European Review for Medical and Pharmacological Sciences 2017; 21: 657-661

The efficacy of modified luteal phase support with intramuscular progesterone in IVF/ICSI cycles: a retrospective observational study

A. CONFORTI[1], I. STRINA[1], A. MOLLO[1], R. AMOROSO[1], V. MARRONE[1], C. ALVIGGI[1], R. MARCI[2], G. DE PLACIDO[1]

[1]Department of Neuroscience, Reproductive Science and Odontostomatology, University of Naples Federico II, Naples, Italy
[2]Department of Morphology Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy

Abstract. – OBJECTIVE: The use of gonadotropin-releasing hormone agonist for ovulation triggering has become an intriguing topic in the last few years. As long as adequate luteal phase support is provided, it may be a valuable alternative to standard hCG triggering, associated with a significant reduction in OHSS incidence. Several luteal phase support options have been proposed, but few studies have addressed the issue of the appropriate route for progesterone administration to women triggered with GnRHa.

The aim of the study was to evaluate the effect of GnRHa triggering on IVF/ICSI outcomes, using modified luteal phase support with intramuscular progesterone.

PATIENTS AND METHODS: A retrospective study was carried out between January 2014 and December 2015, comparing the reproductive outcome in GnRHa triggered women given modified luteal phase support with intramuscular progesterone (Group A) with the outcome in women triggered with standard hCG (Group B) in IVF/ICSI cycles.

RESULTS: 200 (Group A n = 100; Group B n = 100) consecutive normoresponder women were included. No differences with respect to Age, BMI, basal FSH, basal Estradiol and infertility diagnosis were observed between groups. Increased numbers of retrieved oocytes (8.1 ± 3.3 *versus* 6.8 ± 3.5, *p* = 0.009) and mature oocytes (5.8 ± 2.6 *versus* 5.1 ± 2.7, *p* = 0.03) were detected in Group A compared with Group B. Implantation, biochemical pregnancy and ongoing pregnancy rates were similar.

CONCLUSIONS: Our findings confirmed that the GnRHa triggering strategy is associated with increased number of oocytes retrieved and of mature oocytes even in normoresponder women. Moreover, in these patients, the use of intramuscular progesterone during luteal phase support achieved satisfactory IVF outcomes.

Key Words:
GnRH agonist, Ovarian triggering, hCG, IVF.

Introduction

The use of gonadotropin-releasing hormone agonist (GnRHa) for ovulation triggering is an intriguing strategy in the reproductive field[1,3]. The main advantage consists in a significant reduction in ovarian hyperstimulation syndrome (OHSS), which is a common complication of human chorionic gonadotropin (hCG) administration. GnRHa has a shorter half-life and, at the same time, is able to induce oocyte maturation through the "flare up" effect. GnRHa is also able to induce a more physiological ovulation by increasing both FSH and LH levels[4], and fewer patients experience discomfort, reduced ovarian volume, ascites and abdominal pain[5,6].

On the other hand, a recent meta-analysis[7] concluded that this kind of strategy may be associated with lower pregnancy rates, live birth rates and higher incidence of miscarriage. These negative effects are not observed in donor-recipient cycles[7].

The negative impact on IVF has raised many doubts regarding the use of GnRHa for ovulation triggering in assisted reproductive technology (ART). The abnormal luteal phase induced by GnRHa is believed to be the most important physiopathological reason for impaired ovarian response. Specifically, GnRHa is able to induce a LH surge that lasts only 24-36h[8] – not adequate for appropriate luteal support[6].

In order to ameliorate luteal phase support, several strategies have been proposed[9] with satisfactory results even in women not at risk of developing OHSS[4].

Nonetheless, there is no consensus on the optimal luteal phase support protocol[5]. For instance, some authors[9,10] have suggested that progesterone route could be of importance in women triggered with

Corresponding Author: Alessandro Conforti, MD; e-mail: confale@hotmail.it

GnRHa to adequately sustain corpus luteum activity. However, few trials have addressed this issue.

A retrospective observational study was carried out with the aim of evaluating the effect of luteal phase support with intramuscular progesterone in normoresponder women triggered with GnRHa.

