Evaluation of dual trigger with gonadotropin-releasing hormone agonist and human chorionic gonadotropin in improving oocyte maturity rates: A prospective randomized study

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ABSTRACT

BACKGROUND: Mature oocytes are prerequisite for achieving the process of *in vitro* fertilization. Human chorionic gonadotropin (hCG) is the standard trigger used for stimulating ovulation but is associated with ovarian hyperstimulation syndrome (OHSS). Gonadotropin-releasing hormone agonist trigger achieves oocyte maturation and lowers the incidence of OHSS, but it has limitations of higher pregnancy loss rate and miscarriage rates. Coadministration of both hormones is found to improve the pregnancy rates and the number of mature oocytes retrieved. We aimed to assess if the dual trigger is better than the conventional hCG in triggering oocyte maturation. **METHODOLOGY:** The study included 76 female patients aged 24–43 years who were randomly divided into two groups with 38 patients in each arm. The study included patients with antimullerian hormone (AMH) <4 ng/ml, antral follicle counts (AFCs)/ovary <12. The study excluded high responders-AMH >4 ng/ml and AFC/ovary >12 to avoid OHSS risk with hCG trigger. **RESULTS:** The study showed statistically insignificant differences between dual group versus hCG group in terms of the number of oocytes retrieved (10.0 ± 5.6 vs. 8.7 ± 5.0; $P = 0.2816$), the number of mature oocytes recovered (8.4 ± 5.0 vs. 7.2 ± 4.0; $P = 0.2588$), fertilization rate (5.9 ± 4.2 vs. 5.6 ± 3.3; $P = 0.7390$), and the number of usable embryos on day 3 (4.0 ± 3.0 vs. 4.0 ± 2.4; $P = 0.8991$). **CONCLUSION:** The dual trigger is equivalent to hCG in triggering oocyte maturation.

KEY WORDS: Dual trigger, gonadotropin-releasing hormone agonist trigger, oocyte maturation

INTRODUCTION

The follicular phase of the menstrual cycle involves the hourly release of gonadotropin-releasing hormone (GnRH), which binds to GnRH receptors on the gonadotropes. This results in the secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in hourly pulses that regulate follicular growth. At midcycle, rapidly rising estradiol from the dominant follicle and a small rise in progesterone (P) lead to a gonadotrophic surge. An increase in the amplitude of LH and FSH pulses initiates oocyte maturity and triggers ovulation approximately 36–40 h later.[1]

Because of its similarity to LH and its long half-life >24 h,[2] human chorionic gonadotropin (hCG) has been used traditionally to trigger ovulation. In 1973, Nakano *et al*. showed that a bolus of GnRH agonist (GnRHa) given intravenously could induce the LH surge.[3] Subsequently, various authors confirmed that ovulation could be

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achieved successfully when a small bolus of GnRHa was given subcutaneously (s/c).[4-6] GnRHa trigger induces final maturation of follicles through an endogenous surge of LH and FSH, which closely resembles the natural midcycle surge. The additional FSH surge induced is believed to promote the resumption of oocyte meiosis, LH receptor formation, cumulus expansion, and release of proteolytic enzymes involved in ovulation.[7,8] GnRHa trigger has been demonstrated to result in the retrieval of a higher number of mature oocytes as compared with hCG;[9] furthermore, it is believed to eliminate the risk of ovarian hyperstimulation syndrome (OHSS).[10] However, the use of GnRHa alone as a trigger results in a lower pregnancy rate and an extremely high early pregnancy loss rate due to a luteal phase insufficiency.[11]

Studies attempted to test the concept of the dual trigger, which involves combining GnRHa with a low dose of hCG to trigger oocyte maturation.[12,13] It was proposed that dual trigger approach provided better oocyte maturity, blastulation rates, and pregnancy rates.[12,14-18]

Our study attempted to assess if the dual trigger is more efficacious than the conventionally used hCG in obtaining a higher number of mature oocytes and usable day 3 embryos.

