Scheduling cycles with gonadotropin-releasing hormone antagonist protocol in *in vitro* fertilization: Is there a scope in batch *in vitro* fertilization?

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ABSTRACT

In India, a practice of "Batch *in vitro* fertilization (IVF)" has evolved in many infertility centers in an effort to align infertility management with logistics. A "Batch IVF" is an approach where the menstrual cycles of multiple women are programmed, such that they can undergo all the processes; from stimulation until embryo transfer about the same time. In "Batch IVF", the day for initiating stimulation is calculated retrospectively from the day the visiting embryologist is available at the clinic (day of ovum pick-up). Aligning the cycles of multiple women with steroids followed by down regulation with long gonadotropin-releasing hormone agonist (GnRH-A) is one of the currently employed methods for batching. There is sufficient evidence on scheduling cycles with steroids in GnRH-An protocol without compromising on the outcome. The objective of this paper is to provide evidence-based clinical concept on scheduling cycles in "Batch IVF" setup with GnRH-An protocol through literature review.

KEY WORDS: Batch *in vitro* fertilization, gonadotropin-releasing hormone antagonist, *in vitro* fertilization, intra-cytoplasmic sperm insertion, pretreatment, scheduling

INTRODUCTION

In India, there are about 512 registered Assisted Reproductive Technology ART centers.[1] A practice of "Batch *in vitro* fertilization (IVF)" has evolved in many infertility centers in an effort to align infertility management with logistics. A "Batch IVF" is an approach where the menstrual cycles of multiple women are programmed, such that they can undergo all the processes, from stimulation until embryo transfer, approximately the same time. While this practice may optimize the usage of resources such as drugs, media, and consumables,[2] a few drawbacks of this practice could be over utilization of incubators, over-work for embryologist if too many intra-cytoplasmic sperm injections (ICSIs) are done on the same day and too many embryo transfers for clinician/s, which cumulatively may have a negative impact on the success rate. From a programming perspective, a standardized protocol for Batch may not be applicable to all the patients leading to undesirable effects and outcomes in a few. Further, if the clinician or embryologists are visiting consultants, there may also be a huge scope for mistiming the final trigger which may also impact the outcome.

In "Batch IVF," the day for initiating stimulation is calculated retrospectively from the scheduled day of ovum pick-up (OPU), that is, when the consulting embryologist is available at the center.[2] Long gonadotropin-releasing hormone agonist (GnRH-A) protocol has been used in the ART practice for decades, and has created a niche in Batch setup. The usage of sex steroids and specifically oral contraceptive pills (OCPs) has been a common practice, essentially for aligning the menstrual cycles and reducing the functional ovarian cyst.[3] A uniformly down-regulated state provides a stage for the fertility specialists to evenly synchronize the follicular development in all the patients in the Batch. The long GnRH-A protocol has been well-accepted as the first line stimulation approach in "Batch IVF" across most of the responder categories. A typical "Batch IVF" protocol

using OCPs and long GnRH-A protocol is described in Figure 1.

As described in Figure 1, if day 0 is considered as a day of OPU when the embryologist is available at the center, day 2/3 is the day of embryo transfer. 2 days before day 0, day-2 is the day of human chorionic gonadotropin (hCG) trigger. Day − 10 to − 12 is the day when stimulation is initiated. Day − 17 the OCPs would be stopped for all the patients, and day − 21 is when the GnRH-A is started.[2]

Gonadotropin-releasing hormone antagonists (GnRH-An) have been available in the market for over a decade and have gone through an evidence-based journey in terms of their currently proven efficacy and safety.[4,5] Though this protocol is perceived to have challenges related to synchrony and scheduling, studies with GnRH-An protocol have concluded comparable pregnancy outcomes, significant reduction in the number of injections for suppression of the pituitary gland, almost 50% reduction in ovarian hyper-stimulation syndrome (OHSS) and a flexibility to use GnRH-A for triggering, to further reduce the incidence of OHSS.

There is sufficient evidence evaluating scheduling practices with individual GnRH-An protocol without compromising the outcome, which may be translated to "Batch IVF" setup. The objective of this paper was to provide evidence-based clinical concept on scheduling in "Batch IVF" setup with GnRH-An protocol through literature review.

