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Time Interval between HCG Ovulation Trigger and Ovum Pickup & Outcomes of GnRH Antagonist ICSI Cycles in Normal Responders Women; a Randomized Controlled Study

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Abstract

Research Question: Is the time interval between final trigger of oocyte maturation and ovum pickup associated with outcomes of ICSI cycles?

Background: Human chorionic gonadotropin (hCG) is the most commonly used pharmacological agent as a surrogate for the natural luteinizing hormone (LH) surge for triggering of final oocyte maturation in ICSI cycles. The interval between hCG priming and ovum pickup is very crucial , involves a series of essential processes, such as initiation of luteinization, cumulus cells expansion and oocyte meiosis resumption are completed in that time interval.

Objective: This study aims at finding out whether the time interval between the final oocyte maturation trigger by hCG and ovum pickup could affect the outcomes of antagonist protocol ICSI cycles in normal responders. The primary outcomes were the oocyte retrieval rate (ORR) and mature oocytes percentage.

Methods: It is a prospective randomized controlled study, including 351 women undergoing ICSI cycles in the period from November 2019 to November 2020 in Shatby university hospital and two private IVF centers. GnRH antagonist protocol was used in all patients then triggering of final oocyte maturation was performed by administration of recombinant HCG.

Then women were randomized to have their oocyte retrieval either after 34 – 35 hours (group 1, n = 112), after 35 – 36 hours (group 2, n= 112) or after 36 – 37 hours (group 3, n =127).

Results: Statistically significant more oocytes were retrieved in group1 ($p = 0.047$) however, the mature oocytes (MII) percentage was significantly higher ($p < 0.001$) and immature oocytes (MI & GV) were significantly fewer in group3 ($p < 0.001$). There was no significant difference between the three groups in fertilization rate ($p = 0.480$), blastocyst rate ($p = 0.346$), number of top quality embryos ($p = 0.850$), implantation rate ($p = 0.203$), clinical ($p = 0.243$) and ongoing pregnancy ($p = 0.593$) rates and OHSS development rate ($p = 0.560$).

Conclusion: Delaying ovum pickup in GnRH antagonist ICSI cycles after a time interval of 36 – 37 hours after HCG administration is associated with significantly more mature oocytes, less immature oocytes without jeopardizing the oocyte retrieval rate.

Keywords: GnRH Antagonist; Human Chorionic Gonadotropin; Ovum Pickup; Oocyte Retrieval Rate; Randomized Controlled Trial

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Introduction

Triggering final follicular maturation is a pivotal step in IVF/ICSI cycles to get mature oocytes ready for subsequent laboratory processing [1]. When GnRH agonist protocol is used, oocyte maturation triggering must be achieved by hCG, while GnRH antagonist stimulation protocol allows maturation triggering by hCG, GnRH agonist or dual trigger [1]. Since early days of the in vitro fertilization (IVF) era in the 1980s, one of the unique tools used in IVF cycles, that has remained unchanged over time is the use of human chorionic gonadotropin (hCG) (as an alternative to the midcycle surge of gonadotropins) for triggering of ovulation & oocyte maturation [2] , due to its biological activity of human chorionic gonadotropin (hCG) similar to LH. Oocyte release usually occurs 36-40 hours after ovulation trigger similar to natural cycles [3]. Maturation of oocytes and adequate early luteal progesterone production, as stimulated by the HCG trigger, may be optimized to augment outcomes of IVF/ICSI cycles. The combined optimized functions have now changed our perspective of both how oocyte maturation and luteal phase support should be ideally performed [4].

The time lag between HCG bolus trigger administration and ovum pickup is crucial in IVF/ICSI cycles, because a continuum of critical processes, as stimulus for luteinization, cumulus expansion and meiosis II resumption are achieved in this time [5]. The effectiveness of ovum pickup can be evaluated by: (a) calculating oocyte retrieval rate (ORR) by dividing the number of retrieved oocytes by the number of ≥ 11 mm follicles present on final oocyte maturation trigger. Currently, it is unclear whether ORR is dependent on the time between from HCG administration to ovum pickup [6]. (b) Oocyte maturity; during the time period after HCG administration, oocyte maturation inhibition ceases, and oocyte continues meiosis. In contrast to oocyte recovery, maturation of oocytes is a continuous process that does not stop at the time of pickup of oocytes so, both in vitro and in vivo maturation are responsible equally to the final maturation assessment of oocytes [7,8].

