Induction of final follicle maturation with a gonadotropin-releasing hormone agonist in women at risk of ovarian hyperstimulation syndrome undergoing gonadotropin stimulation and intrauterine insemination: proof-of-concept study

J.T. Awwad, A.B. Hannoun, A. Khalil, Z.M.H. Younes, G.S. Ghazeeri

Department of Obstetrics and Gynecology, American University of Beirut Medical Center, Beirut (Lebanon)

Summary

Objective: To evaluate the reproductive performance and safety of gonadotropin-stimulated intrauterine insemination (IUI) cycles in women at risk for ovarian hyperstimulation syndrome (OHSS) when final follicle maturation was induced using a gonadotropin-releasing hormone (GnRH) agonist. *Materials and Methods:* Thirty-three women presenting with a history of cancelled ovarian stimulation for fear of OHSS, underwent repeat gonadotropin ovarian stimulation for IUI. They were all found to be at high-risk for OHSS once more, and were counseled to receive a GnRH agonist to trigger final follicle maturation before insemination. GnRH agonist trigger of ovulation (triptorelin) was given subcutaneously every 12 hours in three repeated doses: 0.3, 0.2, 0.2 mg, respectively. *Results:* Induction with the agonist was associated with a 30.3% take-home pregnancy rate and 20% miscarriage rate. Multiple pregnancy rates were 26.7%. There were no reported cases of clinically significant moderate/severe ovarian hyperstimulation syndrome. *Conclusions:* The use of a GnRH agonist to trigger final follicle maturation in stimulated cycles of hyper responders was associated with a favorable reproductive outcome and no incidence of OHSS. The rate of multiple pregnancies nevertheless was found to be uncontrollably elevated, raising serious concerns regarding the safety of this protocol in standard clinical practice in the context of IUI.

Key words: Gonadotropin-releasing hormone agonist; Follicle maturation; Intrauterine insemination; Multiple gestations; Ovarian hyperstimulation syndrome.

Introduction

With the widespread use of human menopausal gonadotropins (hMG) for ovarian stimulation, the risk of developing ovarian hyperstimulation syndrome (OHSS), recognized as the most serious complication of fertility management, has become a primary concern. The most effective secondary preventive measure to avoid OHSS remains the withholding of the human chorionic gonadotropin (hCG) trigger dose and the cancellation of the treatment cycle. The substitution of hCG with a GnRH agonist to trigger final follicle maturation in the context of in vitro fertilization (IVF) and intracytoplasmatic sperm injection (ICSI) cycles has been reported in literature [1, 2]. The induced luteinizing hormone (LH) surge was demonstrated to initiate first meiotic division events successfully, leading to collection of competent metaphase II oocytes [1-5]. The application of the same trigger technique in the context of IUI by contrast has been poorly investigated. For IUI treatment cycles to achieve a successful outcome, the additional steps of follicle rupture and oocyte release are required. It is known through animal data that LH requirements, in terms of both duration and amplitude of the surge, are much more demanding for mechanical follicle rupture to occur than for meiosis to resume [6, 7]. Clinically, very few studies have reported the use of a GnRH agonist for the triggering of ovulation prior to IUI [8-10].

The aim of this interventional analysis was one of a proof-of-concept, which was to investigate whether the use of a GnRH agonist trigger protocol in gonadotropin-stimulated IUI cycles can achieve conception, while monitoring the risks of OHSS and multiple pregnancies.

Materials and Methods

Patients

All initiated gonadotropin-stimulated IUI cycles that ended in a cycle cancellation for risk of OHSS and which were performed at a tertiary fertility center between June 1, 2003 and December 31, 2004 were reviewed. The criteria for cycle cancellation were: (a) estradiol levels ≥ 1,500 pg/ml and/or (b) four or more follicles ≥ 12 mm in diameter. Inclusion criteria included: (a) history of primary infertility; (b) women age range: 18 to 38 years; and (c) first attempted IUI cycle. Exclusion criteria included: (a) evidence of obstructive tubal disease; (b) moderate/severe endometriosis (ASRM Stage III/IV); and (c) and moderate/severe male factor infertility (< 5 million motile sperm post-wash).

Thirty-nine women who in subsequent stimulation cycles were found to meet again the aforenentioned cancellation crite-

Revised manuscript accepted for publication April 12, 2012

ria were considered for study. Thirty-three of them were consented to receive a GnRH agonist to trigger follicle maturation instead of cancelling their cycle. Approval for the study was obtained from the Institutional Review Board.