METHODS

A search for literature published between 2000 and 2014 was performed in the PubMed database with the following terms: Scheduling, GnRH-An, IVF, ICSI.

DISCUSSION

The objective of programming in "Batch IVF" is: (1) Aligning the menstrual cycles of the various women in a batch and (2) uniformly suppressing

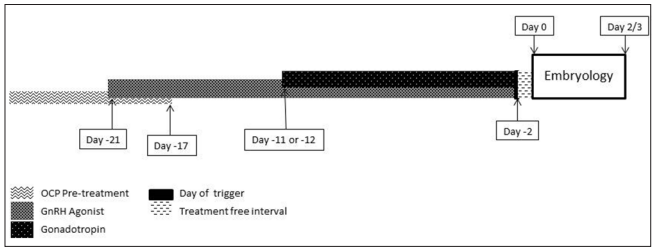

Figure 1: A typical "Batch *in vitro* fertilization (IVF)" long gonadotropin-releasing hormone agonist protocol

the hypothalamic-pituitary-ovarian (HPO) axis for synchronizing inter and intra ovarian follicular development. In the current conventional protocol, the alignment of menstrual cycles is achieved with OCPs or other sex steroids and the follicular synchrony by means of long down regulation with GnRH-A. However, the sex steroids can also suppress the HPO axis, which could be utilized for the benefit of both, aligning the menstrual cycles as well as suppressing the HPO axis, in absence of the initial down regulation.

Although there have been several papers which assessed the outcome with the use of sex steroids for pretreatment prior to stimulation in a GnRH-An protocol, the concept was more systematically assessed by Cédrin-Durnerin *et al*. The study group evaluated the possibility of programming with OCP ($n = 21$), 17 β Estradiol (E2, $n = 22$), and Norethisterone, a synthetic progestogen (Pn, $n = 23$) with GnRH-An protocol in comparison to a group with spontaneous GnRH-An cycles without pretreatment (control, $n = 24$). OCP was started on cycle day 2/3 for 15–21 days, Pn from cycle day 15 for 10–15 days and E2 2 mg twice a day started 10 days before the presumed menses. Hormonal profile and sonography assessments were done after discontinuing the steroid treatment on posttreatment days (PD) 1, 3, and 5 in all the three pretreatment groups and on cycle day 1 and 3 of control group. The assessment for OCP and Pn groups revealed that the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations on PD 5 corresponded with cycle day 3 of the spontaneous cycle, irrespective of the duration of use. For E2 group, no significant suppression of FSH and LH levels were detected as compared to control group and the rebound FSH levels were at maximum by PD 3 and LH levels slightly higher by PD 5. The differences in the size of antral follicles in the OCP and Pn groups were significantly less as compared with natural estrogen or control groups. Stimulation was started for all the four groups, starting from day 5 posttreatment for the study groups and day 3 of spontaneous cycle for controls. A flexible GnRH-An protocol was used to prevent premature LH surge. A comparable outcome in terms of number of retrieved oocytes (OCP: 14 ± 8.3, Pn: 12.6 ± 7.3, E2: 13.1 ± 7, Control: 9.9 ± 5.4), pregnancy rate (PR) per oocyte retrieval (OCP: 25%, Pn: 35%, E2: 21%, control: 50%) and live babies (OCP: 5, Pn: 6, E2: 3, control: 8) was found. The study concluded that a minimum of 5 days withdrawal period during OCP and Pn pretreatment is suggested prior to initiating stimulation and short withdrawal period for estradiol pretreatment for optimum outcomes.[6]

This study presents meaningful information on the concept of programming in GnRH-An protocol, as it provides evidence on the possibility of using various types of sex steroids, their duration of pretreatment and

more importantly the washout period prior to starting the stimulation with GnRH-An protocol.

