

Advancing or postponing the day of human chorionic gonadotropin does not matter for the outcome in assisted reproductive technology

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ABSTRACT

CONTEXT: The primary outcome is to remove the worry of getting immature oocytes with early administration of human chorionic gonadotropin (hCG). **AIM:** The aim was to find out the association between the day of hCG administration and follicular response in relation to the number and maturity of oocytes, and fertilization rate in assisted reproduction to avoid weekend oocyte recovery (OR). **SETTINGS AND DESIGN:** Retrospective study was carried out in the university infertility clinic. **MATERIALS AND METHOD:** Controlled ovarian hyperstimulation (COH) in 94 patients undergoing assisted reproductive technology (2010-2011) with recombinant follicle stimulating hormone and timely gonadotropin-releasing hormone antagonist were analyzed regarding day of hCG from day 8-11. Oocyte maturity and fertilization was analyzed and correlated with the day of hCG administration. **STATISTICAL ANALYSIS:** Kruskal–Wallis test. **RESULTS:** The average number of >18 mm follicles observed from day 8-11 of hCG administration was not statistically different. However, the OR rate (54.2%), number of mature oocytes (92.5%), and fertilization rate (78.5%) was maximum in the patients where hCG was administered on day 8 of COH. **CONCLUSIONS:** The day of hCG administration between 8 and 11 does not affect the OR rate significantly although the number of oocytes recovered on day 8 are marginally higher compared with day 9-11. Hence, it is possible to safely avoid weekend oocyte retrieval, by delaying or advancing hCG administration without compromising the outcome.

KEY WORDS: Human chorionic gonadotropin administration, oocyte maturity, super ovulation

INTRODUCTION

It is important to decide the day of human chorionic gonadotropin (hCG) administration to get the best mature oocyte. By the introduction of gonadotropin-releasing hormone (GnRH) antagonist, weekend oocyte retrievals can be minimized.^[1] Though, the ovarian stimulation is controlled, it is not always predictable. The day of hCG injection depends mainly on the patient's ovarian response to gonadotropins and hence the day of oocyte retrieval cannot be determined in advance. The aim of this study was to look into the primary efficacy end points such as the number of oocytes retrieved per patient, maturity and fertilization rate in relation to the day of hCG administration.

MATERIALS AND METHOD

This retrospective, nonrandomized study was carried out in the university infertility clinic. Ninety-four patients undergoing assisted reproductive technology (ART) cycles between 2010 and 2011 were included. Data were collected by individual case records. The controlled ovarian hyper stimulation was achieved by 200 IU of recombinant gonadotropins (Recagon, MSD Pharmaceuticals), given subcutaneously from day 2 of the cycle followed by the administration of 0.25 mg of GnRH antagonist (Orgalutron, MSD Pharmaceuticals) from day 5 or 6 of the cycle depending on the criteria - 14 mm follicle or serum estradiol >400 pg. Follicular

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response was monitored by ultrasound and serum estradiol estimation. The trigger with hCG of 10,000 IU (Pregnyl, MSD Pharmaceuticals) was given between day 8 and 11 of ovarian stimulation when there were at least four follicles of 18 mm size to avoid weekend OR, as per standard protocol. Injection hCG was avoided on a Friday to avoid Sunday OR and given either on Thursday or Saturday. The follicles were aspirated 35 h later by transvaginal ultrasound guidance and the oocyte number, and nuclear maturity was assessed. The oocyte maturity were considered as follows - germinal vesicle (GV) oocyte, seen with a vesicle and considered as a very immature oocyte; metaphase I (MI) oocyte - absence of GV and polar body; metaphase II - no GV and with first polar body present, considered a mature oocyte. The oocytes were fertilized by intra-cytoplasmic sperm injection (ICSI) and successful fertilization was documented after 16-18 h. Analysis was performed to determine if advancing or delaying the oocyte recovery (OR) by 1 day from the "ideal" day 9 of stimulation, to avoid weekend OR had any impact on OR regarding maturity.

