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Dual Trigger in *in Vitro* Fertilization: A Case-Control Study

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Abstract

Objective: To evaluate the benefit of dual trigger (hCG + GnRH agonist) in patients underwent controlled ovarian stimulation for IVF in an antagonist protocol. ***Methods***: A retrospective case control study was performed (January 2017 to March 2019) in a single IVF center. The dual trigger group (n = 17), ovulation trigger was achieved with both hCG and GnRH agonist while in the single trigger group (n = 34), it was achieved by hCG alone. The first endpoint was the number of mature oocytes retrieved; the secondary endpoints were total number of oocytes retrieved, the number of cleaved embryos obtained (day 3) and blastocysts (day 5/day 6), the number of embryos transferred, the ongoing-pregnancy/miscarriage rate. ***Results***: The dual vs. the single group showed the followings. The number of retrieved oocytes of 7.1 vs. 6.4 (p = 0.68); mature oocytes of 4.6 vs. 4.1 (p = 0.62), day-3-embryos of 2.9 vs. 2.0 (p = 0.2), day-5/6-embryos of 0.3 vs. 0.03 (p = 0.13), transferred embryos of 2.1 vs. 1.8 (p = 0.48); ongoing pregnancy of 1 vs. 9 (p = 0.14); miscarriage of 0 vs. 2 (p = 1). ***Conclusion***: A dual trigger showed no additional clinical benefits. Future large studies are needed to demonstrate a real clinical advantage.

Keywords

Chorionic Gonadotropin, GnRH Agonist, Dual Trigger, *In Vitro* Fertilization

1. Introduction

The method used to trigger ovulation remains one of the keys to the success of controlled ovarian stimulation (COS) for *in vitro* fertilization (IVF) in assisted reproduction technologies (ART). Usually, human chorionic gonadotropin (hCG) is used to trigger ovulation following COS activating luteinizing hormone (LH) receptors, mimicking the LH physiological preovulatory peak and inducing

progesterone secretion by the corpus luteum in the luteal phase. In some cases, hCG administration is associated with an increased risk of Ovarian Hyperstimulation Syndrome (OHSS) [1]. In 1990, the gonadotrophin-releasing hormone agonist (GnRHa) was used for the first time to trigger ovulation with a different mechanism of action [2]. In fact, the administration of a GnRH agonist induces a short-term pituitary flair-up effect, which triggers an endogenous peak of LH and FSH. The endogenous LH ensures the final oocyte maturation and ovulation. This attractive concept is physiologically similar to triggering ovulation by hCG. The GnRH agonist can be used in all GnRH antagonist protocols. Although the efficiency of the GnRH agonist is the same as hCG's for triggering ovulation, its short half-life doesn't allow to extend the corpus luteum function; this can lead to luteal phase deficiency with a lower pregnancy rate [3]. However, the risk of OHSS is very low with triggering by the GnRH agonist.

Over the past few years, some studies showed that triggering of ovulation with an association of GnRH agonist and hCG, significantly improves *in vivo* oocyte maturation. The treatment is known as "Dual Trigger", combining the advantages of the two methods used previously [4] [5]. The objective of this study is to assess whether dual trigger is more effective than hCG alone, usually used to obtain a higher number of mature oocytes.

2. Materials and Methods

This is a retrospective case-control study, conducted at the IVF Unity of the University Hospital Center in Marrakesh, Morocco. A total of 51 IVF cycles were included between January 1, 2017 and March 31, 2019.

2.1. Patients

Our retrospective study included all women who underwent IVF at the university center. Two groups of patients were studied: one group of 17 patients have benefited of a dual trigger and a second group of 34 patients with hCG alone as ovulation trigger.

An initial assessment including antral follicular count (AFC) and hormonal assays at day 3 of previous cycle were carried out for each patient. We also collected medical record data: age, smoking, body mass index (BMI), etiology of primary or secondary infertility.

2.2. Stimulation and Triggering Protocol

All patients received ovarian stimulation with flexible initial doses of recombinant FSH (Gonal-F®), 150 or 300 IU/day from the second day of the cycle according to the results of the ovarian status. The initial dose of gonadotropin was established, based on patient's age, body mass index (BMI), day 3 FSH, AMH (Anti-müllerian hormone), antral follicle count (AFC). The FSH dose was secondarily readjusted according to the ovarian response, monitored by serial transvaginal ultrasound and hormonal survey. GnRH antagonist (Cétrotide®

0.25 mg) was introduced at 250 µg subcutaneously daily once the leading follicle reaches ≥14 mm in diameter and continued until the day of ovulation triggering. Patients were triggered when at least 3 follicles reach ≥18 mm in mean diameter as well as more than 50% of follicles with a diameter ≥ 16 mm with 250 µg of recombinant hCG by subcutaneous way (Ovitrelle® 250 µg) in the control group and subcutaneous bolus of 250 µg of (Ovitrelle® 250 µg) with GnRH agonist 0.2 mg (Decapeptyl® 0.1 mg) in the second group. In both groups, transvaginal ultrasound guided oocyte retrieval was performed 36 hours after trigger injection, and a maximum of 3 embryos, after IVF were transferred on the second or the third day after oocyte retrieval. Depending on their quality, the supernumerary embryos were cryopreserved on day 3. Fourteen days after embryo transfer, the patients performed a quantitative plasma βhCG assay.