ORAL CONTRACEPTIVE PILLS

Conflict

A meta-analysis performed by Griesinger *et al*. in 2008, based on the four randomized controlled trials involving a total of 847 subjects, revealed increased gonadotropin usage by weighted mean difference (WMD) of 542 IU (95% confidence interval [CI]: +127–956), increased duration of stimulation by WMD 1.41 days (95% CI: +1.13–1.68) but no significant difference in the ongoing PRs (odds ratio: 0.74, 95% CI: 0.53–1.03) in OCP pretreatment groups.[7] Griesinger *et al*. in 2010 published an updated meta-analysis involving additional two randomized controlled trials, with total sample size of now 1343. The analysis revealed significantly lower ongoing PRs (relative risk: 0.80, 95% CI: 0.66–0.97), significantly higher duration of stimulation (WMD: +1.33 days, 95% CI: +0.61–2.05) and gonadotropin consumption (WMD: +360 IUs, 95% CI: +158–563) in the OCP pretreatment group.[8]

The meta-analysis however had a few points to consider. Three out of six studies included, had < 30 patients in each arm and one study was on poor responders. The included studies also varied in terms of type of OCP used duration of pretreatment (14–28 days) and wash-out period ranging from 2 to 5 days.[7,8] These variations in the studies provide less confidence on the overall data concluded.

Efficacy

Based on the already proven facts by Cédrin-Durnerin *et al*., Garcia-Velasco *et al*. conducted a randomized controlled clinical trial comparing the outcomes in an OCP pretreated GnRH-An group (OCP group, n = 115) with a group receiving long GnRH-A protocol (no-OCP group, n = 113). The pretreatment group received OCP (30 μg ethinyl estradiol and 150 μg levonorgestrel) for 12–16 days in the previous cycle, starting from day 1 to 2 of spontaneous menses. Stimulation was started after 5 days of wash-out period and GnRH-An was introduced from day 5 or 6 of stimulation. The no-OCP group did not receive pretreatment and were started on GnRH-A on day 20 of the previous cycle. The study found no significant difference in dose of FSH consumption (OCP: 1613 ± 143, no-OCP: 1807 ± 210, P = 0.44), oocytes retrieved (OCP: 10.2 ± 0.8, no-OCP: 11.7 ± 0.9, P = 0.21) and fertilization rate (OCP: 68.1%, no-OCP: 64.8%, P = 0.52). The total duration of stimulation in the OCP group was significantly lesser than the no-OCP group (OCP: 10.3 ± 0.4, no-OCP: 11.3 ± 0.3, P = 0.04). The ongoing PRs (OCP: 47.8%, no-OCP: 53.9%, P = 0.18), miscarriage rate (OCP: 8.9%, no-OCP: 17%, P = 0.09), and live birth rate (OCP: 44.3%, no-OCP: 47%, P = 0.35) were found to be comparable. The study concluded that OCP-pretreatment in GnRH-An protocol could provide comparable outcomes with long GnRH-A protocol.[9]

Effect on endometrium

There may be barriers associated with impact of OCP pretreatment on the quality of endometrium. The question was addressed by Bermejo *et al*. in 2014. The group conducted a prospective study, which assessed the endometrial gene expression related to endometrial receptivity in OCP pretreated women undergoing stimulation with GnRH-An protocol. In the study, 10 young and healthy women underwent controlled ovarian stimulation (COS) for oocyte donation program. 5 women received OCP pretreatment (30 μg and 150 μg levonorgestrel) for 12–16 days and were stimulated after a 5 days wash-out period (Group A). The other 5 donors were stimulated from day 3 of their spontaneous periods (Group B). Microarray data on gene expression were obtained from endometrial biopsies done on day 7 after triggering with hCG. No individual gene expression varied in both the groups and functional analysis revealed 11 biological processes showed significantly enriched in Group A.[10] As against hypothesized earlier, OCP pretreatment does not negatively impact the endometrial quality.

