, were searched for the following keywords. In vitro fertilization (IVF) oral contraceptive (OC) pill: 213 hits, 17 were found pertinent and retained in the article. IVF E2 treatment 1,330 and pretreatment 57. Ultimately, 24 were found most pertinent and retained in this review. IVF luteal phase stimulation: 36 hits, four were retained for this article. IVF progesterone primed OS (PPOS): 89 hits, 18 were retained for the article. DuoStim protocol: 28 hits, six pertinent articles were retained in the review. IVF random start: 248 results × 10 years, five were retained and discussed in the present review.

EARLY FOLLICULAR STIMULATION START: HISTORICAL PERSPECTIVE

The miserable results of early days ART – then called IVF – readily sparked interest in achieving multiple ovulations and retrieving several oocytes. One pioneer team in this endeavor has been Howard Jones' group in Norfolk (3). These investigators adopted beginning in 1981 a novel stimulation protocol using human menopausal gonadotropin (hMG) started on days 2–4. Human menopausal gonadotropin had been developed in pre-ART times for inducing ovulation in women suffering from hypogonadotropic amenorrhea. It contained FSH and luteinizing hormone (LH) in equal proportions and was standardized in terms of bioactivity (4), as gonadotropin assays were not available when hMG was developed. A different article in this series discusses the relative advantages of LH bioactivity containing regimens in OS protocols and those constituted of pure FSH of recombinant origin.

Moreover, exogenous human chorionic gonadotropin (hCG) was used to substitute for the midcycle LH surge (3). Laparoscopy for follicular aspiration was scheduled 36–38 hours after hCG administration (3,5). Soon hMG-based protocols established themselves as superior to clomiphene-based approaches (5).

Concerns for possible deleterious effects of OS on the endometrium were raised from inception. This fear had led Steptoe and Edwards' group to opt for natural cycle ART, used in the first successful ART attempt (6). Hence, attention was given to endometrial morphology when stimulation was initiated by the Jones' group. In their reported series, 11 patients showed an "advanced" pattern and 10 an "in-phase" (7) endometrium. This was estimated according to the debatable Noyes criteria (8). A significant difference in serum progesterone levels on days 16 and 18 was found in these two groups. Serum progesterone levels were significantly higher by day 18, if pregnancy was established (7). In ART, the embryo is placed over the endometrium 24–48 hours earlier than it normally arrives in the endometrial cavity in natural conception. This led to the hypothesize that the "advanced" endometrium encountered in OS – at least in certain women – might be beneficial for embryo implantation (7). Of course, all the emphasis put on these issues of acceleration of endometrial changes in the early days of ART has become obsolete by the advances in cryopreservation and liberal access to deferred embryo transfers (9). The negative impact of OS on endometrial receptivity has now been established. This is notably the case in strong ovarian responders in whom ART outcome is improved by freezing all embryos and reverting to deferred embryo transfer (10).

Today, very large programs that implement a 7-day-a-week activity are often comfortable with early follicular phase stimulations. Smaller programs however aim to even out their activity with different types of pre-ART treatments, including the OC pill, which we will review here.

PROGRAMMING STIMULATION WITH OC PILL

The option of program stimulation cycles with the OC pill dates back to before the use of GnRH analogs in ART and notably, GnRH-a. Gonen et al. (11) studied IVF cycles in 14 women who were randomized to receive either leuprolide acetate (0.5 mg) or 5000 IU hCG to rigger ovulation at midcycle. Interestingly, however, all these patients had been pretreated by OC pills. Although the response to agonist trigger is not the issue discussed here, it is remarkable that no patient in Gonen's cohort presented a premature LH elevation (11). This sparked a new study in which 181 stimulation cycles were pretreated with OC pill (study group) and their results compared with 113 other cycles normally initiated in the early follicular phase (control group) (12). The mean length of ovarian suppression with OC pill in the study group was 35.3 $\pm$ 0.9 days. Remarkably, no spontaneous LH surges occurred when the use of OC preceded ovarian hyperstimulation, whereas in the control group, the incidence of LH surges was 19.5%. The mean amount of human menopausal gonadotropin required was significantly lower in the study group than in the control group (8.9 $\pm$ 0.4 and 10.9 $\pm$ 0.4 ampules, respectively). Significantly more follicles $\geq$1.5 cm in diameter were seen on the day before oocyte retrieval and significantly more oocytes were retrieved per attempt in the study group – pretreated with OC (12). This led the investigators to proclaim that OC pretreatment was useful in ART not only to facilitate the scheduling of cycles but also to prevent spontaneous LH surges (12). These data fell into oblivion, however, as soon later GnRH-a preparations became widely, if not universally, used for blocking premature ovulation.

