THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (July–August 2016) 66(4):295–299
DOI 10.1007/s13224-016-0877-z

SHORT COMMENTARY

# Precycle Estradiol in Synchronization and Scheduling of Antagonist Cycles

**Shilpa Saple**[1] · **Mukesh Agrawal**[1] · **Simi Kawar**[1]

Received: 22 July 2015 / Accepted: 19 March 2016 / Published online: 29 April 2016


## About the Author

**Shilpa Saple** is a Fertility Consultant at Aarush IVF and Endoscopy Centre and has been dedicated to fertility practice for last 12 years. She did her M.D. from the prestigious Grant Medical College, Mumbai. As a diploma holder in Gynae Endoscopy, she has keen interest in fertility-enhancing endoscopic procedures. She is actively involved in all aspects of fertility care and also Incharge of FOGSI-recognized training programmes at Aarush IVF and Endoscopy Centre. She has presented papers in various national and international conferences and won award for the same.

**Abstract** Antagonist cycles have an inherent issue of lack of flexibility. As a result where batching of cycles is desired, it is not the preferred protocol in ART cycles. There is also the limitation of ovarian response in antagonist cycle due to the size heterogenesities of antral follicles at the start of stimulation. Among the different options available, use of estrogen in the luteal phase of the preceding cycle has definitely shown benefits with regard to better control of cycle as well as synchronization of follicles available for stimulation. The article gives a detailed analysis of the different options available for timing the egg collection in antagonist cycles, the advantages and drawbacks, and the method of use of estrogen. Whereas in the majority of the trials where estrogen pretreatment was used, the goal of scheduling of egg collection was definitely achieved, increased duration and dose of gonadotropin stimulation were required. There was definite advantage of higher oocyte yield in these cycles. The possibility of premature LH rise later during stimulation and subsequent poor implantation in these cycles has to be further evaluated. Nevertheless, batching of patient friendly antagonist cycles can be effectively possible by use of precycle estrogen treatment.

Dr Shilpa Saple is an associate director; Dr Mukesh Agrawal is a director, and Dr Simi Kawar is a director at Aarush IVF and Endoscopy Centre, Mumbai, India.

✉ Shilpa Saple
drshilpasaple@gmail.com

[1] Aarush IVF and Endoscopy Centre, Prathamesh Harmony, Gautam Buddha Lane, Opposite Orlem Church, Marve Road, Malad West, Mumbai 400064, India

**Keywords** Antagonist cycle · Precycle estrogen · Synchronization

## Introduction

The two broad protocols of controlled ovarian hyperstimulation worldwide in ART cycles are agonist and antagonist protocols. In spite of comparable results with both the agonist and antagonist protocols, acceptance of antagonist protocol on a much wider scale has as yet not been observed. This is owing to the perceived lack of flexibility of the antagonist protocol [1, 2]. In many IVF setups, a major limiting factor is the availability of visiting experts where inhouse clinical expert and embryologist are not available. Besides, certain setups optimize the use of their IVF laboratories by batching cycles as a routine. Therefore, cycle planning continues to remain necessary to organize workflow of the most ART clinics. Flexibility of long protocol allows for formularized and predictable scheduling of oocyte retrievals and hence retains its popularity over the antagonist cycles in the existing scenario. It is well known that antagonist protocols are shorter in length and patient friendly contributing significantly to patient compliance even in cases needing repeat ART cycles [3–6]. Hence, improving the flexibility of a more patient-friendly antagonist protocol with comparable results seems to be the best way forward.

Follicular recruitment starts in the luteal phase of the preceding cycle under the influence of the intercycle FSH rise starting 3–5 days before the onset of menses. Hence, the cohort which will respond to stimulation started on day 2 or 3 of menses as the antagonist protocol has already been decided before the start of stimulation. This explains the slight reduction in oocyte yield and reduction in OHSS with antagonist protocol compared with long agonist protocol. This is of advantage in hyper-responders where limitation in response of follicular growth is desired.

Asynchronous multifollicular growth seen more in antagonist cycles as compared to long protocol may be a direct consequence of size heterogeneities of early antral follicles during early follicular phases of controlled ovarian stimulation (Fig. 1).

With increasing awareness, there is a more than before emphasis on safer protocols which reduce incidence of OHSS, and hence, antagonist regimens would be the treatment of choice in hyper-responders [7].