Therefore this study was conducted aiming at finding out whether the interval between the final oocyte maturation trigger by human chorionic gonadotropin and ovum pickup could affect the outcomes of ICSI cycles.

Methods

Setting

Shatby University hospital and two private ICSI centers in Alexandria, Egypt.

Study Design

The present study was a registered prospective randomized controlled study (Pan African Clinical Trial Registry: PACTR201911748191910) conducted between November 2019 and November 2020. The Institutional ethical review board approved the study protocol and informed written consent was obtained from all participants after discussing the nature of the study.

Eligible Participants

Couples presented for ICSI cycles (planned for fresh embryo transfer) for various indications were invited to participate in the study if they met our inclusion criteria. We included in women aged 20 - 35 years with expected normal response (according to antral follicle count "AFC" and anti-mullerian hormone "AMH" level) to standard COS attending for ICSI for various indications. The study participants were entered the screening phase of the study included history taking (age, parity, the pattern of the menstrual cycle, history of pelvic surgery and history of previous ICSI cycles), and clinical examination including a pelvic examination. Laboratory investigations (serum E2, LH, FSH, AMH, and PRL) were measured on day 2 of the starting cycle. Semen of the male partners was assessed by CASA for all participants.

We excluded women with PCOS, women with history of ovarian hyper-response and/or OHSS in previous ICSI cycle, women with history of poor ovarian response, women with AMH level < 1.1 ng/dl or > 4.0 ng/dl, women diagnosed with endometriosis, women with congenital uterine malformations and azoospermic males.

Randomization

The eligible women were randomly distributed using computer based randomization (Random Digit Software) into the three study groups: Group I (OPU performed 34-35 hours after HCG administration), Group II (OPU performed 35-36 hours after HCG administration) or Group III (OPU performed 36-37 hours after HCG administration).

Sample Size

Sample size calculation was performed for the primary outcome of the study (oocyte retrieval rate and MII oocyte percentage), based on prior studies [6]. A minimal total sample size of 317 women was calculated to achieves 90 % power to detect a significant effect size in the oocyte retrieval rate in three different time intervals (34, 35 and 36 hours) between HCG

triggering and ovum pickup using a 2 degrees of freedom Chi-Square test with a significance level (alpha) of 0.05.

Controlled Ovarian Stimulation

On the second day of the menstrual cycle (whether spontaneou or induced), ovulation induction was initiated only when serum estradiol (E2) level obtained on that day was less than 50 pg/dl and no follicular activity was seen on TVUS. All patients received a daily dose (150–300 IU according to age, BMI, AFC and AMH level) of Rec-FSH; follitropin alfa (Gonal-F; Merck Serono Europe Ltd, London, UK) for 5 days. Starting on day 5 of stimulation, patients underwent monitoring with transvaginal ultrasound for evaluation of the thickness & pattern of the endometrium and the size & number of the growing follicles and serial assessment of oestradiol level every 2–3 days as required.

To inhibit premature LH surge, a daily subcutaneous dose of 0.25 mg of GnRH antagonist cetrorelix (Cetrotide; Merck Serono Europe Ltd, London, UK) was initiated on day 6 of ovarian stimulation regardless of the size of the dominant follicle "Fixed antagonist protocol" and continued up to day of administration of hCG [9,10]. Follow ups were done repeatedly tailored as required with ultrasonic and E2 analysis and the doses of rec-FSH were adjusted according to the individual response of each patient with possible dose increments of 37.5 – 75 IU till three leading follicles reach 17 mm or more in size, then serum progesterone level & E2 level were tested and the trigger was given [9,11]. Triggering of oocytes maturation was performed using 250 μg of recombinant HCG (Ovitrelle, Merck Serono Europe Ltd, London, UK) [12]. Patients were randomized to have ovum pickup either after 34 hours, 35 hours or 36 hours later, Oocyte retrieval was performed by ultrasound-guided vaginal follicle aspiration under a strictly aseptic technique.