Oral contraceptive pills in "Batch *in vitro* fertilization" setup

Based on the reviewed evidence, it is proven that OCPs can be utilized as an effective option for programming COS with GnRH-An protocol for IVF/ICSI cycles with a rather positive effect on the endometrium. The OCP pretreatment should be strictly, followed by a 5-day wash out period and the duration of pretreatment should be ideally between 12 and 16 days.[9]

As described in Figure 2, if day 0 is considered as a day of OPU when the embryologist is available at the center, day 2/3 is the day of embryo transfer. 2 days before day 0, day − 2 is the day of trigger. Based on the baseline assessment of the patient, stimulation could be started between days − 14 to − 10 and accordingly days − 8 to − 5 would be the day

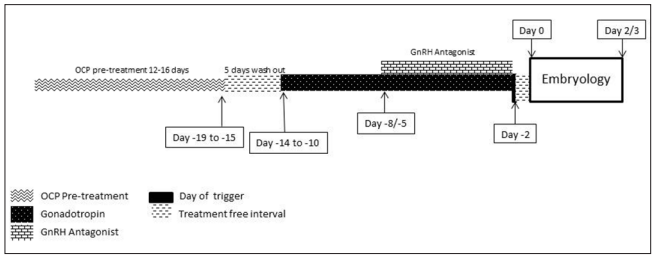

Figure 2: Example of oral contraceptive pill pretreatment with gonadotropin-releasing hormone antagonist protocol in "Batch *in vitro* fertilization"

when GnRH-An would be started. Calculating the 5 days washout from the day of stimulation, OCPs would be stopped between days − 19 and − 15.

ESTRADIOL PROGRAMMING

Fanchin *et al*. in 2003, demonstrated that a pretreatment with luteal phase E2 reduced size discrepancies of early antral follicles during the early follicular phase.[11] This effect exerted by the estradiol can be used for suppressing the endogenous FSH, thereby achieving a homogenous follicular development in COS with GnRH-An protocol.

Efficacy

Guivarc'h-Levêque *et al*. and group conducted a prospective randomized study comparing outcomes of estradiol valerate (EV) pretreated GnRH-An cycles with long GnRH-A protocol. The objective of the study was to assess the possibility of programming GnRH-An cycles with EV pretreatment to prevent weekend oocyte retrievals without compromising on the outcome. The assumption made was that if stimulation were initiated from Thursdays to Sundays, 95% of the oocyte retrievals could be conducted between Mondays and Fridays. The control group was started on GnRH-A from day 20 of the previous cycle. The study group received EV 4 mg a day starting from day 25 of the previous cycle until the day before stimulation. The ongoing PRs in the intent to treat as well as per embryo transfer was found to be comparable across both the groups, (28.6% vs. 27.9%) and (37% vs. 34.8%) respectively.[12]

The same group conducted a nonrandomized prospective study to verify if estrogen pretreatment beyond variable number of days of menses would impact on IVF outcomes and birth rate in a GnRH-An protocol. Totally, 1080 women between 25 and 38 years of age who presented with a classic indication for IVF/ICSI between September 2004 and January 2009 were enrolled. There was no prior randomization and all the patients received EV 4 mg/day starting from 3 days prior to theoretical date of menses until the 1st day of stimulation (between Thursday and Sunday). For anovulatory or dysovulatory women, treatment with a progestogen, dydrogestrone, was initiated for 10 days until starting EV treatment. The patients were retrospectively then divided into six groups based on the number of days of EV treatment since the 1st day of menses (D1) up to the start of stimulation. Group A (n = 283) received EV until D1 and D2, Group B (n = 258) until D3, Group C (n = 296) until D4, Group D (n = 272) until D5, Group E (n = 245) until D6 and Group F (n = 249) until D7 and D8. No significant difference was observed between groups for the mean number of oocytes retrieved (A: 8.9 ± 7, B: 8.9 ± 5.7, C: 8.2 ± 4.9, D: 8.4 ± 5.6, E: 8.2 ± 5.2, F: 8.1 ± 4.9); the ongoing PR per transfer (A: 26.9%, B: 31.4%, C: 30.0%, D: 28.6%, E: 30.0%, F: 34.8%), and the delivery rate per transfer (A: 23.1%, B: 26.4%, C: 23.5%, D: 22.4%, E: 24.2%, F: 29.5%). The mean number obtained, transferred, and cryopreserved embryos were also found to be comparable. Although not significant, a longer treatment with EV (as seen in group F) yielded a higher ongoing PR. The study concluded that estrogen pretreatment beyond variable number of days of menses had no deleterious effect on outcomes.[13]