Antagonist protocol would also be the stimulation of choice in poor responders with low antral follicular counts where the suppressive effects of pituitary desensitizers on ovarian function inevitable in long agonist protocol may not be ideal, since that will further reduce the oocyte yield [8]. GnRH antagonist in poor responders is associated with lower consumption of gonadotropin and shorter duration of stimulation and gives comparable results [9].

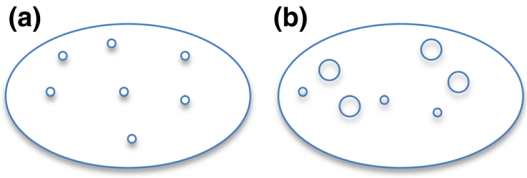


**Fig. 1** Comparison of size heterogeneities in **a** downregulated and **b** spontaneous cycles on day 2 of menses

## Programming of Antagonist Cycles

In antagonist cycle, stimulation begins with the day of spontaneous menses which could fall on any day of the week and it is not possible to avoid the egg pickup and ET procedures over weekends or do batch IVF. Various options like use of oral contraceptive pills (OCP), estrogen or antagonist in luteal phase of preceding cycle and even delay in administration of hCG has been tried to schedule the egg retrievals.

In women pretreated with OCP, a randomized prospective trial has shown that 78 % of retrievals could be performed Monday through Friday for GnRH antagonist cycle [10]. But use of OCP prior to stimulation in antagonist cycle is associated with an increased gonadotropin consumption and increased duration of stimulation and with a trend toward a reduction in ongoing pregnancy rate [11]. It is felt that gestagen component of OCP could have negative impact on endometrial receptivity in subsequent cycle; low endogenous LH concentrations after OCP pretreatment might impair oocyte competence or endometrial receptivity when ovarian stimulation is performed with recombinant FSH only in GnRh antagonist cycles [11].

GnRH antagonists block the GnRH receptor in a competitive fashion and hence reduce LH and FSH secretion within a period of 8 h, without any flare effect. The inhibition of LH is more pronounced than that of FSH. If used in late luteal phase, GnRH antagonist can induce luteolysis and prevent FSH rise and hence can be used as an adjunct to GnRH antagonist cycle either alone or in combination with estrogen [12, 13].

Delay in hCG is another tool to schedule egg retrievals. Prolongation of follicular phase for 2 days, after a point when 3 or more follicles were 17 mm, resulted in lower pregnancy rates per oocyte retrieval and embryo transfer compared to no delay. This difference was probably due to secretory changes in the endometrium and not due to the number and quality of embryos transferred [14]; in contrast, Tremellan and Lane [15] demonstrated that

advancement or delay of hCG by 1 day had no adverse effect on IVF live birth success [14, 15].

## Concept of Estradiol in Luteal Phase

The nature of the mechanisms that control the intercycle FSH elevation remains a subject for debate. Roseff et al. [16] have proposed that in the menstrual cycle it is the decrease in inhibin occurring following the demise of the corpus luteum that represents the triggering signal for the early follicular phase FSH elevation. de Ziegler et al. [17] in their earlier study have postulated that it is the end luteal phase decrease in circulating estradiol concentrations that plays the prime stimulating role for the intercycle FSH rise, a hypothesis concordant with findings made in non-human primates by Zeleznik et al. [18]. In this earlier study, after an extension of luteal phase by 3 days with estradiol a proportional delay in FSH rise was seen without end luteal decrease in inhibin levels. Maximum FSH rise was observed 3 days after withdrawal of estradiol treatment [17, 19, 20].

During luteo-follicular transition, FSH preserves early antral follicles from atresia and ensures their growth. According to their intrinsic sensitivity to this hormone, some follicles are better able to respond to lower FSH levels than the others, and therefore, development starts earlier during the luteal phase. Since larger follicles are more FSH responsive than the smaller follicles, exogenous gonadotropin further intensifies size discrepancies of growing follicles during COH.

Ovarian $E_2$ exerts a negative feedback within the reproductive axis that includes inhibition of GnRH secretion and suppression of GnRH responsiveness. The concept of luteal $E_2$ was first suggested by Fanchin et al. [21]. According to his hypothesis, luteal phase estradiol administration could prevent uncoordinated development of FSH-sensitive follicles and foster growth synchronization. The administration of estradiol in the luteal phase may induce FSH receptor formation in more resistant follicles and result in more coordinated gonadotropin response [21].