Interestingly pretreatment with the OC pill was shown to dampen the agonist phase of the response to the agonist. This was seen as a practical advantage when agonists became used in OS. Keltz et al. (13) reported that pretreatment with the OC pill showed a similar FSH response to the agonist, as compared with nontreated controls. Conversely, the LH response was significantly quenched. In a different trial, Biljan et al. (14) showed pretreatment with OC abolished ovarian cyst formation, and shortened the time required to achieve pituitary suppression. Furthermore, gonadotropin requirements were decreased without any negative effect on pregnancy rates (14). A cyst developed in 27 patients in the control group (52.9%) but in no patients pretreated by OC (odds ratio [OR], 115; 95% confidence interval [CI], 10–617) (14). Patients in the study group achieved pituitary suppression faster (median difference, 7 days; 95% CI, 4–14) and required fewer ampules of gonadotropin (median difference, 10; 95% CI, 6–14) (14). Together, these data led to a wide use of OC pill pretreatment in combination with GnRH-a stimulation protocols primarily, for reducing the risk of cyst formation.

The advent of GnRH antagonist progressively replaced the agonist for OS, although the debate about their equal efficacy lasted for quite a while. Finally, in a large Cochrane Review, Al-Inany et al. (15) reported data comparing the use of GnRH-a and the new antagonist in ART primarily looking at live birth rates (LBRs). Their review based on data of moderate quality evidence showed no evidence of a difference in LBR between GnRH antagonist and long-course GnRH-a (OR, 1.02; 95% CI, 0.85–1.23; 12 randomized controlled trials [RCTs], n = 2303) (15). The risk of ovarian hyperstimulation syndrome (OHSS) was however decreased in women receiving the antagonist. Later however, Lambalk et al. (16) reported that in the general IVF population, GnRH antagonist protocols were associated with lower ongoing pregnancy rates but confirmed the lower incidence of OHSS. Kolibianakis et al. (17) objected, however, indicating that there were flaws in that analysis. This was notably due to the presence in the antagonist group of women who had received OC pill pretreatment but with a far too short interval before starting OS, which hampered results (17). Today there is a general consensus to consider that agonist and antagonist protocols are equivalent. The medical community, however, largely prefers antagonist stimulation protocols because of the decreased risk of OHSS. When assessing the outcome of frozen transfer cycles, both protocols have been found equivalent (18).

Certain administer the antagonist on a fixed day – day 6 – although other investigators follow a flexible approach based on follicular size and E2 levels, with report of better results in the fixed strategy (19). Although the consensus in favor of the antagonist protocol is generally admitted, there are still reports suggesting that certain poor responders might do better with the agonist (20).

For us, the issue at stake here – programming the ART cycle for better efficacy – the general adoption of antagonist protocols has revived the problem. Indeed antagonist ART cycles are normally started on cycle days 2–4. Hence, clinicians were found at a loss without the programming possibilities that agonist protocols offered. Hence efforts have been deployed for adapting pre-ART treatments to program ART cycles, for the sake of clinical efficacy and patient preference.

Logically, the first interest has been for OC pill pretreatment, which would allow us to program in advance the timing of ART treatments. A first systematic review and meta-analysis has however slowed the initial enthusiasm, as it reported that OC pretreatment was associated with lower ART outcomes (21). In this review by Griesinger et al. (21), two of the four studies retained for the meta-analysis had however an unreasonably short pill-OS interval of only 2 days. Importantly, these two studies carried all the burden of the whole negative impact of OC pill pretreatment calculated in the meta-analysis of these first four studies (21). Of note too, all four studies retained in the meta-analysis used recombinant FSH exclusively during the stimulation (21). The possible negative impact of OC pill pretreatment appeared corroborated by a large Cochrane systematic review and meta-analysis (22). Of note, this meta-analysis did not sort results according to the stop OC pill – ART interval nor the type of gonadotropin used, with or without LH bioactivity.