Ovarian stimulation

All eligible women were stimulated using human menopausal gonadotropins (hMG) beginning on day three of their menstrual cycle. Triggering of ovulation using the GnRH agonist was performed when at least one follicle measured ≥ 18 mm in diameter, in the following manner: triptorelin in repeated subcutaneous doses of 0.3, 0.2, and 0.2 mg at 12-hour intervals. IUI was scheduled 36 to 40 hours following the first triggering dose. Potential adverse effects, namely OHSS and multiple gestations, were thoroughly explained to all women throughout the study period. All patients approved to undergo selective embryo reduction in the event of high-order multiple gestations.

Follow-up and management

The women received 4 mg of estradiol and 40 mg of synthetic progesterone orally and daily in two divided doses. Luteal supplementation was begun on the day following IUI and continued until gestational week 11 in the event of pregnancy.

OHSS was diagnosed according to the criteria by Navot *et al*. [11]. The identification of at least one intrauterine gestational sac by ultrasound was considered the basis for a clinical pregnancy. A miscarriage was defined as a pregnancy loss following verification of a positive urinary pregnancy test and prior to 20 weeks of gestation. A pregnancy was considered ongoing if viability was documented by ultrasound beyond 20 weeks of gestation.

Outcome measures

The primary outcome measures were the rates of clinical/ongoing/take-home pregnancies and miscarriages rates. The secondary outcome measures were the incidence of clinically significant moderate/severe OHSS and multiple gestations.

Statistical analysis

Metric and nominal variables were analyzed descriptively for lack of controls. Values are expressed as mean ± standard deviation.

Results

Thirty-three women, who received the GnRH agonist for final follicle trigger, met the inclusion criteria and were considered for evaluation. Patient demographics and stimulation characteristics are shown in Table 1. The primary causes of infertility were polycystic ovary syndrome (PCOS) (n = 23), mild male factor infertility (n = 5), unexplained infertility (n = 4), and minimal endometriosis (n = 1). Mean final serum E2 levels on the day of GnRH agonist trigger were 3,337.5 ± 871.9 pg/ml (range: 1,700 pg/ml to 4,987 pg/ml).

Outcome measures are presented in Table 2. Fifteen (45.5%) of the 33 women cycles achieved pregnancy, of whom three (20.0%) had a miscarriage and four (26.7%) had twin gestations. No cases of high-order multiple gestations were reported. One set of twins were lost at 22 weeks gestation when they presented full cervical dilatation. No incidents of clinically significant moderate or severe OHSS were reported.

Table 1. — *Demographic and stimulation characteristics of gonadotropin stimulated IUI cycles in women at risk for OHSS using GnRH agonist trigger for final follicle maturation.*

	Mean	Standard deviation
Age of patients (years)	28.8	4.7
BMI (kg/m^2)	27.6	5.0
Duration of infertility (years)	3.1	2.0
Duration of stimulation (days)	9.1	1.2
Total gonadotropin dose (IU)	1363.6	458.6
Final no. of follicles ≥ 12 mm	18.8	4.7
Final no. of follicles ≥ 16 mm	7.6	1.7
Final serum E2 level (pg/ml)	3337.5	871.9

Table 2. — *Outcome measures of gonadotropin stimulated IUI cycles in women at risk for OHSS using GnRH agonist trigger for final follicle maturation (n = 33).*

Primary Outcome Measures	N (%)
Clinical pregnancy rates	15 (45.5)
Ongoing pregnancy rates	12 (36.4)
Take-home pregnancy rates	10 (30.3)
Miscarriage rates	3 (20.0)
Secondary Outcome Measures	**N (%)**
Mild OHSS	3 (9.1)
Clinically significant OHSS	0 (0.0)
Multiple gestations	4 (26.7)

Ultrasound examinations of the ovaries performed during the menstrual phase of the next cycle in 18 women and between seven and eight weeks gestation in 15 women, revealed normal-appearing ovaries with absence of any corpora lutea exceeding ≥ 12 mm in diameter.