METHODOLOGY

Study population

The study included 76 female patients aged 24–43 years with antimullerian hormone (AMH) <4 ng/ml, antral follicle counts (AFCs)/ovary <12 and those ready to sign an informed consent. The study excluded high responders-AMH >4 ng/ml and AFC/ovary >12 to avoid OHSS risk with hCG trigger.

Ethical statement

This randomized prospective pilot study was conducted at an infertility center. The study was approved by an Independent Ethics Committee. All the patients provided written informed consent before their enrollment in the study. The study followed good clinical practices as required by the International Conference on Harmonization guidelines, the ethical guidelines for biomedical research on human subjects (ICMR, 2006), and the Declaration of Helsinki.[19]

Dosage schedule

An antagonist protocol with gonadotropin stimulation was used. Starting dose of gonadotropin was based on age, AMH, AFC, and body mass index (BMI).

A combination of recombinant FSH GONAL-f (Merck Serono) for first 5 days followed by Menopure (Ferring Pharmaceutical Pvt. Ltd.,) was used in all patients as per our standard protocol.

For ovulation trigger, the patients were divided into two groups: hCG group received an ovulation trigger of hCG 10,000 IU I/M (Bharat Serum and Vaccines Ltd.,) and dual group were triggered with luperide 1 mg s/c (Sun Pharmaceuticals Ltd.,) plus hCG 5000 IU (Bharat Serum and Vaccines Ltd.,) administered at the same time.

Intracytoplasmic sperm injection was performed in all the patients. Oocyte maturity and embryo grading were done as per the laboratory protocol.

Monitoring

Baseline estrogen (E_2) level, *P* level, and ultrasound were done on day 2 of the cycle. Ovarian stimulation was started when all the values were normal, i.e. endometrium <5 mm, no follicle >10 mm in the ovaries, E_2 <50 pg/ml, and *P* < 0.9 ng/ml. The first monitoring was done on day 5 of stimulation. GnRH antagonist, cetrorelix (0.25 mg, s/c; Intas Pharmaceutical Ltd.,) was started in a flexible regime when the lead follicle reached 13 mm, and/or endometrial thickness was >6 mm – suggesting a rising E_2 level. The dose of gonadotropin was adjusted as per individual requirement. Ovulation trigger was given when at least three follicles were >18 mm. E_2 and *P* levels were measured on the morning of the trigger. The primary outcome measure was to compare the number of Metaphase II (MII) oocytes and number of usable embryos (embryos good for transfer and cryopreservation) on day 3 in the two groups. A subgroup analysis was performed for patients with AMH <1.4 ng/ml.

RESULTS

A total of 76 patients were randomly assigned to either the dual group (*n* = 38) or the control hCG group (*n* = 38). Simple randomization was performed using sequentially numbered sealed envelopes. The envelope was opened by our head nurse. The two groups were matched for age, BMI, basal hormone levels, and cause of infertility. The mean age of the patients in dual group versus hCG group was 32 ± 5 years (range: 24–42) and 33 ± 4 years (range: 25–43), respectively. The groups did not significantly differ with regard to the baseline characteristics such as age, BMI, basal FSH, LH, and AMH levels [Table 1]. Etiology of infertility in patients of both the groups was similar and is presented in Figure 1.

The outcome of ovarian stimulation and hormonal characteristics are presented in Tables 2 and 3, respectively. The duration of stimulation and the average total dose of gonadotropins given to the patients did not differ between the groups compared [Table 2]. Although the average number of total oocytes retrieved (10.0 ± 5.6 vs. 8.7 ± 5.0; *P* = 0.2816) and MII oocytes (8.4 ± 5.0 vs. 7.2 ± 4.0; *P* = 0.2588)

Table 1: Baseline characteristics of the patients in study group

	Dual trigger	hCG	*P*
Number of patients (*n*)	38	38	
Age (years)	32.4±4.5	33.1±4.1	0.4878
BMI (kg/m^2)	25.8±3.9	24.2±3.2	0.0532
FSH (mIU/ml)	7.7±3.0	7.2±2.5	0.5055
LH (mIU/ml)	5.3±3.1	4.8±2.8	0.4715
AMH (ng/ml)	2.3±1.3	2.0±1.0	0.3184