Consequentially if the elevation in endogenous FSH has not yet taken place when gonadotropin treatment is initiated, exogenous gonadotropins become the sole source of ovarian stimulation which may increase the treatment needs (number of gonadotropin ampoules).

## Precycle Estradiol Treatment Regimen

Estradiol valerate ($E_2$) is administered from midluteal phase (post-ovulation after 7 days in the previous cycle or 5 days before expected date of next menses) in a dose of 2 mg twice a day for maximum 10 days. Stimulation with r-FSH should

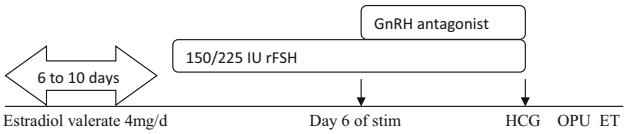


**Fig. 2** Typical cycle plan for precycle estradiol

be started with the gap of 1 day after the last dose of $E_2$. The last day of $E_2$ can be selected so that the retrieval procedures fall on weekdays (considering gonadotropin stimulation of 9 days and 10th day trigger) (Fig. 2).

It is desirable to keep a 1-day washout period after cessation of estradiol before starting stimulation as it allows FSH levels to rise after 2 days.

## Clinical Observations

Study of 37 cases of pretreatment with estradiol by Blockeel et al. [22] showed:

- Higher total dose of gonadotropins used and longer duration of stimulation period in estradiol pretreatment group.
- Similar number of COC retrieved in both groups.
- At start of stimulation $E_2$ was higher, and FSH and $P$ were lower in pretreatment group. Higher estradiol was observed on day of hCG in the same group [22].

In a prospective randomized trial by Hauzman et al. [23] comparing use of OC pills and $E_2$ as pretreatment, no statistically significant differences were found between the two groups. Of note is the fact that poor responders were excluded from the study. Moreover, the pill-free interval and start of stimulation were very short [23].

Other studies also came to the same conclusion that $E_2$ pretreatment prevents intercycle FSH rise that reduces the pace of growth of the follicles, improves size homogeneity of antral follicles on day 8 of r-FSH treatment and increases the number of follicles reaching maturation at once. This approach represents a potential, more physiological alternative to GnRH agonist or oral contraceptive pre-treatment to synchronize multi-follicular development and improve COH results [24, 25].

In the comparison of synchronization of stimulation by use of antagonist for luteolysis along with $E_2$ and $E_2$ alone in the preceding cycle, there was no difference in baseline FSH levels before stimulation in both groups, mean number of oocytes retrieved was similar in both groups, cancelation rates did not differ, and premature LH rise, fertilization rate, number of cleavage embryos and embryos transferred did not differ. There was no difference in implantation, or clinical PR, delivery rates and pregnancy loss were similar [13].

When precycle $E_2$ was compared to downregulation efficacy of agonists, it was concluded that suppression of

FSH is more than that of LH with $E_2$ pretreatment; hence, this method has a higher serum LH level in the whole COH and a concomitantly increased incidence rate of premature LH, compared to the long GnRH agonist protocol. Although there were no significant differences in overall IVF/ICSI outcomes, $E_2$ pre-treatment protocol produces relatively low implantation, clinical pregnancy and live birth rates and higher early pregnancy loss rate compared with the long GnRH agonist protocol [24].

On the other hand, in a study by Chang et al. [26], with a cohort size of 115 it was concluded luteal $E_2$ gave better ovarian response as compared to standard antagonist protocol and may reflect a slower and more coordinated stimulation process, resulting from improved homogeneity of antral follicles. Cancelation rates were significantly lower using the luteal $E_2$ protocol, and number of retrieved oocytes was significantly increased following $E_2$ pretreatment. Although no supernumerary blastocysts were available in the standard cycle, a mean of 1.7 blasts per cycle was cryopreserved in seven patients after $E_2$ pretreatment [26].