Patients and Methods

From January 2014 to December 2015 we ret-rospectively analyzed only normogonadotropic normoresponder Caucasian women. The following inclusion criteria were adopted: age between 21-44 years, body mass index (BMI) 18-40 kg/m^2, FSH < 10 UI/L. We excluded patients with endocrine inflammatory disorders, immune disorders and uterine malformations.

All patients underwent GnRH antagonist cycle with exogenous gonadotropin, using individualized starting dosages according to BMI, age and baseline hormonal characteristics[11,12]. The ovarian response was monitored by ultrasound examination and the dose was adjusted on the basis of response.

Ovarian maturation was induced with GnRHa in the study group (Ferring S.P.A., Milan, Italy) and with hCG in the control group (Gonasi HP; IBSA Farmaceutici Italia Srl, Lodi, Italy) when at least three follicles reached a mean diameter of 17 mm at the dosage of 10.000 UI and 0.2 mg. Oocytes were retrieved 35 h after ovulation induction.

When GnRha was adopted for ovarian triggering, modified luteal phase support was provided with hCG 1500 IU i.m. at the time of oocyte retrieval plus estradiol valerate (Progynova Bayer S.p.A. Milan, Italy) 4 mg per day and intramuscular injection of progesterone 50 mg per day (IBSA Farmaceutici Italia S.r.l., Lodi, Italy). In the hCG group, luteal phase support was provided vaginally in the form of 400 mg micronized progesterone (Prometrium; Rottapharm S.p.A., Milan, Italy).

Signed written informed consent was obtained from all participants, who also consented to the anonymous processing of their personal data.

A biochemical pregnancy was defined as a positive βhCG concentration test and ongoing pregnancy by direct visualization of gestation sac by ultrasound.

The primary outcome of this study was the ongoing pregnancy rate. The secondary outcomes were: the number of oocytes retrieved, the number of mature oocytes, the implantation rate and the ongoing pregnancy rate.

Statistical Analysis

Results were analyzed using the statistical package SPSS 22 for Windows (SPSS IBM, USA).

Student's *t*-test was used to compare con-tinuous variables while the χ^2-test was adopted to compare categorical data. Continuous data were expressed as mean ± standard deviation. Categorical data were expressed as percentages. A *p*-value < 0.05 was considered statistically significant.

Results

A total of 200 consecutive women were included: Group A consisted of 100 patients who underwent GnRHa at the time of triggering; Group B of 100 women served as the control group, in which hCG was adopted for follicle maturation (n = 100). No difference with respect to age, BMI, FSH and estradiol baseline levels and infertility diagnosis were observed between groups (Table I). The duration of ovarian stimulation, the total amount of exogenous FSH and the stimulation duration were all comparable between groups (Table II). The number of follicles observed at the time of triggering did not differ between groups (Table II).

An increased number of retrieved oocytes (8.1 ± 3.3 *versus* 6.8 ± 3.5, $p = 0.009$) and mature oocytes (5.8 ± 2.6 *versus* 5.1 ± 2.7, $p = 0.03$) was detected in Group A compared with Group B. Nonetheless, the implantation rate, biochemical pregnancy rate and ongoing pregnancy rate were similar in the two groups (Table I).

Discussion

Our study has provided further evidence showing that ovulation maturation induced by GnRHa triggering has a positive effect in terms of number of oocytes retrieved and mature oocytes. Moreover, satisfactory pregnancy, implantation and ongoing pregnancy rates were observed in the study group (Table II). The hypothesis that GnRHa triggering may improve the number of mature oocytes has been advocated since 2005[1]; however, conflicting results have been reported[9,13]. The phenomenon was attributed to the release of a more physiological surge of gonadotropins, containing not only LH as hCG, but also FSH. Particularly the FSH surge seems to have an effect on oocyte maturationprocesses[14].

Table I. Basal characteristics.

	Group A (n = 100)	Group B (n = 100)	*p*-value
Age (years)	32.8 ± 4.9	33.9± 4.3	NS
BMI kg/m^2	24.2 ± 6.2	24.7 ± 6.2	NS
FSH (UI/L)	5.9 ± 2.4	6.4 ± 2.4	NS
Basal estradiol (pg/ml)	70.9 ± 80.3	74.3 ± 106.2	NS
Infertility causes (%)			
Ovulation disorders	16%	15%	NS
Male	37%	48%	NS
Tubal	9%	10%	NS
Unexplained	23%	17%	NS
Others	15%	10%	NS

Continuous data are expressed in mean ± standard deviation; Categorical data are expressed in percentage %; BMI: body mass index; FSH: follicle stimulating hormone; NS: no statistical significance.