Values are expressed as mean±SD. SD=Standard deviation, BMI=Body mass index, FSH=Follicle stimulating hormone, hCG=Human chorionic gonadotropin, LH=Luteinizing hormone, AMH=Antimullerian hormone

Table 2: Stimulation characteristics and outcome variables in the study group

Variable (mean±SD)	Dual trigger	hCG	*P*
Total days of stimulation (days)	10.0±1.0	10.3±1.4	0.1897
Total dose of gonadotropins (IU/ml)	2851.6±573.0	2879.6±809.9	0.8626
Oocytes retrieved (*n*)	10.0±5.6	8.7±5.0	0.2816
MII oocytes (*n*)	8.4±5.0	7.2±4.0	0.2588
2PN zygotes (*n*)	5.9±4.2	5.6±3.3	0.7390
Usable embryos (D3)	4.0±3.0	4.0±2.4	0.8991

hCG=Human chorionic gonadotropin, SD=Standard deviation, MII=Metaphase II, 2PN=Two-pronuclear

Table 3: Hormonal data in the study group on the day of triggering final oocyte maturation

Variable (mean±SD)	Dual trigger	hCG	*P*
E_2 (pg/ml)	2121.9±985.3	1717.1±1051.7	0.0876
P (pg/ml)	1.0±0.5	0.9±0.5	0.3041

hCG=Human chorionic gonadotropin, SD=Standard deviation

were more in the dual group as compared to hCG group, the difference was insignificant [Table 2]. The difference between outcomes of the other variables including number of two-pronuclear (2PN) zygotes (5.9 ± 4.2 vs. 5.6 ± 3.3; *P* = 0.7390) and usable embryos (4.0 ± 3.0 vs. 4.0 ± 2.4; *P* = 0.8991) also varied insignificantly among the two groups [Table 2]. There were no differences between the groups in the serum E_2 and *P* levels on the day of triggering final oocyte maturation [Table 3].

In addition, subgroup analysis was performed to assess the effect of the dual trigger on oocyte maturation and embryos quality in patients with AMH <1.4 ng/ml. The sub-group analysis included total of 25 patients; dual group (*n* = 14) and hCG group (*n* = 11). There were no significant differences in the baseline characteristics between the two groups [Table 4].

Under subgroup analysis, the comparison of outcomes revealed greater average number of total oocytes retrieved (6.5 ± 5.2 vs. 4.2 ± 2.9; *P* = 0.2009) and MII oocytes (5.5 ± 5.1 vs. 3.7 ± 2.6; *P* = 0.3045) in dual group as compared to hCG group; however, the difference was insignificant [Table 5]. No significant differences were found in the outcomes of

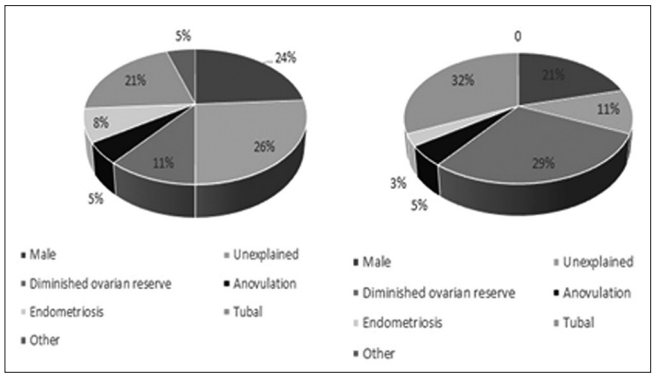

Figure 1: Etiology of infertility in dual trigger and human chorionic gonadotropin group

the other variables including the number of 2PN oocytes (3.4 ± 3.6 vs. 2.8 ± 2.0; *P* = 0.6167) and usable embryos (2.6 ± 2.7 vs. 2.5 ± 1.8; *P* = 0.9783) between the two groups [Table 5]. The levels of E_2 and *P* on the day of triggering final oocyte maturation were insignificantly different between the groups [Table 6].