A prospective study by Ye *et al*. involving 220 women compared the EV 4 mg pretreatment in women undergoing COS with flexible GnRH-An protocol (study) with a group undergoing COS with long GnRH-A protocol (control). The women in the study group were started on EV 4 mg/day starting from day 21 of the previous cycle until day 2 of the next cycle. From day 3 onward, a stimulation was started and GnRH-An introduced when lead follicles reached a diameter of 12–14 mm. The control group received triptorelin 0.1 mg SC starting from day 21 of the previous cycle until down regulation and there on dose reduced to 0.05 mg until trigger. A statistical comparable dose of recombinant follicle-stimulating hormone, stimulation days and endometrial thickness were observed in both the groups. In terms of outcomes, a comparable number of oocytes retrieved (12.8 ± 5.7 vs. 13.8 ± 5.4); fertilization rate (85.5% vs. 86.6%), implantation rate (34.7% vs. 37.8%), and live birth rate (34% vs. 37.1%) were seen.[14]

Estradiol in "Batch *in vitro* fertilization"

When used for programming, estradiol has to be started essentially in the mid[6] or late luteal phase[12] in the previous cycle and can be used for up to 10 days from menses followed by stimulation immediately.[13] In "Batch IVF" set up, where patients may have different menstrual cycle duration falling on different calendar dates, the cycles can be synchronized using OCPs in the previous cycle/s followed by estradiol pretreatment in the cycle preceding stimulation. In WHO type II, anovulatory women alternately an additional 10 days progestogen prior to estradiol treatment may be required.

As described in Figure 3, the menstrual cycles of all the patients will have to be aligned using OCPs in the previous cycle/s. If day 0 is considered as the day of OPU when the

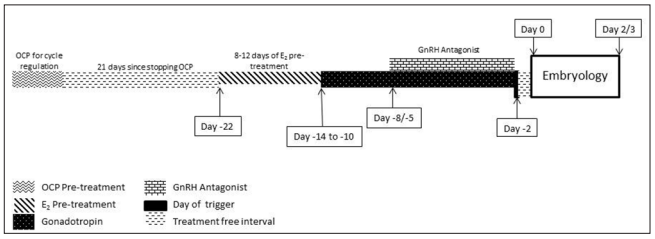

Figure 3: Example of estradiol pretreatment with gonadotropin-releasing hormone antagonist protocol in "Batch *in vitro* fertilization"

embryologist is available at the center, day 2/3 is the day of embryo transfer. 2 days before day 0, day − 2 is the day of trigger. Based on the baseline assessment of the patient, stimulation could be started between day − 14 and − 10 and accordingly day − 8 to − 5 would be the day when GnRH-An would be started. Day − 15 to day − 11 when estradiol is discontinued, and day − 22 is when the pretreatment is initiated. In WHO type II, anovulatory women alternately a progestogen will have to be initiated on day − 32 until − 22.

PROGESTOGEN PROGRAMMING

Efficacy

Use of progestogens for cycle scheduling is not researched much with GnRH-An protocol. In 2010, Smulders *et al*. published a systematic Cochrane review of various literatures related to cycle scheduling in COS cycles. In all, eight studies were considered for progestogen programming out of which six studies were on GnRH-A protocol, one on GnRH-An protocol and one study did not use any GnRH analog. The start date of progestogen ranged between day 1 and day 19 of the previous cycle. The GnRH-An study considered was by Cédrin-Durnerin *et al*. 2007 and the analysis failed to detect any significant difference in PRs, oocytes retrieved, and pregnancy loss.[15]

Progestogen in "Batch *in vitro* fertilization"

Despite of the limited available evidence, it can be hypothesized that using a progestogen, starting from early luteal phase for 10–15 days, may be used for programming and will have a similar effect as OCPs. A 5 days washout period should be considered prior to starting stimulation. Like the estradiol pretreatment, the cycles of all the patients will have to be aligned using OCP in the previous cycle/s.