The three study groups were as follow:

Group I: 112 women had their oocyte retrieval 34-35 hours after HCG administration.

Group II: 112 women had their oocyte retrieval 35-36 hours after HCG administration.

Group III: 127 women had their oocyte retrieval 36-37 hours after HCG administration.

ICSI Procedure

Fertilization was performed by ICSI after assessment of oocyte quality; good quality mature oocytes were injected by sperms after removal of cumulus cells from COCs after oocyte retrieval. The culture conditions used were: 37°C, 6% CO_2 and 5% O_2. Then fertilized oocytes were followed till the day of embryo transfer. Embryo transfer (ET) was performed either on day 2/3 (cleavage stage) or day 5/6 (blastocyst transfer) according to availability of embryos. Surplus embryos of excellent quality were cryopreserved (vitrification method).

Luteal Phase Support

Luteal phase was supported through administration of daily 100 mg of progesterone in oil intramuscularly and vaginal suppositories (400 mg twice daily) starting on the day after the ovum pickup and were continued until pregnancy was assessed by serum β-HCG after 15 days. Four weeks after a positive pregnancy test starting from the HCG check day, the patients were examined by TV-US to confirm the presence of cardiac pulsations and to exclude the possibility of multiple pregnancies, luteal phase support was continued till approximately 12-14 weeks gestation.

Study Outcomes

The primary outcomes were oocyte retrieval rate (ORR): the ratio of the number of cumulus–oocyte–complex (COC) retrieved to the number of follicles ≥11 mm present on the day of HCG administration and percentage of MII (mature) oocytes (were defined by the presence of round ooplasm & first polar body). The secondary outcomes included Fertilization rate (defined as the mean number of two pronuclear (2PN) zygotes divided by MII-aspirated oocytes), Blastocyst rate (defined as the number of blastocysts (day 5/6 embryos) divided by MII- injected oocytes), Implantation rate (calculated as the number of intrauterine gestational sac(s) observed through trans- vaginal ultrasound divided by the number of transferred embryos), number of grade A embryos, Clinical pregnancy rate (calculated by considering clinical pregnancy, determined by the visualization of a viable gestational sac within the uterine cavity by ultrasound 3– 4 weeks after embryo transfer), Ongoing pregnancy rate (defined as pregnancy progressing beyond 12 weeks gestation) and rate of development of OHSS in the study population; women who developed OHSS were classified according to severity into mild, moderate, severe and critical OHSS [13].

Statistical Analysis

Data were collected and entered into a Microsoft Access database then analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) [14] Qualitative data were described using number and percent. The Kolmogorov- Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum),

mean, standard deviation, median and interquartile range (IQR). For analysis, $p < 0.05$ was considered to be significant.

Results

Three hundred and eighty one women were counselled for participation in the study; however 20 women did not meet the inclusion criteria and 11 women declined the participation in the trial. Three hundred and fifty one women were randomly distributed to the three study groups, those who were statistically analyzed at the end of study (Figure 1). The three groups were similar in baseline demographic and clinical characteristics with no significant difference in age, BMI, duration of infertility, indication of ICSI. Additionally there was no difference between groups regarding AFC, serum AMH level and partners' semen quality by CASA. For the COS details as demonstrated in Table 1, there was no significant difference in total rec-FSH dose used, number of follicles >11 mm that were present on day of HCG administration. There was a significant difference in the peak estradiol (pg/mL) level measured on day of HCG administration ($p = < 0.001$).