DISCUSSION

The results of this study found no significant differences in the number of oocytes retrieval between Group 1 receiving hCG and Group 2 receiving the dual trigger. Differences in fertilization rate and usable embryos on day 3 were also insignificant between the two groups. Our study results emphasize that there is no significant benefit associated with the use of a dual trigger in comparison to conventionally used hCG for increasing the number of mature oocytes and usable day 3 embryos in *in vitro* fertilization (IVF). Various studies in past have been conducted to compare the efficacy of hCG with GnRHa in triggering ovulation for IVF with varying results.

Kolibianakis *et al*. conducted a randomized study on 106 patients to compare the efficacy of hCG with GnRHa in triggering oocyte maturation. The study showed no significant differences in the proportion of MII oocytes, fertilization rates, or the number and quality of embryos transferred between the two groups. The study was suspended due to significantly lower ongoing pregnancy in the GnRHa group (odds ratio 0.11; 95% confidence interval 0.02–0.52).[11]

Humaidan *et al*. (2005) also compared the efficacy of GnRHa with hCG in triggering ovulation in 121 patients who were given 0.5 mg GnRHa (*n* = 55) or 10,000 IU of hCG (*n* = 67). They reported significantly more number of oocytes retrieved in GnRHa group. However, their study also revealed lower implantation and clinical pregnancy rate and a higher rate of early pregnancy loss with the use of GnRHa trigger.[20] The study by Engmann *et al*. which

Table 4: Baseline characteristics of the patients in subgroup analysis

	Dual trigger (AMH <1.4)	hCG (AMH <1.4)	*P*
Number of patients (*n*)	14	11	
Age (years)	34.3±4.8	35.9±3.9	0.3758
BMI (kg/m^2)	27.3±3.6	25.5±2.1	0.1601
FSH (mIU/ml)	9.4±3.1	8.4±3.9	0.4927
LH (mIU/ml)	4.6±2.1	4.2±2.7	0.6941
AMH (ng/ml)	1.0±0.3	0.8±0.2	0.1241

Values are expressed as mean±SD. SD=Standard deviation, BMI=Body mass index, FSH=Follicle stimulating hormone, hCG=Human chorionic gonadotropin, LH=Luteinizing hormone, AMH=Antimullerian hormone

Table 5: Stimulation characteristics and outcome variables in the sub-group analysis

Variable (mean±SD)	Dual trigger (AMH <1.4)	hCG (AMH <1.4)	*P*
Total days of stimulation (days)	9.6±1.0	10.0±1.5	0.4003
Total dose of gonadotropins (IU/ml)	2914.3±511.9	2986.4±838.4	0.7929
Oocytes retrieved (*n*)	6.5±5.2	4.2±2.9	0.2009
MII oocytes (*n*)	5.5±5.1	3.7±2.6	0.3045
2PN zygotes (*n*)	3.4±3.6	2.8±2.0	0.6167
Usable embryos (D3)	2.6±2.7	2.5±1.8	0.9783

hCG=Human chorionic gonadotropin, SD=Standard deviation, AMH=Antimullerian hormone, MII=Metaphase II, 2PN=Two-pronuclear

Table 6: Hormonal data in the sub-group on the day of triggering final oocyte maturation

Variable (mean±SD)	Dual trigger (AMH <1.4)	hCG (AMH <1.4)	*P*
E_2 (pg/ml)	1663.8±944.3	1027.2±1002.5	0.1170
P (pg/ml)	0.9±0.6	0.8±0.4	0.6697

hCG=Human chorionic gonadotropin, SD=Standard deviation, AMH=Antimullerian hormone

compared GnRHa with hCG found no difference in terms of the proportion of mature oocytes, number of oocytes, and fertilization rate. Implantation rate, clinical pregnancy rate, and delivery rate were also similar in both the groups.[21] It is now established that GnRHa trigger is associated with corpus luteum dysfunction leading to luteal phase insufficiency with an increased rate of miscarriages and a decreased pregnancy rate.[11,22]

