Comparison of two different dosage of GnRH agonist as ovulation trigger in oocyte donors: a randomized controlled trial

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ABSTRACT

Objective: To compare the results obtained with two different GnRH agonist dosages: 0.3mg versus 0.4mg to trigger ovulation in oocyte donor cycles.

Methods: Experimental controlled randomized trial including 40 patients from a private practice center. The patients were randomized into two groups. Group A received a single dose of Triptorelin 0.3mg (Decapeptyl®) 36 hours before pick-up. Group B patients received Triptorelin 0.4mg (Decapeptyl®) before pick-up to final oocyte maturation. We evaluated the total number of oocytes collected, the number of mature oocytes and total days of ovarian stimulation.

Results: The average of total collected oocytes were 16 (Group A) versus 15 (Group B), and the mean number of mature oocytes were 13 versus 12 respectively. The only variable showing a difference was the percentage of mature oocytes, which was greater in Group A, resulting in 84.6%, in contrast with those treated with 0.4mg of Triptorelin (78.6%), although these differences were not statistically significant ($p=0.35$). Days of stimulation did not differ between groups. No cases of empty follicle syndrome were reported.

Conclusions: We found that an increase from 0.3 to 0.4mg of triptorelin in an oocyte donation program might not improve outcomes. Nevertheless, more studies might be necessary, not only in oocyte donors but in sterile women as well, to evaluate how GnRH agonist dosage could affect the results among other factors.

Keywords: oocytes, oocyte Donation, ovulation, Gn-RH

INTRODUCTION

Classically, assisted reproductive treatments (ART) have employed hCG as a substitute for endogenous LH surge, to induce oocyte maturation. hCG offers structural similarities to LH, acting on the same receptors. Its main difference lies in the longer half-life of hCG. The increased and lasting LH surge may cause an ovarian hyperstimulation syndrome (OHSS) (Damewood *et al.* 1989; Whelan & Vlahos, 2000). OHSS is one of the most feared complications of ART, causing high comorbidity among patients submitted to this type of treatment (Golan *et al.*, 1989). Because the GnRH antagonist does not desensitize hypophysis receptors, as they were introduced, a new window of possibilities to trigger LH surge using GnRH agonist was opened (Olivennes *et al.*, 1996; Tarlatzis *et al.*, 2006; Griesinger *et al.*, 2006). The GnRH agonist bolus causes an initial FSH and LH discharge from the hypophysis, a "flare up" effect, resembling the one caused by a natural cycle, and enough to reduce oocyte maturation, thus the risk of OHSS (Hoff *et al.*, 1983; Pundir *et al.*, 2012; Bodri *et al.*, 2010; Engmann *et al.*, 2008). Itskovitz *et al.* (2000) were the first to suggest GnRH agonist as an alternative to prevent OHSS. Today, a GnRH agonist bolus is used as

the standard method to trigger final maturation in young patients, or in women with an increased ovarian reserve due to its relevant safety profile. Although its usage has been standardized lately, there still are unsolved questions about its usage.

One of the main disadvantages of employing GnRH agonists, is the decreased pregnancy rate reported after fresh embryo transference. This effect has been attributed to luteal phase deficiency, which affects endometrial quality (Youssef *et al.*, 2011; Babayof *et al.*, 2006). Several trials have demonstrated similar pregnancy rates using different luteal phase support combinations; however, none have achieved enough evidence - reason why the freeze-all policy and delayed embryo transfer is the most commonly used method after GnRH agonist bolus (Youssef *et al.*, 2014; Radesic & Tremellen, 2011; Papanikolaou *et al.*, 2011; Humaidan *et al.*, 2011).

Besides, another difficulty concerning the use of GnRH agonist is the standard dosage to achieve a sufficient LH surge for follicular maturation. Suboptimal results have been described after GnRH bolus, due to a deficient LH surge (Castillo *et al.*, 2012). Numerous dosage protocols have been proposed to trigger follicular maturation; from as low as 0.1mg to as high as 0.4mg, without having clear evidence of neither one's benefit (Buckett *et al.*, 1998; Empeaire *et al.*, 2004).