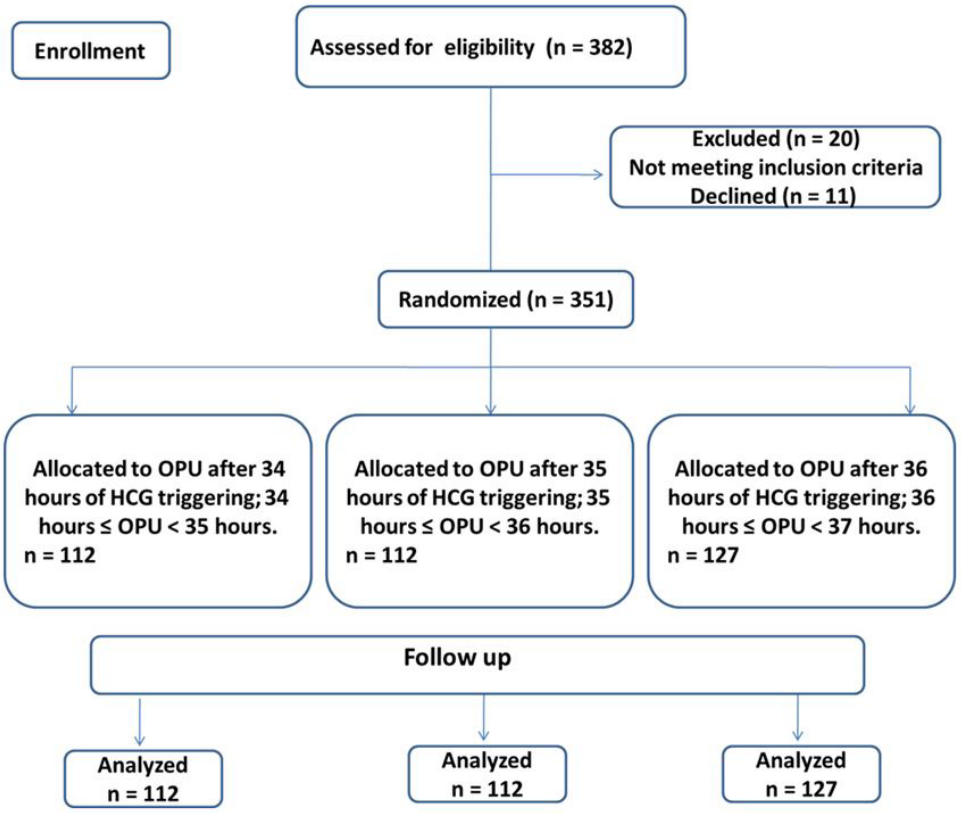

Figure 1: Flowchart of the study

Table 1: Baseline characteristics and ovarian stimulation details of the study groups

Parameter	Group 1	Group 2	Group 3	P	Test of significance
Mean age (years) ± SD	29.80 ± 3.77	30.54 ± 3.85	30.32 ± 4.10	0.347	F= 1.061
Mean BMI (Kg/m^2) ± SD	27.97 ± 2.94	27.84 ± 2.96	27.23 ± 2.52	0.092	F= 2.401
Median & IQR of duration of infertility (years)	5.50(3.0–8.0)	5.0(2.70–8.0)	4.0(3.0 – 6.90)	0.114	H= 4.351
Median & IQR of AMH level (ng/dl)	2.36(1.78–2.95)	2.25(1.62–2.68)	1.98(1.40–2.95)	0.052	H= 5.928
Mean antral follicular count (AFC) ± SD	15.87 ± 3.73	15.53 ± 3.35	15.54 ± 4.25	0.751	F= 0.287
Median (IQR) of Total FSH dose (IU)	1600(1500–2000)	1650(1500–2000)	1800(1500–2100)	0.388	H= 1.892
Median & IQR of follicles (≥11 mm) on day of trigger	15.50(12.0–20.0)	15.0(12.0–20.0)	15.0(11.0–20.0)	0.6	H= 1.023
Median & IQR of peak estradiol on day of trigger (pg/ mL)	3967.5(2541.5–5754)	3166.5(2174.5–4384)	2408(1437.5 –3638.5)	<0.001*	H= 34.891*
Median & IQR of peak progesterone on day of trigger (ng/ mL)	0.88(0.59–1.20)	1.01(0.58–1.36)	0.89(0.54–1.28)	0.34	H= 2.160

F: F for ANOVA test H: H for Kruskal Wallis test
p: p value for comparing between the three studied groups
*: Statistically significant at $p \leq 0.05$