Over the past few years, the use of dual trigger has gained acceptance in triggering oocyte maturation in patients undergoing IVF.[14,23] It has been found that the administration of hCG simultaneously with GnRHa trigger negates its luteolytic effects.[24] Haas *et al*. suggested that coadministration of GnRHa and hCG, i.e., dual trigger can be used for final oocyte maturation in patients with low/poor oocyte yield. These patients had normal follicular development with normal E_2 levels with optimal hCG levels on the day of ovum pickup after hCG trigger but a poor oocyte yield.[25] Beck-Fruchter *et al*. reported a case suffering from recurrent empty follicle syndrome who was successfully triggered with a combination of GnRHa and hCG. Improvement in oocyte recovery after dual trigger suggests that GnRHa can improve clinical outcome. Griffin *et al*. conducted a study to compare dual trigger with hCG alone and found improvement in the percentage of mature oocytes retrieved in the group receiving a dual trigger, but implantation, clinical, and ongoing pregnancy rates were 11.8%, 26.1%, and 17.4%, respectively. The authors speculated that lower pregnancy rates in spite of a higher number of oocytes retrieved might be due to an underlying oocyte dysfunction.[26]

It has been suggested that the greater oocyte maturity reported with GnRHa might be related to the more rapid increase in serum LH after agonist trigger when compared with the rise of serum hCG level after 10,000 IU IM injection of hCG,[27] the concurrent FSH surge, or possibly both.[28] An increase in the number of mature oocytes recovered would theoretically improve IVF results by providing more embryos.[29]

Research has shown improved oocytes maturation rates if retrieved 38 h after the hCG bolus administration.[30,31] The improved oocyte maturation rates in the study by Griffin *et al*. might have been the result of increased trigger/oocyte retrieval time. This speculates that the use of dual trigger could not be indisputably associated with improved oocyte maturation. It appears that the use of hCG alone is helpful in achieving the same number of metaphase oocytes as compared to its combined use with GnRHa.

Our study showed contrasting results to the study by Griffin *et al*. The dose of hCG in the dual trigger in Griffin's study varied from 5000 IU to 10,000 IU, the hCG group underwent agonist down-regulation whereas the dual trigger group was given an antagonist protocol. In our study, the dose of hCG in dual trigger was fixed to 5000 IU. The increased dosage of hCG might have favored the increase in oocyte maturation rate in the study by Griffin *et al*.[14]

A study by Lin *et al*. assessed the effectiveness of dual trigger as compared to conventional hCG trigger in improving live birth, clinical pregnancy, and implantation rates. This was probably due to a significantly higher number of patients with at least one embryo of excellent quality in patients of the dual trigger group. However, in this study, oocyte maturation rates were not measured.[15] These study findings were not in agreement with the study by Griffin *et al*.[14]

AMH level is known to decline with age in women and is recognized as a crucial marker for the poor response to ovarian hyperstimulation in IVF.[32] Lukaszuk *et al*., in his study, found that AMH <1.4 ng/ml is associated with less success rate of live birth in women undergoing

IVF.[33] We conducted a subgroup analysis of women with AMH <1.4 ng/ml who were triggered with hCG and dual trigger. We found no significant difference in the number of usable embryos in both the groups.