Discussion

The findings of this proof-of-concept study have shown that the use of the GnRH agonist, triptorelin, to trigger final follicle maturation in gonadotropin stimulated IUI cycles at risk for OHSS, is associated with a highly-favorable reproductive outcome, compared to IUI outcomes reported in the literature. These findings constitute an indirect confirmation of the occurrence of LH-mediated ovarian events, namely resumption of meiosis, follicle rupture, and oocyte release following GnRH agonist trigger. These findings contrast with those of IVF/ICSI cycles, in which a series of randomized clinical trials lately casted serious doubts regarding the reproductive performance of GnRH agonists when used as substitutes for hCG for ovulation triggering [3-5]. Although the GnRH agonist trigger protocol was not shown to influence the number and quality of oocytes retrieved [3-5], lower pregnancy and higher miscarriage rates were repeatedly reported in these studies [3, 4, 12]. The compromised reproductive outcome associated with IVF/ICSI cycles

was believed to be due to endometrial/luteal insufficiency, rather than the result of an oocyte/embryo developmental problem [13]. The unusually favorable pregnancy rates found in this study could be interpreted on the basis of the following explanations: (a) estradiol/progesterone combined luteal supplementation was continued until 11 weeks gestation. The early interruption of luteal supplementation was associated with unusually elevated miscarriage rates in one study [3]; (b) it is also possible that the high number of ovulated oocytes from super-ovulated ovaries may have leveraged the presumed endometrial/luteal insufficiency associated with GnRH agonist trigger protocols, acting as a salvage mechanism. Challenging a defective endometrium with a high number of fertilized oocytes may have counterbalanced its restricted reproductive performance.

Proposed mechanisms for the protective effect offered by GnRH agonists against OHSS are the prolonged pituitary down-regulation with reduction of LH support to the corpora lutea and the initiation of intracellular signaling cascade mediating apoptosis with irreversible luteolysis [10, 14-17]. The findings of the present study demonstrated the complete elimination of moderate and severe OHSS in 33 cycles undergoing ovarian gonadotropin stimulation for IUI, despite a very high number of pre-ovulatory follicles, highly-elevated mean final E2 serum levels, and the presence of past history of cycle cancellation due to risk of OHSS (Table 1). The ultrasound findings of normal looking ovaries devoid of any corpora lutea > 12 mm diameter following failed cycles and during the first trimester of pregnancy supports the irreversible luteolysis hypothesis proposed by Nevo *et al*. [17] despite rising endogenous placental hCG titers. Nevertheless, a final conclusion on this topic cannot be made without proper quantification of risk through prospective controlled trials in larger female populations. It should also be noted that the GnRH agonist trigger protocol described in this study was arbitrarily modified from the conventional single dose to the repeated dose regimen.

The finding of a high multiple pregnancy rate associated with the GnRH agonist trigger protocol when used in the context of IUI cycles in high-responding women, is probably the most significant drawback of this treatment approach. The uncontrollable nature of this complication with potentially very serious perinatal sequels is a major source of concern. The absence of high-order multiple pregnancies despite a high number of pre-ovulatory follicles at the time of ovulation trigger is however intriguing. Potential explanations may be traced to the previously proposed endometrial/luteal insufficiency reducing implantation rates [13, 18-20], and/or to a crowding effect within the super-ovulated ovary increasing the chance of rupture for superficial follicles only and entrapment for deeper ones.

The main limitations of this study were the retrospective collection of the data and the uncontrolled nature of the study, which may have overestimated the size effect of the intervention. The actual effect of the GnRH agonist trigger protocol in pregnancy rates in IUI cycles may also have been skewed due to selection bias as a result of the inclusion criteria in which only young women with high ovarian response and absent tubal and/or male factor infertility were included.

In conclusion, despite the good favorable impact of GnRH agonists in pregnancy outcome and risk of OHSS when used to trigger final follicle maturation in women at risk for OHSS undergoing IUI cycles, this study does not provide safety data regarding the risk of high-order multiple gestations. It should be acknowledged that standard clinical practice dictates mono- or bi-follicular development in stimulated IUI cycles, and that multi-follicular growth is best managed by cycle cancellation.

References

[1] 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.

[2] Manzanares M.A., Gómez-Palomares J.L., Ricciarelli E., Hernández E.R.: "Triggering ovulation with gonadotropin-releasing hormone agonist in in vitro fertilization patients with polycystic ovaries does not cause ovarian hyperstimulation syndrome despite very high estradiol levels". *Fertil. Steril*., 2010, *93*, 1215.