As shown in Table 2, according to the oocyte retrieval characteristics which were the primary outcomes of the study, there were no cycle cancellations in the three groups. A statistically significant difference towards more oocytes retrieved when ovum pickup was performed after 34-35 hours of HCG triggering i.e. in group (I) compared to groups II & III (16.94 ± 9.45 vs. 15.14 ± 7.71 vs. 13.61 ± 6.71, p = 0.047); Post Hoc paired comparison showed a high significant difference between group I & group III (p = 0.01). There was also a significant difference in ORR (%) between groups (99.26 ± 34.23vs. 90.12 ± 25.41 vs. 82.70 ± 16.78, p < 0.001). Comparing the three groups, a statistically significant difference was noticed in MII oocytes percentage; more percentage of mature oocytes collected when ovum pickup was performed after 36 hours of HCG triggering i.e. group (III) and the difference was significant between the three groups (71.75 ± 16.30 vs. 76.72 ± 19.32 vs. 81.27 ± 16.50, p < 0.001);

Post Hoc paired comparison showed a high significant difference between group I & group III (p< 0.01). There were more immature oocytes retrieved (MI & GV oocytes) in group I compared with groups II & III and the difference was statistically significant (p= < 0.001). Regarding fertilization & embryos development, Table 3 shows that there were no differences between groups in fertilization rate (p = 0.480), number of grade "A" embryos (p= 0.850) and blastocyst rate (p = 0.346).

Table 2: Characteristics of oocyte yield in the three study groups

Parameter	Group 1	Group 2	Group 3	p	Test of significance
Median (IQR) oocytes retrieved	15.0 (10.0–22.0)	14.0 (10.0–19.0)	14.0 (9.0–18.0)	0.047*	H = 6.117*
Median ORR (%)	92.86	90	87.5	< 0.001*	H = 15.342*
Mean ± SD MII oocytes percentage	71.75 ± 16.30	76.72 ± 19.32	81.27 ± 16.50	< 0.001*	F = 8.911*
Median (IQR) MI oocytes percentage	14.64(6.90 – 22.65)	10.0(0.0–20.0)	10.0 (0.0 – 17.71)	0.031*	H = 6.924*
Median (IQR) GV oocytes percentage	10.53(4.77–20.0)	7.14(0.0–15.38)	0.0(0.0–9.09)	< 0.001*	H =40.588*

F: F for ANOVA test H: H for Kruskal Wallis test
p: p value for comparing between the three studied groups
*: Statistically significant at p ≤ 0.05

Table 3: Fertilization, implantation & blastocyst rates in the three study groups

Parameter	Group 1	Group 2	Group 3	P	Test of significance
Median (IQR) fertilization rate (%)	73.50(61.0–85.0)	77.35(66.50–90.0)	75.0(63.0–90.0)	0.48	H= 1.466
Median (IQR) implantation rate (%)	50.0(0.0–50.0)	25.0(0.0–50.0)	50.0(0.0–50.0)	0.203	H= 3.192
Median (IQR) blastocyst rate (%)	50.0(33.33–66.67)	66.7(33.33–66.67)	50.0(26.79–100.0)	0.346	H= 2.124
Median (IQR) number of grade A embryos	1.0(0.0–2.0)	1.0(0.0–2.0)	1.0(0.0–2.0)	0.85	H= 0.325

H: H for Kruskal Wallis test
p: p value for comparing between the three studied groups