Subsequently, other studies provided results going against the Cochrane study (22). Montoya-Botero et al. (23) studied the effects of OC pill administration for 12–30 days

for the purpose of programming the ART cycle, respecting a washout interval of 5 days before starting ART. The study included 3,517 women who were pretreated by the pill and 599 who did not and served as controls. The use of oral contraceptive pill (OCP) was independently associated with a small increase in the number of oocytes retrieved after adjusting for age, body mass index, use of OCP, cause of infertility, initial dose (IU), type of gonadotropin, stimulation days, and total stimulation units (23). The study revealed that OC pill had a similar probability of achieving a live birth as compared with patients not using OCPs after fresh embryo transfer (OR, 0.89; 95% CI, 0.69–1.15) and similar cumulated live births after the use of fresh and frozen embryos (OR, 0.94; 95% CI, 0.73–1.21) (23). These findings were supported by other studies such as those of Bellver et al. (24) showing no impact of OC pill pretreatment on the risk of miscarriage and Kim et al. (25) no alteration in poor responders. Pereira et al. (26) showed that pretreatment with OC pill provided equivalent results obtained after pretreatment with transdermal E2.

A different study – RCT – respecting a 5-day time interval between stopping OC and the onset of stimulation likewise showed no difference in ART outcome (23). Antagonist protocols may cause an excessive reduction in endogenous LH levels which could be exacerbated by OC pill and increase needs in LH bioactivity, as discussed in a different article (27).

Interestingly, a very strong argument in favor of OC pretreatment in antagonist protocols came from US ART centers, which generally have the best ART results in the world. Indeed, a recent article looking at the common practices among the best-performing centers in the United States indicated that nearly all used OC pretreatment and a combination of FSH and hMG in their OS regimen (28). It is likely therefore that the profound LH suppression induced by OC pill benefits from OS regimen using LH bioactivity containing hMG preparation (28).

In summary, therefore, the OC pill pretreatment is a valid way of programming ART treatments for the sake of the connivance and efficacy of ART teams. The proper pill-stimulation interval of 5 days should be observed and the use of stimulation protocols containing LH bioactivity considered. Despite the accumulated evidence that OC pill treatment has no adverse consequence on ART and is handy for the scheduling cycle, the European Society Human Reproduction's guidelines talk against it (https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Ovarian-Stimulation-in-IVF-ICSI).

E2-BASED PROGRAMMING: A PHYSIOLOGICAL APPROACH

During the intercycle interval, two hormonal signals – a drop in luteal E2 and progesterone – take place and two distinct events ensue. These are the onset of menses; and intercycle FSH elevation (Fig. 1). In a prospective trial, we demonstrated that the drop in progesterone is solely responsible for triggering the onset of menses independently of E2 levels (29). Conversely, the drop in E2 on corpus luteum demise controls the timing of the intercycle FSH elevation, independently of progesterone levels (29) (Fig. 1).

Applications of this lesson have allowed us to control the timing of the intercycle FSH elevation by timely administration of E2, with FSH elevation occurring on the third day after stopping E2 (30). This therefore amounts to block the onset of the new follicular phase until E2 treatment is discontinued. Prior work has demonstrated that E2 treatment (2 mg of oral E2 twice a day or 0.1 mg of transdermal E2/d) can reliably postpone FSH elevation and ensuing follicular recruitment for $\leq$2 weeks (31).