Cédrin-Durnerin et al. assessed the effects of estrogen pre-treatment in GnRH antagonist protocol. This was a prospective randomized study that analyzed 472 patients undergoing IVF/ICSI. Patients were randomized to receive 17-$E_2$ (4 mg/days) or no pre-treatment before daily recombinant FSH administration started on 1st day of estrogen discontinuation or on Cycle Day 2 in non-pretreated women. The mean numbers of retrieved oocytes ($10.9 + 5.7$ vs. $10.2 + 5.6$) and obtained embryos ($5.5 + 3.7$ vs. $4.8 + 3.7$) were not significantly different between women allocated to estrogen pre-treatment ($n = 238$) and no pre-treatment ($n = 234$). Total FSH amount ($1557 + 408$ vs. $1389 + 347$ IU) and stimulation duration ($10.8 + 1.4$ vs. $10.0 + 1.5$ days) were slightly but significantly increased in pretreated patients. Positive pregnancy tests, ultrasound PR and delivery rate per cycle were similar (36, 33 and 26.6 %, respectively, vs. 38.2, 35.4 and 30 %). The authors concluded that $E_2$ pre-treatment is associated with the requirement of higher FSH doses and longer duration of stimulation without any significant increase in the number of retrieved oocytes. Estrogen does not affect cycle outcome and therefore might be used in clinical practice for programming IVF retrievals during working days.

During the washout period after both OCP and progestogen pre-treatments, the endocrine profile shifted from strongly suppressed FSH and LH values to values similar to those observed in a spontaneous cycle, while the follicle size inside the cohort remained homogeneous. Therefore, these results suggest that a 5-day washout period is optimal for patients pre-treated with progestogen and OCP. In contrast, natural estrogen pre-treatment did not significantly reduce serum FSH levels, and follicle sizes within the cohort appeared as heterogeneous as observed on spontaneous Cycle Day 3. Moreover, the abrupt FSH rebound after stopping estrogen intake with a concomitant increase in follicle sizes argues for a short washout interval of 1 or 2 days [27, 28].

Dragesic et al. [12] retrospectively evaluated 68 prior poor responders in 80 IVF cycles who were administered estradiol in the form of a 0.1 mg transdermal patch started in the luteal phase and GnRH antagonist was initiated 2 days later and continued for 3 days. Gonadotropin stimulation was begun, and the antagonist was discontinued with menses. GnRH antagonist was then reinitiated when adequate ovarian stimulation had been achieved. There was a significant reduction in cycle cancellations in comparison with the prior cycle along with an increase in number of mature and fertilized oocytes obtained with an ongoing pregnancy rate of 26.2 % [12].

Enough data support an improvement in the quality and number of embryos in IVF poor responders when treated with a luteal phase estradiol protocol. The luteal estradiol protocol may represent a novel and more successful way to treat poor responders during IVF cycles. In the trial by Frattarelli et al. [28], patients were being used as their own historical control, and because their preceding cycle was a poor, response failed cycle, and hence, it was illogical to compare pregnancy outcomes from one cycle to the next. However, when the pregnancy outcomes for only the second cycle were analyzed on the basis of a luteal estradiol versus a standard protocol, the luteal estradiol outcomes were all superior to the standard protocol with a power analysis revealing the need for 971 patients to show statistical significance [28].

## Conclusion

Traditionally used and time-proven long protocol as the name itself suggests is long and patient non-friendly. However, it is associated with a good outcome and more importantly allows for batching protocols. Batching is still followed in many centers owing to limitations in terms of not having a full-time embryologist or IVF consultant for optimum use of drugs and time management. With the advent of antagonist, we now have a protocol which is friendlier to the patient and is shorter in length. The success achieved by this protocol is comparable to the long protocol. Certain situations of hyper-responders where the HCG trigger can be replaced by an agonist trigger thereby decrease the risk of OHSS significantly, and in poor responders where the downregulation of the long protocol is not desirable, the antagonist cycle has proven itself to be very useful.

The need to make antagonist cycles more flexible and more amenable to batching was felt. Among all the

different options tried toward this end, the precycle $E_2$ shows much promise. It is simple and effective. Moreover, it does not affect the pregnancy rates adversely, and it may even actually improve it.

In poor responders, the increase in the egg yield in antagonist cycles may even improve the cycle results. More well-controlled randomized, prospective studies, however, are needed for conclusive evidence.

**Compliance with Ethical Standards**

**Conflicts of interest** None.

**Ethical statement** There are no ethical issues and no financial association.

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