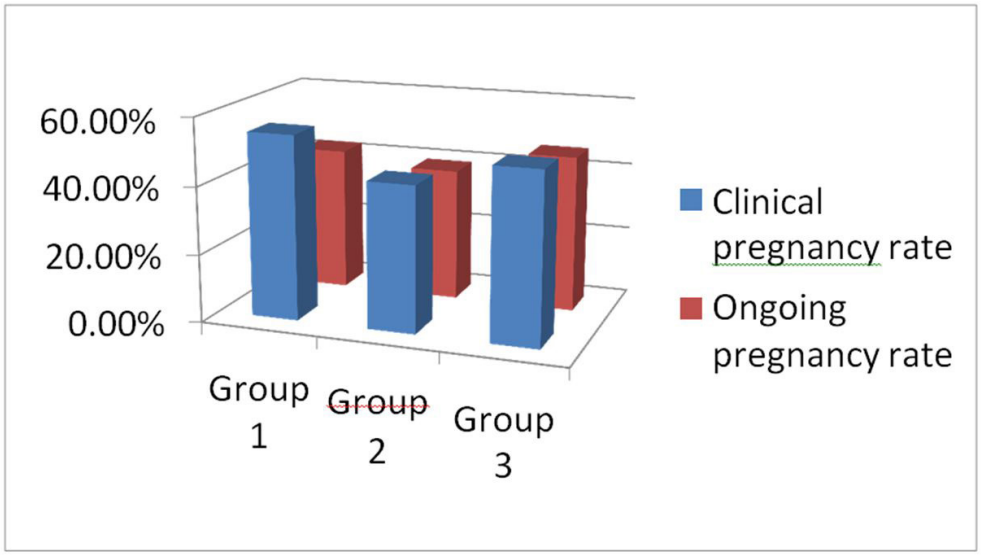

Figure 2: Clinical & ongoing pregnancy rates in the three study groups

Table 4: Comparison between the three studied groups according to OHSS

OHSS	Group 1 No.		Group 2		Group 3		λ^2	p
	No.	%	No.	%	No.	%		
No OHSS	97	86.6	102	91.1	115	90.6	2.987	0.56
Mild OHSS	13	11.6	9	8	12	9.4		
Moderate OHSS	2	1.8	1	0.9	0	0		

λ^2: Chi square test
p: p value for comparing between the three studied groups

There was no statistically significant difference between the three groups regarding mean number of embryos transferred per patient (p = 0.099). There was no statistically significant difference between the three groups according to implantation rate (p = 0.203), clinical pregnancy (p = 0.243) and ongoing pregnancy (p = 0.593) as shown in Figure 2. Regarding ovarian hyperstimulation syndrome, as shown in Table 4 there was no statistically significant difference between the three groups regarding rate of development of OHSS (p = 0.560). There were no cases with severe or critical OHSS.

Discussion

The present study reported significantly higher percentage of mature oocytes retrieved and lower proportion of immature oocytes with delaying ovum pickup after time interval of 36 – 37 hours from HCG administration, moreover without compromising the effectiveness of oocyte retrieval (defined by ORR). However there was no effect of the time interval between HCG injection and OPU on fertilization, blastocyst, grade A embryos, implantation and pregnancy rates. A plausible explanation for that in our study; that the patients enrolled in the study were young (20 – 35 years), with normal ovarian reserve and we excluded cases of previous/ predicted poor response and we also excluded azoospermic males. Hence the background success rates of ICSI in our patients were basically high. Notably, although there was no significant difference between the three groups in fertilization/clinical outcomes, these outcomes were satisfactory in the three groups. For example, the mean of fertilization rate in the current study groups ranged from 72.66 – 74.7%, clinical pregnancy rate ranged from 43 – 54.6 % and ongoing pregnancy rate ranged from 39.2 – 46.1%, all these rates were comparable to the background estimated success rates of IVF/ICSI [15].

The available literature is conflicting regarding the optimal time interval between oocyte maturation trigger and oocyte retrieval. Some authors have found that lengthening time interval is not associated with more MII oocytes or improved clinical outcomes [16-18], others have found that longer time intervals may lead to retrieval of more MII oocytes [5,7,19-21] or better clinical outcomes [22] as better fertilization rate [23], higher blastocyst rate [24], improved pregnancy rates [25]. Moreover, it has been shown in some studies that longer time intervals between HCG administration and ovum pickup could be associated with more mature oocytes proportion without a similar effect on the pregnancy rates [26,27].

Our results are in consistent with Tien NV *et al.* study which reported that oocyte maturation rate was significant lowest in group of OPU ≤35 h (86.6%) compared to groups of G2 (OPU≤ 36h), G3 (OPU ≤ 37h) and G4 (OPU > 37 hours) (97.7%; 97.7%; 92.6% respectively). The study also showed a statistically significant higher fertilization rate in G3 (OPU ≤ 37h) than in groups 1 & 2 [28]. Additionally, a retrospective study conducted by Weiss, *et al.* [26] agrees with the result of the present study. It reported a significant increase in the number of Metaphase II oocytes when lengthening the time interval between HCG administration and OPU ≥ 36 hours compared to shorter time intervals. Fertilization, pregnancy rates were similar in all groups.