In a study including 122 women randomized to receive 10000 IU hCG or 0.5 mg of buserelin, the GnRHa group developed a higher number of mature oocytes, but had a lower pregnancy rate[1]. A significant impact on oocyte maturation was also reported by Reddy et al[15] and Otkay et al[16] in patients with breast cancer undergoing COS for fertility preservation with an aromatase inhibitor. In line with our results are findings from Lin et al[17], who adopted a dual trigger with 250 mg of recombinant hCG plus 0.2 mg of triptorelin. Specifically, the authors observed significantly higher pregnancy and live birth rates in the "dual trigger" group compared with the standard hCG trigger.

Our findings are consistent with Lin et al[17] in terms of number of oocytes retrieved and of mature oocytes. However, we did not detect any difference with respect to implantation rate and ongoing pregnancy rate. Although GnRHa may ameliorate the quality of oocytes, the impaired luteal phase support associated with this approach should be avoided. Specifically, in our study, we adopted modified luteal phase support according to Humaidan et al[18] with a low adjuvant dose of hCG at the time of oocyte retrieval. Instead of vaginal administration, we used intramuscular injections of progesterone. Although the route of progesterone administration does not seem to influence reproductive outcome in standard IVF, the effect may be different in patients triggered with GnRHa.

Some authors[9] have claimed that the use of intramuscular progesterone may be important for a successful intensive luteal phase in this subgroup

Table II. Ovarian stimulation outcome.

	Group A (n = 100)	Group B (n = 100)	*p*-value
Total FSH dosage	1126.6 ± 744.9	1268.7 ± 958.7	NS
Duration of stimulation (n. day)	9.1 ± 2.5	9.2 ± 1.7	NS
N. follicles day of triggering <15 mm	9.1 ± 3.1	8.5 ± 3.8	NS
Estradiol day 5 (pg/ml)	464.8 ± 368.9	427.6 ± 275.7	NS
Estradiol day 8 (pg/ml)	1068.2 ± 692.6	907.5 ± 492.1	NS
Estradiol peak (pg/ml)	1630.7 ± 862.7	1385.4 ± 997.1	NS
N. oocytes retrieved	8.1 ± 3.3	6.8 ± 3.5	0.009
N. mature oocytes	5.8 ± 2.6	5.1 ± 2.7	0.03
N. embryo transferred	2.04 ± 0.57	2.13 ± 0.59	NS
Implantation rate	20.9%	15.3%	NS
Biochemical pregnancy	39%	35%	NS
Ongoing pregnancy rate	27%	23%	NS

Continuous data are expressed in mean ± standard deviation; Categorical data are expressed in percentage %; FSH: follicle stimulating hormone; NS: no statistical significance.

of women. To date, we still do not know which progesterone route is preferable. The use of intramuscular progesterone for luteal phase support has already been adopted in women at high risk of OHSS syndrome[13,19,20]. To our knowledge, this is the first study where the use of intramuscular progesterone was adopted in normal responder women triggered with GnRHa with a positive trend regarding the ongoing pregnancy rate and implantation rate in the GnRHa triggered group. The trend did not reach statistical significance (Table II).

Nonetheless, larger randomized trials are required to clarify whether the route of progesterone administration is of importance in this group of patients. Optimal luteal phase support in GnRHa triggered women is still a matter of debate and there is no clear consensus on dosage and timing.

Hopefully, a specific model will be designed with the aim of providing tailored luteal phase support based on individual profiles[9]. For instance, the administration of hCG might not be indicated, when the ovarian response is excessive in terms of number of follicles or estradiol peak.

Conclusions

According to our findings, the GnRHa triggering strategy may be a valuable alternative even in women not at risk of developing OHSS, as long as adequate luteal phase support is provided. Furthermore, luteal phase support using intramuscular progesterone is associated with higher pregnancy and ongoing pregnancy rates than standard hCG triggering.

Conflict of interest

The authors declare no conflicts of interest.