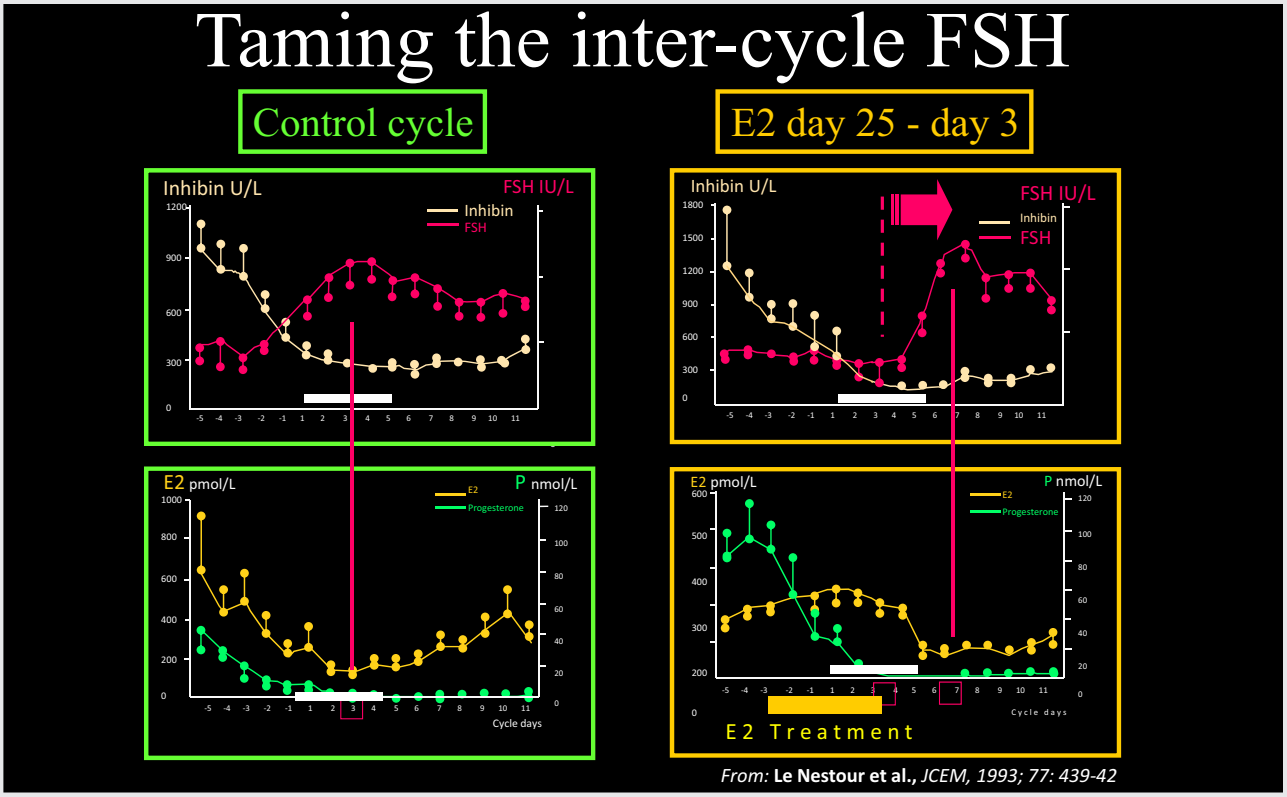
The ability to control FSH elevation by E2 treatment has allowed us to effectively program the onset of stimulations. Some have claimed E2 pretreatment improved results notably because FSH suppression was less profound than with OC pill. In addition, the hypothesis has been made that E2 pretreatment in the luteal phase of the preceding cycle provided a more homogeneous cohort of follicles and in turn better ART outcome (32). According to these investigators, luteal E2 treatment was meant to prevent early follicular recruitment due to a premature intercycle FSH signal (32). Similar effects have also been reported by the same investigators with the timely use of an antagonist during the luteal phase for the same purpose (33). These results were challenged by Elassar et al. (34) who reported no difference in either normal or poor responders. Guivarc'h-Levêque et al. (35) reported that luteal E2 could be prescribed for programming ART cycles and avoiding retrievals on weekends without any deleterious effects.

The superiority of E2-based programming claimed by some (32), notably in poor responders, has been challenged in many publications. For example, an RCT showed that pretreatment with oral E2 from day 7 after ovulation to day 2 of the next cycle did not increase oocyte yield in patients with a low ovarian response compared with no pretreatment (36). Chang et al. (37) used a luteal E2 treatment protocol at the dose of 4 mg/d initiated on luteal day 21 and showed no difference in outcome. Similarly, Ye et al. (38) observed no significant effect on implantation, clinical pregnancy, live birth, and early pregnancy loss rates between E2 pretreated and untreated patients. A different retrospective study showed no difference in poor responders between E2 pretreated – transdermal patch – antagonist and the microdose GnRH-a protocol (39).

Garcia Velasco's group compared ART priming with luteal E2 and OC pill in a randomized controlled trial (40). One hundred consecutive patients undergoing IVF with the GnRH antagonist protocol were randomized to either the OCP or E2 pretreatment arms. No differences were observed in the fertilization rates (68.1% vs. 64.8%), the total number of embryos obtained (5.9 vs. 6.2), the mean number of embryos transferred (1.8 vs. 1.8), implantation rate (36% vs. 39%), miscarriage rate (8.9% vs. 17%), ongoing pregnancy rate (47.8% vs. 53.9%), or LBR (44.3% vs. 47%) (40).