In the study of Shen X, *et al.* [29] again agrees with our results, they defined the optimal time interval between HCG injection and OPU as "the time interval for getting more than 60% oocyte retrieval rate and 80% mature oocyte rate". This retrospective study was conducted for 4673 patients with normal ovarian reserve testing undergoing IVF/ICSI cycles using different stimulation protocols; 819 patients using long agonist protocol, 1703 patients using short agonist protocol, 1627 with mild stimulation protocol and 524 patients with GnRH antagonist protocol. The group of ovum pickup after 36.01–37.00 hours had the highest odds of retrieving > 80% MII oocytes: (OR 1.309, 95% CI 1.028–1.666, P = 0.029). The oocyte retrieval rate was almost higher than 60% in GnRH antagonist protocol when ovum pickup performed 33.8–37.7 h after hCG trigger. More than 80% mature oocyte rate was observed in antagonist protocol when ovum pickup was performed 34.5–36.3h after hCG trigger. Concerning outcomes of IVF/ICSI cycles with antagonist protocol, there was no relation between the ovulation trigger–OPU time interval and implantation rate, CPR, LBR/transfer and cumulative LBR.

In contrary to the present study, Bosdou, *et al.* [23] conducted a randomized controlled trial for 156 women who were randomly distributed to have oocyte retrieval performed after 36 hours or 38 hours after administration of HCG. The ORR was not statistically different between the 36 h and the 38 h groups. ORR was not associated with the interval between HCG administration and ovum pickup; only woman's age was

a significant predictor of oocyte retrieval rate in multivariate analysis. Fertilization rate, embryos of top quality, implantation rate, CPR and LBR were similar in both groups. The Metaphase II oocyte percentage was > 70 % in both groups with no statistically significant difference [23]. This difference can be explained by the fact that in our study, we limit the time interval before performing to a maximum of 37 hours.

Against our results, Park, *et al.* [30] performed a prospective observational study including 2079 patients underwent IVF cycles using GnRH antagonist protocol. The patients were divided into three groups by interval between triggering and oocyte aspiration; Group A: 36 hours ≤ interval ≤ 37hours, Group B: 37 hours ≤ interval ≤ 38 hours, Group C: 38 hours ≤ interval ≤39 hours. There was no difference between the three groups in number of oocytes retrieved, percentage of MII oocytes, fertilization rate and pregnancy rate [30]. The different time intervals used in this study was a logical explanation for the contradiction with our results. Despite of the published literature in GnRH agonist ICSI cycles which supports the beneficial effect on oocyte maturation, by lengthening the time interval between administration of the bolus trigger of HCG and ovum pickup to more than 35 hours; this appears to be not the case concerning an extension from 36 hours to 38 hours in GnRH antagonist ICSI cycles.

Our study has the advantage of being a prospective randomized study, which enrolled a notably large sample size than that calculated statistically (317). The results showed that performing ovum pickup after a minimum of 36 hours after hCG trigger in antagonist cycles is associated with reasonable ORR (IQR= 80.0 – 92.0 %) and a statistically significant more mature oocytes (IQR= 75.0 – 93.5%). However the study ended when an ongoing pregnancy (at least 12 weeks gestation) is achieved and follow up for a live birth or take home baby was not done. We also did not include in the study the evolving method for ovulation triggering in antagonist cycles (GnRH agonist) which have been shown to be associated with a comparable oocyte retrieval rate & MII percentage and importantly significantly less OHSS and with a modified luteal phase support, a similar pregnancy rates [31,32]. The time intervals included in the present study were limited to 34 – 37 hours; we did not perform OPU before 34 hours or after 37 hours although this is reported in many similar studies, these time intervals were selected to avoid compromised oocyte yield in case of early (before 34 hours) OPU and spontaneous ovulation in case of delayed (more than 37 hours) OPU.

Conclusion

Delaying ovum pickup in GnRH antagonist ICSI cycles after a time interval of 36 – 37 hours after HCG administration is associated with significantly more mature oocytes, less immature oocytes without jeopardizing the oocyte retrieval rate.

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