2.3. Study Evaluation Criteria

The primary endpoint was the number of mature oocytes defined by the ratio of the number of mature oocytes to the total number of oocytes collected, while the secondary endpoints measures were the total number of oocytes recovered on the day of oocyte retrieval, the number of embryos obtained on day 3 and 5, the number of embryos transferred, the pregnancy rate and finally the miscarriages rate.

2.4. Statistical Analysis

Statistical analysis was performed using SPSS (version 23). We proceeded to the descriptive and analytical analysis of the data. During this step we calculated the percentages and numbers for the qualitative variables and the average of the quantitative variables.

3. Results

A total of 51 patients were included between January 2017 and March 2019. The stimulation protocols were the same between the two groups, all patients using an antagonist protocol. Regarding the triggering methods, 68% of the cycles (n = 34) were performed according to the hCG triggering protocol, 32% of the cycles (n = 17) were performed according to the dual trigger protocol.

Table 1 shows the characteristics of both patients and stimulation protocols. No statistically significant differences were observed between the hCG and the dual-triggered cycles for demographics characteristics, total recombinant FSH dose; duration of stimulation; and number of follicles < 14 mm, between 14 and 16 mm and >16 mm in diameter on the day of triggering.

Table 2 shows ovarian stimulation and gestational outcomes. Moreover, no differences were found between the groups compared regarding the number of oocytes retrieved, the number of mature oocytes, the number of embryos obtained on day 3 and 5, and the number of embryos transferred with p respectively (0.68; 0.62; 0.2; 0.13 and 0.48). Pregnancy outcomes were not significantly

Table 1. Baseline characteristics of the groups.

Parameter	Dual-trigger group (n = 17)	Standard group (n = 34)	P value
Age or patients (years)	34.2	31.4	0.08
Age of partners (years)	42.2	39.7	0.27
Duration with regular unprotected sex (months)	112.8	90.8	0.26
BMI (kg/m^2)	28.2	27.7	0.64
AFC (follicles)	6	6	0.84
Total dose of gonadotropins (UI)	2698.5	2569.1	0.58
No. of follicles on the day of triggering (mean)	14.8	15.4	0.8
No. of follicles < 14 mm (mean)	5.3	6.5	0.31
No. of follicles between 14 mm and 16 mm (mean)	4.3	4.2	0.94
No. of follicles > 16 mm (mean)	5.3	4.4	0.41

BMI: Body mass index; AFC: Antral follicle count.

Table 2. Ovarian stimulation outcomes and cycle characteristics of the groups.

Parameter	Dual-trigger group (n = 17)	Standard group (n = 34)	P value
No. of oocyte retrieved (mean)	7.1	6.4	0.68
No. of mature oocytes (mean)	4.6	4.1	0.62
No. of embryos at day 3 (mean)	2.9	2	0.2
No. of embryos at day 5 (mean)	0.3	0.03	0.13
No. of embryos transferred (mean)	2.1	1.8	0.48
Pregnancy rate (%)	5.9	26.5	0.14
Miscarriage rate (%)	0	22.2	1

different between the 2 triggering methods. Only one case of severe ovarian hyperstimulation syndrome (OHSS) was observed in the single trigger group, requiring hospitalization for close monitoring, as well as symptomatic treatment.

4. Discussion

Current knowledge on human ovarian physiology has challenged the process of folliculogenesis, creating new opportunities for COS protocols in ART. With the introduction of GnRH antagonists in COS protocols during the 1990s, the use of a single bolus of GnRH agonist to trigger an endogenous LH surge and, thus final oocyte maturation and ovulation, was proposed as an alternative to hCG [2]. GnRH agonist also induces an FSH surge, which may act synergistically with LH to promote oocyte nuclear maturation and cumulus expansion.

Several studies have reported the retrieval of a higher number of mature oocytes and better quality embryos after triggering with GnRHa than after the traditional triggering with hCG [6]. However, when embryonic implantation rates are compared according to the type of triggering (GnRH agonists versus hCG), a

low implantation rate and significantly more spontaneous miscarriages were noted when triggered by GnRH agonist. Indeed, GnRHa leads to a luteal insufficiency due to severe luteolysis of the corpus luteum with, as a consequence, a decrease secretion of steroids and a lack of vasoactive factors such as VEGF, necessary for implantation [7]. Humaidan *et al.* have shown that the addition of a bolus of hCG after triggering ovulation by GnRHa, may support the luteal phase with, consequently, an improvement of ongoing pregnancy rate and a decrease of miscarriage rate [7]. Thus, in the double triggering of ovulation by hCG and GnRHa, the LH activity of hCG may compensate for the luteolytic effects of GnRHa. The so-called "dual trigger" significantly improves clinical outcomes compared to the standard hCG trigger in GnRH antagonist protocols [8] [9].