CONCLUSION

There is no significant difference in the outcomes in terms of the number of mature oocytes, fertilization rate, and number of usable embryos by day 3 on using either dual trigger or hCG. The use of any kind of trigger can be based on the type of patient, for example, for a patient who is at risk of OHSS and needs to go with a fresh embryo transfer, dual trigger can be opted for as it uses a lower dose of hCG. However, future studies and research are required to confirm our findings and improve our understanding.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Hoff JD, Quigley ME, Yen SS. Hormonal dynamics at midcycle: A reevaluation. J Clin Endocrinol Metab 1983;57:792-6.
2. Damewood MD, Shen W, Zacur HA, Schlaff WD, Rock JA, Wallach EE. Disappearance of exogenously administered human chorionic gonadotropin. Fertil Steril 1989;52:398-400.
3. Nakano R, Mizuno T, Kotsuji F, Katayama K, Wshio M, Tojo S. "Triggering" of ovulation after infusion of synthetic luteinizing hormone releasing factor (LRF). Acta Obstet Gynecol Scand 1973;52:269-72.
4. Itskovitz-Eldor J, Kol S, Mannaerts B, Coelingh Bennink H. First established pregnancy after controlled ovarian hyperstimulation with recombinant follicle stimulating hormone and the gonadotrophin-releasing hormone antagonist ganirelix (Org 37462). Hum Reprod 1998;13:294-5.
5. Gonen Y, Balakier H, Powell W, Casper RF. Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for *in vitro* fertilization. J Clin Endocrinol Metab 1990;71:918-22.
6. Imoedemhe DA, Sigue AB, Pacpaco EL, Olazo AB. Stimulation of endogenous surge of luteinizing hormone with gonadotropin-releasing hormone analog after ovarian stimulation for *in vitro* fertilization. Fertil Steril 1991;55:328-32.
7. Yding Andersen C, Leonardsen L, Ulloa-Aguirre A, Barrios-De-Tomasi J, Moore L, Byskov AG. FSH-induced resumption of meiosis in mouse oocytes: Effect of different isoforms. Mol Hum Reprod 1999;5:726-31.
8. Eppig JJ. FSH stimulates hyaluronic acid synthesis by oocyte-cumulus cell complexes from mouse preovulatory follicles. Nature 1979;281:483-4.
9. Humaidan P, Kol S, Papanikolaou EG; Copenhagen GnRH Agonist Triggering Workshop Group. GnRH agonist for triggering of final oocyte maturation: Time for a change of practice? Hum Reprod Update 2011;17:510-24.
10. Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing *in vitro* fertilization prevents the risk of ovarian hyperstimulation syndrome: A prospective randomized controlled study. Fertil Steril 2008;89:84-91.
11. Kolibianakis EM, Schultze-Mosgau A, Schroer A, van Steirteghem A, Devroey P, Diedrich K, *et al.* A lower ongoing pregnancy rate can be expected when GnRH agonist is used for triggering final oocyte maturation instead of HCG in patients undergoing IVF with GnRH antagonists. Hum Reprod 2005;20:2887-92.
12. Shapiro BS, Daneshmand ST, Restrepo H, Garner FC, Aguirre M, Hudson C. Efficacy of induced luteinizing hormone surge after "trigger" with gonadotropin-releasing hormone agonist. Fertil Steril 2011;95:826-8.
13. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Thomas S. Gonadotropin-releasing hormone agonist combined with a reduced dose of human chorionic gonadotropin for final oocyte maturation in fresh autologous cycles of *in vitro* fertilization. Fertil Steril 2008;90:231-3.
14. Griffin D, Benadiva C, Kummer N, Budinetz T, Nulsen J, Engmann L. Dual trigger of oocyte maturation with gonadotropin-releasing hormone agonist and low-dose human chorionic gonadotropin to optimize live birth rates in high responders. Fertil Steril 2012;97:1316-20.
15. Lin MH, Wu FS, Lee RK, Li SH, Lin SY, Hwu YM. Dual trigger with combination of gonadotropin-releasing hormone agonist and human chorionic gonadotropin significantly improves the live-birth rate for normal responders in GnRH-antagonist cycles. Fertil Steril 2013;100:1296-302.
16. Werner MD, Forman EJ, Hong KH, Franasiak JM, Neal SA, Scott RT. Dual trigger with GnRH agonist (GnRHa) and varying doses of hCG increases the blastulation rate amongst high responders. Fertil Steril 2014;102:220-1.
17. Melnick AP, Amrane S, Murphy EM, Reichman DE, Davis OK, Rosenwaks Z. Dual trigger versus low-dose hCG for patients with high peak E2. Fertil Steril 2014;102:201.
18. Orvieto R. Triggering final follicular maturation – HCG, GnRH-agonist or both, when and to whom? J Ovarian Res 2015;8:60.
19. Hurst SA. Declaration of Helsinki and protection for vulnerable research participants. JAMA 2014;311:1252.
20. Humaidan P, Bredkjaer HE, Bungum L, Bungum M, Grøndahl ML, Westergaard L, *et al.* GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: A prospective randomized study. Hum Reprod 2005;20:1213-20.
21. Engmann L, Siano L, Schmidt D, Nulsen J, Maier D, Benadiva C. GnRH agonist to induce oocyte maturation during IVF in patients at high risk of OHSS. Reprod Biomed Online 2006;13:639-44.
22. Pritts EA, Atwood AK. Luteal phase support in infertility treatment: A meta-analysis of the randomized trials. Hum Reprod 2002;17:2287-99.
23. Castillo JC, Moreno J, Dolz M, Bonilla-Musoles FJ. Successful pregnancy following dual triggering concept (rhCG+GnRH agonist) in a patient showing repetitive inmature oocytes and empty follicle syndrome: Case report. J Med Cases 2013;5:221-6.
24. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Comparison of "triggers" using leuprolide acetate alone or in combination with low-dose human chorionic gonadotropin. Fertil Steril 2011;95:2715-7.
25. Haas J, Zilberberg E, Dar S, Kedem A, Machtinger R, Orvieto R. Co-administration of GnRH-agonist and hCG for final oocyte maturation (double trigger) in patients with low number of oocytes retrieved per number of preovulatory follicles – A preliminary report. J Ovarian Res 2014;7:77.
26. Griffin D, Feinn R, Engmann L, Nulsen J, Budinetz T, Benadiva C. Dual