Recently, Cedrin-Durnerin et al. (41) reported a multicentric trial on 324 women who received pretreatment with micronized E2 (2 mg twice a day). Results were compared with 160 nontreated patients. There were no differences in the number of retrieved oocytes (8.4 [6.1] vs. 9.1 [6.0]), in the number of metaphase 2 oocytes (7 [5.5] vs. 7.3 [5.2]) nor the number of obtained embryos (5 [4.6] vs. 5.2 [4.2]) in E2 pretreated patients compared with non-pretreated controls.

FIGURE 1



Intercycle hormone profiles: (**A**) control cycle: the white box represents menses. Before menses, we see a decrease in inhibin A (*upper* diagram) and a drop in E2 and progesterone (*lower* diagram). The onset of menses is preceded by a drop in luteal E2 and progesterone. Serum FSH increases and reaches a peak on the third day of menses. (**B**) Intervention cycle: during the following cycle women received exogenous E2 starting on the 11th after the LH surge. Before menses, E2 did not decrease, reflecting the exogenous administration. This did not prevent menses to occur when serum progesterone dropped. Exogenous E2 was stopped on the third day of menses. Serum FSH remained suppressed (by E2) and only increased after E2 was discontinued, peaking 3 days after E2 was stopped. FSH = follicle-stimulating hormone; LH = luteinizing hormone.

Sokteang. Programming ovarian stimulation. Fertil Steril 2025.

The LBR after fresh transfer (16.2% vs. 18.5%, respectively), and the cumulative LBR per patient (17.7% vs. 22.9%, respectively) were similar in both groups. In a subgroup of poor responders (anti mullerian hormone <1.2 ng/mL and/or antral follicle count <5); however, there was a larger number of oocytes retrieved – 1.7 mean – but no difference in cumulative LBR (41).

In all, programming ART cycles with E2 initiated in the luteal phase (or on cycle day one) can be safely executed for the benefit of "programming" ART cycles according to the group's needs. Luteal E2 is effective for that purpose, but the expected advantage of luteal E2 programming for poor responders has not been proven despite early hopes. Programming ART cycles with either luteal E2 or other preparations such as the OC pill notably, are equivalent (42, 43).

LUTEAL PHASE, PROGESTERONE PRIMED STIMULATION, AND DUOSTIM PROTOCOLS

Luteal phase OS

The first report of OS conducted during the luteal phase came from China (44). In this early report, the ART outcome was similar to that of stimulations conducted in the follicular phase (44). Of course, embryos had to be cryopreserved and their transfer was deferred because the endometrium was not receptive. These findings were confirmed by Qin et al. (45) who found no differences in the mean number of mature oocytes retrieved in the conventional group, late follicular phase group, and luteal phase group (5.7 ± 3.6, 5.2 ± 3.7, and 5.2 ± 3.9, respectively). Similarly, no significant differences were observed in the viable embryo rate per oocyte retrieved (37.9%, 38.5%, and 43.6%), clinical pregnancy rates (41.5%, 45.5%, and 38.9%), and implantation rates (30.7%, 30.2%, and 27.1%) in the three groups (45).

A more recent study confirmed and extended these results (46). The latter data by Martinez et al. (46) consisted in conducting two identical stimulations in oocyte donors in the follicular and luteal phase looking at possible differences in the same patients. Follicular phase stimulation resulted in a significantly shorter duration of OS and a lower total dose of FSH was needed compared with luteal phase stimulation. The number of oocytes and blastulation rates were similar however. Most importantly, the mean number of euploid blastocysts was equivalent in follicular and luteal phase

stimulations at 1.59 and 1.61 for the follicular and luteal phase stimulation, respectively (46).

Of note, pituitary suppression using the antagonist was not necessary for luteal phase stimulation due to the antigonadotropin properties of endogenous progesterone (44). This observation has led to the development of progestin OS protocols in which the use of antagonists to prevent premature ovulation is replaced by progestin treatment. These progestin stimulation protocols are often, but incorrectly, called progestin primed protocol, using the acronym PPOS. The term priming is indeed incorrect, as progestins are used to block ovulation and do not prime anything.