References

1) Humaidan P, Bredkjaer HE, Bungum L, Bungum M, Grondahl ML, Westergaard L, Andersen CY. GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study. Hum Reprod 2005; 20: 1213-1220.
2) Acevedo B, Gomez-Palomares JL, Ricciarelli E, Hernandez ER. Triggering ovulation with gonadotropin-releasing hormone agonists does not compromise embryo implantation rates. Fertil Steril 2006; 86: 1682-1687.
3) Beckers NG, Macklon NS, Eijkemans MJ, Ludwig M, Felberbaum RE, Diedrich K, Bustion S, Loumaye E, Fauser BC. Nonsupplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinizing hormone, or gonadotropin-releasing hormone (GnRH) agonist to induce final oocyte maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment. J Clin Endocrinol Metab 2003; 88: 4186-4192.
4) Humaidan P, Kol S, Papanikolaou EG. GnRH agonist for triggering of final oocyte maturation: time for a change of practice? Hum Reprod Update 2011; 17: 510-524.
5) Engmann L, Benadiva C, Humaidan P. GnRH agonist trigger for the induction of oocyte maturation in GnRH antagonist IVF cycles: a SWOT analysis. Reprod Biomed Online 2016; 32: 274-285.
6) Garcia-Velasco JA, Motta L, Lopez A, Mayoral M, Cerrillo M, Pacheco A. Low-dose human chorionic gonadotropin *versus* estradiol/progesterone luteal phase support in gonadotropin-releasing hormone agonist-triggered assisted reproductive technique cycles: understanding a new approach. Fertil Steril 2010; 94: 2820-2823.
7) Youssef MA, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, Nagi Mohesen M, Aboulfoutouh I, van Wely M. Gonadotropin-releasing hormone agonist *versus* HCG for oocyte triggering in antagonist-assisted reproductive technology. Cochrane Database Syst Rev 2014; 10: Cd008046.
8) Itskovitz J, Boldes R, Levron J, Erlik Y, Kahana L, Brandes JM. Induction of preovulatory luteinizing hormone surge and prevention of ovarian hyperstimulation syndrome by gonadotropin-releasing hormone agonist. Fertil Steril 1991; 56: 213-220.
9) Engmann L, Benadiva C, Humaidan P. GnRH agonist trigger for the induction of oocyte maturation in GnRH antagonist IVF cycles: a SWOT analysis. Reprod Biomed Online 2016; 32: 274-285.
10) Papaleo E, Quaranta L, Molgora M. Intramuscular *vs* intravaginal natural progesterone in patients undergoing *in vitro* fertilization-embryo transfer cycles. A retrospective observational, case-control study. Eur Rev Med Pharmacol Sci 2010; 14: 103-106.
11) La Marca A, Sunkara SK. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Hum Reprod Update 2014; 20: 124-140.
12) Marci R, Graziano A, Lo Monte G, Piva I, Soave I, Marra E, Lisi F, Moscarini M, Caserta D. GnRH antagonists in assisted reproductive techniques: a review on the Italian experience. Eur Rev Med Pharmacol Sci 2013; 17: 853-873.
13) 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.

14) Yding Andersen C. Effect of FSH and its different isoforms on maturation of oocytes from pre-ovulatory follicles. Reprod Biomed Online 2002; 5: 232-239.

15) Reddy J, Turan V, Bedoschi G, Moy F, Oktay K. Triggering final oocyte maturation with gonadotropin-releasing hormone agonist (GnRHa) *versus* human chorionic gonadotropin (hCG) in breast cancer patients undergoing fertility preservation: an extended experience. J Assist Reprod Genet 2014; 31: 927-932.

16. Oktay K, Turkcuoglu I, Rodriguez-Wallberg KA. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. Reprod Biomed Online 2010; 20: 783-788.

17) 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: 1296-1302.

18) Humaidan P, Ejdrup Bredkjaer H, Westergaard LG, Yding Andersen C. 1,500 IU human chorionic gonadotropin administered at oocyte retrieval rescues the luteal phase when gonadotropin-releasing hormone agonist is used for ovulation induction: a prospective, randomized, controlled study. Fertil Steril 2010; 93: 847-854.

19) 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: 2715-2717.

20) 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: 826-828.