trigger with gonadotropin-releasing hormone agonist and standard dose human chorionic gonadotropin to improve oocyte maturity rates. Fertil Steril 2014;102:405-9.
27. Fauser BC, de Jong D, Olivennes F, Wramsby H, Tay C, Itskovitz-Eldor J, *et al.* Endocrine profiles after triggering of final oocyte maturation with GnRH agonist after cotreatment with the GnRH antagonist ganirelix during ovarian hyperstimulation for *in vitro* fertilization. J Clin Endocrinol Metab 2002;87:709-15.
28. Shapiro BS, Andersen CY. Major drawbacks and additional benefits of agonist trigger – Not ovarian hyperstimulation syndrome related. Fertil Steril 2015;103:874-8.
29. Beck-Fruchter R, Weiss A, Lavee M, Geslevich Y, Shalev E. Empty follicle syndrome: Successful treatment in a recurrent case and review of the literature. Hum Reprod 2012;27:1357-67.
30. Son WY, Chung JT, Chian RC, Herrero B, Demirtas E, Elizur S, *et al.* A 38 h interval between hCG priming and oocyte retrieval increases *in vivo* and *in vitro* oocyte maturation rate in programmed IVM cycles. Hum Reprod 2008;23:2010-6.
31. Wang W, Zhang XH, Wang WH, Liu YL, Zhao LH, Xue SL, *et al.* The time interval between hCG priming and oocyte retrieval in ART program: A meta-analysis. J Assist Reprod Genet 2011;28:901-10.
32. van Rooij IA, Broekmans FJ, te Velde ER, Fauser BC, Bancsi LF, de Jong FH, *et al.* Serum anti-Müllerian hormone levels: A novel measure of ovarian reserve. Hum Reprod 2002;17:3065-71.
33. Lukaszuk K, Liss J, Kunicki M, Jakiel G, Wasniewski T, Woclawek-Potocka I, *et al.* Anti-Müllerian hormone (AMH) is a strong predictor of live birth in women undergoing assisted reproductive technology. Reprod Biol 2014;14:176-81.