Progestin stimulation protocols

Results obtained in luteal phase stimulations unveiled that luteal phase progesterone protects against premature LH elevation, rendering the use of antagonists unnecessary (44). This led to test whether exogenous progestins could replace GnRH antagonists if given during the follicular phase (47, 48). Of course, progestin protocols imply that all embryos are cryopreserved – freeze all – and embryo transfers deferred (48). Several comparisons have been conducted between the efficacy of progestin and regular stimulation protocols, including large meta-analyses conducted by Ata et al. (49, 50). Ten studies compared progestin protocols to antagonist protocols and six to long agonist protocols. The quality of the studies was poor – most of them emanating from one center in China – and ART outcome was reported in pregnancy rates per transfer, not per retrieval. For analyzing progestin protocols in which freeze all and deferred embryo transfer are mandatory, one would have desired to look at cumulative pregnancy rates (49). This information is unfortunately lacking. Overall, the duration of stimulation, gonadotropin consumption, and oocyte yield were similar with progestins and GnRH analogs. However, sensitivity analyses suggested that progestins were associated with significantly lower gonadotropin consumption than the long GnRH-a protocol. Overall, live birth, ongoing, and clinical pregnancy rates per transfer were similar with progestins and GnRH analogs. This confirms the results from another review (51). In this latter report, LBRs per embryo transfer were similar in progestin and GnRH antagonist cycles (relative risk, 1.16; 95% CI, 0.93–1.44). Miscarriage rates were equally similar in progestin and antagonist cycles (relative risk, 1.01; 95% CI, 0.65–1.55) (51).

Deng et al. (52) reported a systematic review of progestin protocols in a subgroup of women suffering from PCOS. A total of eight studies were retained covering 2,156 PCOS women undergoing ART with progestin protocol and comparing results to historical controls (52). The incidence of OHSS was reported as very low and ART outcome was similar. This is important, as PCOS patients undergoing ART are commonly recommended a freeze all and deferred transfer for optimizing results and minimizing risk (OHSS) (53). In a comparison of progestin vs. long agonist protocol, Xi et al. (54) found no difference in ART outcome, but observed, as expected, a marked decrease risk in OHSS in the progestin group. The types of progestins and doses used were also compared. Departing from the original use of medroxy progesterone acetate (MPA), progestin protocols have also been successfully achieved using dydrogesterone at the dose of 20 mg/d. In a study on 18,593 ART patients, the investigators (55) observed with no difference in ART outcome and miscarriage rate (56). No difference was found when MPA, dydrogesterone, or oral micronized, 10 or 4 mg of MPA, or 200 or 100 mg of micronized progesterone was used (50, 56, 57).

A study by La Marca et al. (58) included women undergoing IVF and preimplantation genetic testing. Forty-eight patients were treated with MPA and their results were compared with those of age-matched historical controls (n = 144) who were treated with a GnRH antagonist. The percentage of patients with euploid embryos and the total number of euploid blastocysts per patient (median and interquartile range) in the PPOS group was 38.7 (25.5–52.9) and 2 (1.3–3.1), respectively. These figures were not significantly different in women treated with the GnRH antagonist protocol, i.e., 42 (28–53.8) and 2.1 (1.3–2.9), respectively (58).

Newer progestin protocols propose a flexible approach in which progestin treatment is not started on stimulation day 1, but rather on day 6 or 7, as done with GnRH antagonists. Early results seem to indicate that the novel flexible progestin protocol achieves higher cumulative LBRs than the regular regimen, but that remains to be confirmed (59).

The most compelling evidence of the safety and efficacy of conducting ART using a progestin protocol recently came from an article just published by Vidal et al. (60). In this study, 44 women underwent two stimulation cycles with an identical fixed dose of recombinant FSH (225 or 300 IU/d) in both cycles. Prevention of ovulation in the first cycles was performed with the use of an antagonist protocol and they underwent oocyte retrieval. After a washout period of 1 month, women underwent a new stimulation for ART, this time using a progestin protocol with 200 mg of oral micronized progesterone orally from stimulation day 1. Ultimately all the blastocysts underwent genetic analysis for aneuploidy (preimplantation genetic testing for aneuploidy [PGT-A]). There were no differences in ART outcome and in the number of blastocysts biopsied and euploidy rate (60). This constitutes to date the strongest evidence for the safety and efficacy of the progestin protocol notably, using a single capsule of oral micronized progesterone (200 mg) as progestin (60).

The primary interest in progestin protocols lies in the simpler – no injection of antagonist – and lower cost of treatment. Evans et al. (61) calculated that in the United States in case of planned freeze all and deferred transfer – as in the case of PGT-A, or risk of OHSS – the financial saving of using a progestin protocol amounted to $2,079 (61). The financial difference between progestin and classical antagonist protocol associated with freeze all will obviously vary in the different parts of the world.