The goal of our trial was to evaluate the number of collected mature oocytes (MII) after controlled ovarian stimulation, using a fixed gonadotropin (rFSH) protocol and multiple GnRH agonist doses to trigger final maturation.

MATERIAL AND METHODS

Experimental controlled randomized trial including 40 women belonging to a single medical care center, carried out from January to March 2016. All patients signed an informed consent. The trial fulfilled Helsinki's declaration, good clinical practice and decree law 9/2014 to regulate oocyte donation.

Studied population

Our study included only oocyte donors in which oocyte maturation was accomplished using GnRH agonist. The inclusion criteria were: age ranging 18-30 years, BMI<30. No history of diseases contraindicating the treatment, recent normal gynecological control, ≥ 16 antral follicles and satisfying results in previous cycles (>8 mature oocytes or achieved pregnancy).

We also aimed at analyzing secondary variables, such as the total number of collected oocytes, mature oocyte percentage and total days of ovarian stimulation.

Procedure

The patients were randomized into two groups. Randomization was performed through randomization tables, for a total of 40 patients included. When oocyte

donors came to the clinic to initiate the cycle, the medical staff on duty that day used the table for randomization and assigned the patient to one of the two groups.

Group A received a single dose of Triptorelin 0.3mg (Decapeptyl®) 36 hours before pick-up. Group B received Triptorelin 0.4mg (Decapeptyl®) 36 hours before pick-up for final maturation.

Statistical analysis

Qualitative variables were represented as absolute frequencies and percentages, and were analyzed in a descriptive way. The quantitative variables were resumed in average (standard deviation) or median (p25; p75), according to their asymmetry. Normality was assessed by the Shapiro-Wilk's test and homogeneity by the Levenne's test.

Losses were analyzed in each group using the Fisher's exact test. Age and BMI were evaluated by the Student T-test, acquiring a 95% interval of confidence for the differences. Remaining variables were analyzed using the Mann-Whitney test. Statistical significance was set at 5% ($p < 0.05$). the IBM SPSS19.0 software was used for complete analysis.

RESULTS

A total of 40 patients were included in the trial, all were previously randomized into two groups: Group A (n=20) and Group B (n=20). 4 patients did not complete the study. Two patients in Group A rejected donation and one was cancelled because of unsatisfactory response to stimulation. In Group B, one patient was cancelled for insufficient response. Losses were similar in both groups ($p = 0.605$). The 36 remaining patients were 34 years old in average and had BMI of 22.9. The mean number of collected oocytes was 15.5 (12; 30.5). Eighty-six point-one percent of the women had 12 days of controlled ovarian stimulation.

The group assessment did not confirm significant age differences. Group A and B showed similar mean values (23.9 vs. 24.2 years old). A minor difference in BMI was found between the groups: Group B had 2.48 units more than Group A (Table 1).

The average of collected oocytes were 13 vs. 12, and the total numbers were 16 vs. 15. The single variable showing a difference was the percentage of mature oocytes which was greater in the 0.3mg group (A), resulting in 84.6(71.5; 88.3), in contrast with those treated with 0.4 mg: 78.6 (65.6; 86.6), although this difference was not statistically significant. Days of stimulation did not differ between groups (Table 2). No cases of Empty Follicle Syndrome (EFS) were reported.

DISCUSSION

Our study, which compared the usage of triptorelin 0.3mg and 0.4mg in oocyte donors, did not show any difference in the number of collected oocytes, metaphase II, or days of stimulation.