As described in Figure 4, the menstrual cycles of all the patients will have to be synchronized using OCPs in the previous cycle/s. If day 0 is considered as a day of OPU when the embryologist is available at the center, day 2/3 is the day of embryo transfer. 2 days before day 0, day − 2 is the day of trigger. Based on the baseline assessment of the patient, stimulation could be started between day − 14 to − 10 and accordingly day − 8 to − 5 would be the day when GnRH-An would be started. Day − 30 is when the pretreatment is initiated and as per the planned start date for stimulation, can be discontinued between days − 19 and − 15.

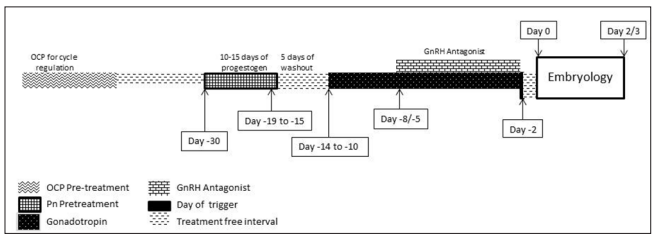

Figure 4: Proposed example of progestogen pretreatment with gonadotropin-releasing hormone antagonist protocol in "Batch *in vitro* fertilization"

A final note

Based on the review of published evidence on cycle scheduling with steroids in GnRH-An protocol, it is now clear that cycles may be effectively scheduled without compromising on the outcome. The essence of programming with sex steroids lies in the type and accordingly the duration and wash out period employed. When programming with OCP and progestogen, the treatment should start in the early follicular phase for 12–16 days and early luteal phase for 10–15 days, respectively, followed by a 5-day washout period prior to stimulation. Estradiol programming should be started in the mid or late luteal phase of the cycle and can extend beyond menses, however immediately followed with stimulation.[6]

While the evidence on progestogen is limited, OCP and estradiol are comparatively well published for scheduling. There may be questions related to the comparative effectiveness of each of the options mentioned. Cédrin-Durnerin *et al*. proved a comparable outcome for retrieved oocytes, PR and live babies across all three pretreated groups when compared with control.[6] Another study published by Hauzman *et al*. compared the outcomes of OCP and estradiol pretreatment in GnRH-An protocol. No significant difference was seen in terms of gonadotropin consumption (OCP: 1627 ± 565 vs. EV: 1692 ± 488, P = 0.54), implantation rate (43.5% vs. 47.4%, P = 0.79), ongoing PRs per cycle (OCP: 46.0%, EV: 44.0% risk difference, −2.0% [95% CI – 21.2–17.3%]), clinical miscarriage rate (7.1% vs. 7.7%, risk difference, 0.6% [95% CI – 16.4–18.3%]), and live birth rate (42.0% vs. 40.0%, risk difference, −2.0% [95% CI – 21.0–17.1%]).[16] The results published so far indicate that all the three steroids for pretreatment provide comparable outcomes in GnRH-An protocol and the choice of one over the other should be made, based on individual clinic's convenience and discretion.

This review provides practical concepts for scheduling with GnRH-An cycles in "Batch IVF" setup. The hazards of "Batch IVF" practice such as undesired response to treatment and mistiming of trigger for some patients may still arise indicating the need for process optimization. Even if the treatment is offered in a batch, the dose and duration of stimulation, type of triggering agent and decision for

vitrification needs to be individualized as per patient's baseline assessment and response. Rather than a fixed day for initiation of treatment, a range of days are presented in the examples, as there may be an inter cycle variation during stimulation as per the baseline characteristics of the patients and gonadotropin dosing practices of different centers. Evidence suggests an average of 4 days range, between 8 and 12 days of stimulation needed to meet the final trigger criteria in GnRH-An protocol.[17] The recruitment of patients in a batch may often range from several weeks to months and the time can be better utilized for initiating the steroids after necessary assessments. In absence of literature which evaluates the outcomes for the already established "Batch IVF," this review could provide some insights based on the proven evidence and understanding of reproductive endocrinology.

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