In sum, we can reasonably conclude that progestin protocols are safe and efficacious notably when using micronized progesterone at the dose of 200 mg/d. Progestin protocols are thus particularly indicated when a freeze all approach is planned, be it because of genetic testing, endometriosis, or excessive ovarian response.

Duostim protocol

A different spinoff of luteal phase stimulation has been the dual consecutive – follicular followed by luteal phase – stimulation or DuoStim. This has been originally proposed by Capalbo et al. (62) particularly, in poor ovarian responders to maximize the number of oocytes collected. In their trial, DuoStim resulted in a similar euploid blastocyst formation rate (62). Stimulation was conducted using an identical protocol in the follicular and luteal phases of the same menstrual cycle. It resulted in a similar number of blastocysts in patients with reduced ovarian response (62). In a different trial, Racca et al. (63) report that fresh embryo transfer can be conducted from the follicular phase harvest. Our own experiences indicated that DuoStim was well perceived by women who saw the experience more like a long OS process rather than true distinct OSs (64). Indeed, DuoStim in poor-prognosis patients undergoing PGT-A cycles achieves a similar euploidy rate while reducing the time required to obtain an euploid blastocyst (65). Other investigators however do not favor this approach, indicating that it lacks rationale and evidence for poor responders (66).

Euploid blastocysts obtained after luteal phase stimulation show the same clinical, obstetric, and perinatal outcomes as follicular phase stimulation-derived ones: a multicenter study. No difference was observed between FPS- and LPS-derived euploid blastocysts after vitrified-warmed single embryo transfer (67). A low birthweight was registered in 2.5% and 5% of the newborns, whereas 4% and 7% showed high birthweight, in FPS- and LPS-derived euploid blastocyst, respectively. Encompassing the 81 FPS-derived newborns, a total of 9% were small and 11% large for gestational age. Among the 102 LPS-derived newborns, 8% were small and 6% were large for gestational age. No significant difference was reported for all these comparisons (67).

In summary, DuoStim is a reproducible strategy to obtain more oocytes and competent embryos in a short time frame with similar ploidy rates and obstetric outcomes (67). This may be interesting in cases of fertility preservation and other IVF purposes, such as anticipated poor response in women undergoing embryo genetic testing (67). In a survey conducted on women undergoing social fertility preservation, a majority of participants indicated that they would have been interested in DuoStim, if it had been proposed (68).

RANDOM START STIMULATION

The possibility to conduct OS during the luteal phase led also to test the option of so-called random start stimulation. This was first used in cases when time constraints exist, for example, in oocyte preservation in certain oncological cases (69–71). Indeed, random start stimulation provides a significant advantage by decreasing the total time for the oocyte preservation cycle and, as we will see, without compromising oocyte yield and maturity (69).

The favorable results observed in oncology led to also test random stimulation in regular ART patients (72). In a recent report, no notable variations were found in clinical outcomes using oocytes obtained from random start protocols and those proceeding from conventional OS in oocyte donation treatments (73). Random start stimulation strategy does not impair the potential of the oocyte yield or clinical outcomes in oocyte donation cycles (73).

One caveat of random start protocols is the risk of OHSS in case of an inadvertent pregnancy during the stimulation (74). Random start protocols however add flexibility in fertility clinics when there is no intention of a fresh embryo transfer, but may be associated with insidious risk of OHSS (74).

CONCLUSION

The seemingly intangible physiological principle that commended to start OS in the early follicular phase has been seriously challenged by the advent of several new alternatives. Indeed, there is now available evidence indicating that various ways of programming stimulation protocols are available. These include pretreatment with the contraceptive pill or E2 started in the luteal phase or on cycle day 1. Although a belief had been placed in luteal E2 protocols for enhancing the results of poor responders, this has not materialized as discussed. The practicality of E2 for programming ART remains however and may be found simpler than the OC pill in certain situations. Moreover, OS can be initiated in the luteal phase and even randomly when a freeze all and deferred transfer option is preferred. All these approaches, including stimulation regimens using progestins for blocking ovulation – PPOS – offer similar outcomes and are available to choose from.

CRediT Authorship Contribution Statement

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

Declaration of Interests

S.S. has nothing to disclose. P.O. has nothing to disclose. C.T. has nothing to disclose. D.d.Z. has nothing to disclose.

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