GnRH-agonist-induced FSH and LH surges resembles the natural cycle in a better way than hCG bolus, although the LH surge is reduced and shorter when compared to the natural cycle. This situation induces luteal phase insufficiency, luteal corps' injury and decreased LH levels (Yding Andersen *et al.*, 1999; Beckers *et al.*, 2003; Humaidan *et al.*, 2012). Nevertheless, the advantage brought about by the GnRH agonist is the FSH surge, which stimulates the development of LH receptors in the granulosa cells, optimizing luteal corps' function (Zelinski-Wooten *et al.*, 1995; Humaidan *et al.*, 2009). Moreover, GnRH agonist endorses oocyte maturation, reinitiating meiosis and cumulus' expansion, and reporting high mature oocyte rates (Andersen *et al.*, 2006; Humaidan *et al.*, 2011).

Several GnRH agonists, such as buserelin, leuprolide acetate and triptorelin, have proven useful for oocyte maturation (Bodri *et al.*, 2009; Engmann *et al.*, 2008; Humaidan *et al.*, 2005). Parneix *et al.* (2001) evaluated thirteen different protocols for GnRH agonist bolus, and they concluded that none showed differences triggering maturation.

The dosages used vary from 0.1mg to 0.5mg. Trying to establish the most effective dosage, Vuong *et al.* (2016) published a trial including oocyte donors and comparing different triptorelin doses (0.2mg, 0.3mg and 0.4mg). It included 165 patients randomized into three groups, 55 women in each. No differences were found among the main variables: mature oocytes and good quality embryos. Though, statistical differences were found on LH levels, higher in the 0.4mg group compared to 0.2 and 0.3mg groups. Progesterone levels in day 6 were also found to be higher in the 0.4mg group. It remains to elucidate if the lower LH levels could cause clinical impairment as an increase in the number of empty follicle syndrome (EFS) cases (Stevenson & Lashen, 2008; Beck-Fruchter *et al.*, 2012).

Although these cases have been like a-GnRH and hCG cases, the mechanism causing it might be different (Castillo *et al.*, 2010). Different theories have been proposed, among them: ovarian aging, insufficient dosage and genetic receptor changes (Toledo *et al.*, 1996; Aktas *et al.*, 2005). Blazquez *et al.* (2014) published a retrospective study including 12,483 oocyte donation cycles. There were 74 cases of EFS (0.59%) described from 2006 to 2013. hCG was used to trigger maturation until 2009; latter, triptorelin at 0.2 or 0.3mg were used. Although more cases were reported in the 0.2mg group, they were not statistically significant. The Empty Follicle Syndrome incidence has not been shown to be higher with the use of GnRH, nor has it been possible to demonstrate a higher incidence with lower doses, because of its low prevalence and few studies. There were no cases of this syndrome reported in our study.

CONCLUSIONS

Thus, we believe that an increase from 0.3 to 0.4 mg in an oocyte donation program might not provide

Table 1. Group evaluation: age and BMI

Groups	Group A decapeptyl 0.3mg (n=17)	Group B decapeptyl 0.4mg (n=19)	P^a	Difference	Confidence interval 95%
Age (years)	23.9(3.3)	24.2 (3.2)	0.771	-0.3	-2.5; 1.9
BMI (kg/m ²)	21.5 (2.9)	24.1 (3.6)	0.031	-2.5	-4.7; -0.2

Table 2. Group evaluation: age and BMI

	Group A decapetyl 0.3mg (n=17)	Group B decapetyl 0.4mg (n=19)	P^a
MII	13 [10; 24.5]	12 [9; 21]	0.727
Total oocytes collected	16 [12.5; 30]	15 [12; 32]	0.812
MII (%)	84.6 [71.5; 88.3]	78.6 [65.6; 86.6]	0.350
Stimulation days	12 [12; 12]	12 [12; 12]	0.692

Note: Data are presented in median (p50) [p25; p75] ^a: U Mann-Whitney.

any outcome benefits. Nevertheless, more studies might be necessary, not only among oocyte donors, but also in sterile women, to evaluate how GnRH agonist dosage might differ according to other factors.

DISCLAIMERS

The opinions expressed in this paper are those of the authors and does not reflect that of to the position of the assigned institution.

SOURCE OF SUPPORT

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CONFLICT OF INTERESTS

No conflict of interest has been declared.

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