RESULTS

The mean number of total follicles tapped was the lowest on day 8 (10.75), compared to day 9 (16.9), day 10 (16.0) and day 11 (17.5) [Figure 1]. The average number of >18 mm follicles observed from day 8-11 of hCG administration was not statistically different. However, the mean number of follicles of 14-18 mm size was approximately 4.5 on day 8, which then increased to 8.0 on day 9, 7.3 on day 10 and 8.7 on day 11 [Figure 2]. This shows that on delaying the administration of hCG, the mature follicles were not significantly different, though there was a rise in immature follicle from day 8 to day 9, 10 and 11. As shown in Figure 3, the highest OR rate was observed on day 8 (54.2%) of hCG administration, compared with day 9, 10, 11 which were 47.6%, 46.7%, and 45.1%. As the days progressed, it appeared that there was a decline in the OR rate which was statistically not significant. As shown in Table 1, the mean percentage of GV oocytes was more on day 11 (8.5%, standard error of mean [SEM]=4.4), when compared to day 8 (6.7%, SEM = 3.5), day 9 (7.1%, SEM = 12.9), day 10 (4.5%, SEM = 1.5). As the SEM was high in all the values, it was not statistically significant. The mean percentage of MI oocyte retrieved, was 0.83% (SEM = 0.83) on day 8, 5.18% on day 9 (SEM = 8.89), 6.15% on day 10 (SEM = 2.08) and 7.52% (SEM = 4.93) on day 11. This was not statistically significant. The number of MII oocytes was the highest on day 8 (92.5%, SEM = 3.8), when compared to day 9, 10 and 11 which were 87.7% (SEM = 15.4), 89.3% (SEM = 2.7%), and 83.9% (SEM = 6.0), though it is not statistically significant. The maximum fertilization rate (78.5%) was observed in the patients where hCG was administered on day 8, when compared to 71% on day 9, 76.4% on day 10 and 66.6% on day 11 [Table 1]. This was not statistically significant.

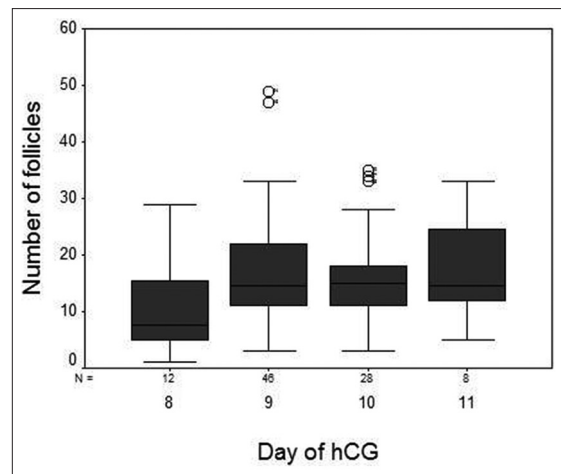


Figure 1: Total number of follicles tapped and day of human chorionic gonadotropin

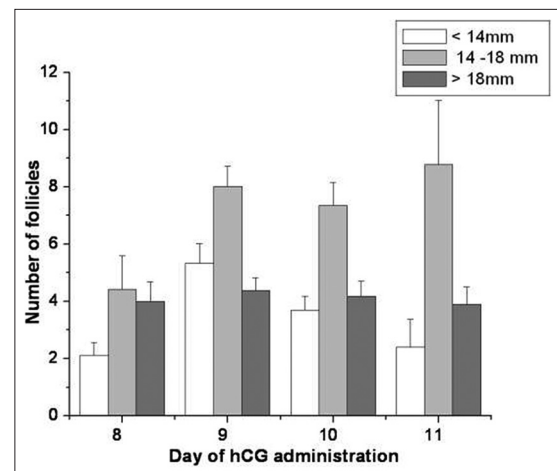


Figure 2: Number of various follicle sizes and day of human chorionic gonadotropin

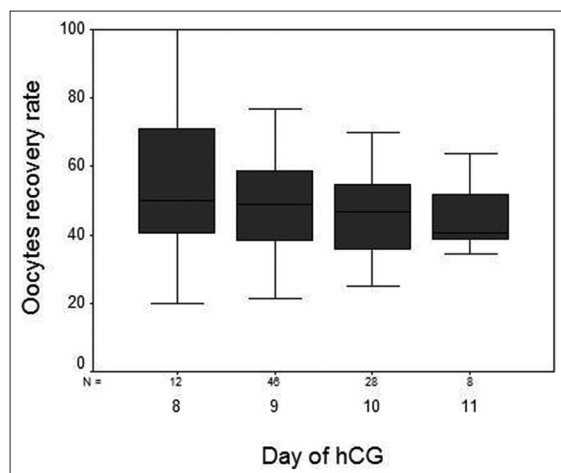


Figure 3: Oocyte recovery rate and day of human chorionic gonadotropin

An extra day of antagonist did not show any ill-effect on ovarian stimulation or pregnancy rates.

Table 1: Day of hCG, oocyte maturity, and fertilization rate

Day of hCG	Number of patients	Oocyte maturity (%)			Fertilization rate
		GV	Metaphase I	Metaphase II	
8	12	6.7	0.8	92.5	78.5
9	46	7.0	5.2	87.8	71.0
10	28	4.5	6.2	89.4	76.4
11	8	8.5	7.5	84.0	86.6

hCG=Human chorionic gonadotropin, GV=Germinal vesicle

Statistical analysis

The statistical analysis was performed using Kruskal–Wallis test. The data were expressed as mean \pm SEM. The graphs were plotted using SPSS version 15 (SPSS South Asia, Bengaluru, Karnataka, India).