Most of studies aimed to evaluate the ability of dual trigger to improve oocyte maturity are summarized in **Table 3**. Our study demonstrates that dual trigger has no benefit on oocyte maturity. Our results are consistent with those already reported, showing that there was no significant increase in the number of mature oocytes [10] [11] [12] [13] [14]. In these studies, the samples were not large, which weakened their conclusions. In some studies the oocyte and embryonic biological parameters has not been improved by the dual trigger compared to hCG; However, clinical pregnancy rate tend to be better in the dual trigger groups [11] [15] [17]. In other studies authors suggested that GnRHa addition could also have a beneficial effect on implantation.

Table 3. Reproductive outcomes in studies comparing the double trigger by GnRHa/hCG with the trigger by hCG in IVF.

Authors & studies Design	No. de MII	MII rate (%)	Clinical pregnancy rate	Study size
RCT				
Decleer [10]	10.3 vs. 9.5	ND	31 vs. 44	120
Kim [11]	9.0 vs. 8.9	ND	53 vs. 33*	120
Mahajan [12]	8.4 vs. 7.2	ND	ND	76
Eftekhar [13]	8.8 vs. 7.9	ND	26 vs. 22	192
Schachter [17]	ND	ND	44 vs. 29*	211
Observ				
Zhou [15]	6.6 vs. 5.8	75 vs. 73	62 vs. 52	325
Fabris [20]	5.3 vs. 2.4*	79 vs. 43*	43 vs. 26*	81
Zilberberg [21]	6.5 vs. 3.6*	68 vs. 47*	50 vs. 0*	12
Herbemont [22]	9.1 vs. 5.5*	71 vs. 47*	31 vs. 23	47
Lin **[23]**	2.75 vs. 2.85	ND	33 vs. 20	427
Meta-analysis				
Chen [17]	a	ND	b	527
Ding [16]	a	ND	b	527
Our study	4.6 v 4.1	ND	5.9% vs. 26.5%	51

MII: metaphase II; *: significant result ($p < 0.05$); ND: not determined; a: similar results; b: superior results after dual trigger; RCT: randomized controlled trials; Observ: Observational study.

Maggi *et al.* demonstrated the presence of GnRH receptors in both embryo and endometrial cells during the implantation window. GnRHa would have a crucial role in endometrial receptivity, via the embryo adhesion, facilitating also the trophoblast invasion (regulation of endometrial stroma extracellular matrix degradation via type 2 and 5 metalloproteinases). Its immunomodulatory effect acts by modifications of the endometrial secretions (HOXA-10 expression) and a direct effect on the expanding blastocyst [18].

Our study showed contrasting results to other studies, which had observed an improved mature oocytes rate in dual trigger compared to hCG triggering and consequently, an increased number of good morphological quality embryos and a better cumulative clinical pregnancy rate [4] [9] [19] [20] [21] [22]. Despite a higher rate of mature oocytes Griffin *et al.*, observed poor implantation, clinical and ongoing pregnancy rates. The authors hypothesized that this could be due to underlying oocyte dysfunction [4].

Recently, Lin *et al.*, in a large retrospective study demonstrated a significantly higher oocyte fertilization rate, clinical pregnancy rate and live birth rate, in the dual trigger group compared to hCG in women with diminished ovarian reserve (DOR) [22]. The improvement of embryological and clinical outcomes could be explained by the endogenous FSH surge induced concomitantly to LH.

Our study, like most randomized controlled studies, did not suggest a beneficial effect of dual trigger on reproductive clinical outcomes. In patients with normal ovarian reserve, some observational studies suggested an improvement of mature oocytes, top embryos and clinical pregnancy rate with dual trigger [23].

The most important limitation of this study is the sample size, it was small and power calculation was not done.

5. Conclusion

There is growing evidence that triggering GnRH associated with hCG is a better choice for final oocyte maturation in the HOS with under GnRH antagonist. This strategy not only permits to avoid OHSS, but also could improve cumulative pregnancy rate. However, in our study of 51 patients, there was no statistically significant difference, neither in terms of total oocytes number, nor in terms of mature oocytes number, or pregnancy rate and early miscarriages between patients who were triggered with both GnRH and hCG and those triggered only with hCG. Large randomized studies are needed to confirm our results and establish an evidence-based recommendation.

Consent

Informed consent was obtained from all participants.

Conflicts of Interest

The authors declare no conflicts of interest.

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Abbreviations

AFC: Antral follicular count
AMH: Anti-müllerian hormone
ART: Assisted reproductive technology
BMI: Body mass index
COS: Controlled ovarian stimulation
FSH: Follicle-stimulating hormone
GnRH: Gonadotropin-releasing hormone
GnRHa: Gonadotropin-releasing hormone agonist
hCG: Human chorionic gonadotropin
IVF: *In vitro* fertilization
LH: luteinizing hormone
OHSS: Ovarian hyperstimulation syndrome
VEGF: Vascular endothelial growth factor