[3] Humaidan P., Bredkjaer H.E., Bungum L., Bungum M., Grondahl M.L., 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.

[4] Kolibianakis E.M., 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.

[5] Griesinger G., Diedrich K., Devroey P., Kolibianakis E.M.: "GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis". *Hum. Reprod. Update*, 2006, *12*, 159.

[6] Bomsel-Helmreich O., Vu N Huyen L., Durand-Gasselin I.: "Effects of varying doses of HCG on the evolution of preovulatory rabbit follicles and oocytes". *Hum. Reprod*., 1989, *4*, 636.

[7] Peluso J.J.: "Role of the amplitude of the gonadotropin surge in the rat". *Fertil. Steril*., 1990, *53*, 150.

[8] Olivennes F., Fanchin R., Bouchard P., Taieb J., Frydman R.: "Triggering of ovulation by a gonadotropin-releasing hormone (GnRH) agonist in patients pretreated with a GnRH antagonist". *Fertil. Steril*., 1996, *66*, 151.

[9] Pirard C., Donnez J., Loumaye E.: "GnRH agonist as novel luteal support: results of a randomized, parallel group, feasibility study using intranasal administration of buserelin". *Hum. Reprod*., 2005, *20*, 1798.

[10] Van der Meer S., Gerris J., Joostens M., Tas B.: "Triggering of ovulation using a gonadotrophin-releasing hormone agonist does not prevent ovarian hyperstimulation syndrome". *Hum. Reprod*., 1993, *8*, 1628.

[11] Navot D., Bergh P.A., Laufer N.: "Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment". *Fertil. Steril*., 1992, *58*, 249.

[12] Babayof R,. Margalioth E.J., Huleihel M., Amash A., Zylber-Haran E., Gal M. *et al*.: "Serum inhibin A, VEGF and TNF alpha levels after triggering oocyte maturation with GnRH agonist compared with HCG in women with polycystic ovaries undergoing IVF treatment: a prospective randomized trial". *Hum. Reprod*., 2006, *21*, 1260.

[13] Acevedo B., Gomez-Palomares J.L., Ricciarelli E., Hernandez E.R.: "Triggering ovulation with gonadotropin-releasing hormone agonists does not compromise embryo implantation rates". *Fertil*. *Steril*., 2006, *86*, 1682.

[14] Itskovitz J., Boldes R., Levron J., Erlik Y., Kahana L., Brandes J.M.: "Induction of preovulatory luteinizing hormone surge and prevention of ovarian hyperstimulation syndrome by gonadotropin-releasing hormone agonist". *Fertil*. *Steril*., 1991, *56*, 213.

[15] Nevo O., Eldar-Geva T., Kol S., Itskovitz-Eldor J.: "Lower levels of inhibin A and pro-_C during the luteal phase after triggering oocyte maturation with a gonadotropin releasing hormone agonist versus human chorionic gonadotropin". *Fertil*. *Steril*., 2003, *79*, 1123.

[16] Yano T., Yano N., Matsumi H., Morita Y., Tsutsumi O., Schally A.V., Taketani Y.: "Effect of luteinizing hormone-releasing hormone analogs on the rat ovarian follicle development". *Horm*. *Res*., 1997, *48*, 35.

[17] Takekida S., Deguchi J., Samoto T., Matsuo H., Maruo T.: "Comparative analysis of the effects of gonadotropin-releasing hormone agonist on the proliferative activity, apoptosis and steroidogenesis in cultured porcine granulosa cells at varying stages of follicular growth". *Endocrine*, 2000, *12*, 61.

[18] Fauser B.C., 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.

[19] Andersen C.Y., Humaidan P., Ejdrup H.B., Bungum L., Grondahl M.L., Westergaard L.G.: "Hormonal characteristics of follicular fluid from women receiving either GnRH agonist or hCG for ovulation induction". *Hum*. *Reprod*., 2006, *21*, 2126.

[20] Beckers N.G., Macklon N.S., Eijkemans M.J., Ludwig M., Felberbaum R.E., Diedrich K. *et al*.: "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.

Address reprint requests to:
G. GHAZEERI, M.D.
American University of Beirut Medical Center
Department of Obstetrics and Gynecology
P.O. Box: 113-6044
Beirut (Lebanon)
e-mail: gg02@aub.edu.lb