DISCUSSION

The current study suggests that earlier triggering of final oocyte maturation by day 8 of ovarian stimulation, as soon as three or more follicles of 18 mm, does not appear to be associated with the retrieval of immature oocytes. A study conducted by Tremellen and Lane,^[1] with a total of 1642 nonprogrammed *in vitro* fertilization (IVF) antagonist cycles, showed that advancing the OR by 1 day resulted in a small but significant decrease in the number of oocytes collected. However, deviation did not show a significant effect on live birth rate. The same study concluded that it is possible to safely avoid weekend ORs during GnRH antagonist cycle by advancing hCG administration by 1 day. Similarly, other studies^[2-4] showed similar results of no difference in a negative impact on embryos and day of hCG.

There is a concept of giving estrogen for postponement of the cycle and to adjust the oocyte pick up and avoiding the weekends. It is highly unlikely that any type of pretreatment aiming to allow initiation of stimulation on a certain day will result in avoidance of weekend oocyte retrievals, when predefined criteria for triggering final oocyte maturation are used.^[5] A randomized clinical trial (engage) assessed whether adjusting the start day of ovarian stimulation and/or day of hCG trigger could minimize oocyte retrieval during weekends without adverse effects on clinical outcome.^[6] There was no effect in the number of oocytes retrieved and pregnancy rates by start day and/or delay in hCG administration. In recombinant follicle stimulating hormone (rec-FSH)/GnRH antagonist regimens, by choosing day of initiation of ovarian stimulation, it appears possible to minimize weekend oocyte retrieval. Oestradiol valerate during the luteo-follicular transition period prior to the initiation of ovarian stimulation with daily dose of 2 mg \times 2 mg from day 25 of the preceding cycle onwards, during 6-10 consecutive days, depending on the day of the week was analyzed in a randomized control trial.^[7] The study concluded that the pretreatment with estradiol valerate results in a significantly lower proportion of

patients undergoing oocyte retrieval during a weekend day and can be a valuable tool for the organization of an assisted reproduction center.

In a study of 120 patients where they were divided into two category: hCG when three follicles were 16 mm or more which was the early hCG group and the other group was one day later and were categorized as late hCG group. There was no significant differences were observed between the early-hCG and the late-hCG group regarding positive hCG and ongoing pregnancy rates.^[8] All the above studies were in contrast to the older study, which showed that prolongation of the follicular phase in patients stimulated with rec-FSH and GnRH antagonists for IVF does not affect oocyte or embryo quality but is associated with a significantly lower ongoing pregnancy rate.^[9] Though in this study, follicle size was a definite criteria there were more than four follicles of 18 mm when hCG was administered as on any of the chosen day. We did not see any significant changes in the nuclear maturity and fertilization rate with delayed aspiration. Although studies have shown increased incidence of polyspermic fertilization in postmature oocytes from delayed aspiration, use of ICSI in the present study did not change fertilization rate. Endometrium was identical in all groups and there was no significant difference in thickness. Concern of delay of antagonist by a day did not show any detrimental or adverse effects.

It has been shown that the total antral follicle count was inversely associated with the odds of oocyte capture. Further, follicular size was associated significantly with the OR rate.^[10] Our study showed the average number of >18 mm follicles observed from day 8-11 of hCG administration was not statistically different.

To reduce ovarian hyper stimulation syndrome (OHSS) the practice of “coasting” has been tried where in hCG was delayed for few days to bring down the estradiol levels. A study on 81 women who had their stimulation cycles coasted, were grouped according to the number of coasting days.^[11] Women in whom coasting lasted for ≥ 4 days had significantly fewer oocytes retrieved ($P < 0.05$) and decreased implantation rate ($P < 0.05$) compared to those coasted for 1-3 days. Pregnancy rate/embryo transfer and live birth rate did not differ between groups. In conclusion, coasting appears to decrease the risk of OHSS without compromising the IVF cycle pregnancy outcome. Prolonged coasting is, however, associated with reduced implantation rates, perhaps due to the deleterious effects on the endometrium rather than the oocytes.

Though, the observations are interesting and helpful in the clinical management of stimulated cycles, due to limited sample size, we could not establish statistical power in this study. Hence, larger prospective studies are required

to validate our observation. In addition, RCT would have been more appropriate to understand the day of hCG administration.

CONCLUSION

The day of hCG administration between 8 and 11 does not affect the OR rate significantly; although, the number of oocytes recovered on day 8 are marginally higher compared to day 9-11. It is possible to safely avoid Sunday oocyte retrieval by delaying or advancing injection hCG administration in Assisted Reproduction to avoid burden on the ART center over a weekend.

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