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ScienceDirect

Journal of the Chinese Medical Association 79 (2016) 387−393

www.jcma-online.com

Original Article

The benefit of individualized low-dose hCG support for high responders in GnRHa-triggered IVF/ICSI cycles

Chen-Yu Huang [a,b], Miawh-Lirng Shieh [a], Hsin-Yang Li [a,b,*]

[a] *Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[b] *Division of Obstetrics and Gynecology, Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*

Received September 11, 2015; accepted February 15, 2016

Abstract

Background: To assess the pregnancy outcome and ovarian hyperstimulation syndrome (OHSS) incidence in high responders receiving gonadotropin-releasing hormone agonist (GnRHa) trigger plus individualized support of low-dose human chorionic gonadotropin (hCG). Such support includes 500−1000 IU hCG given at trigger and, if serum estradiol (E_2) dropped to below 800 pg/mL before the 6th day after oocyte retrieval, an additional rescue dose of 300 IU hCG.
Methods: This was a retrospective study of potential high responders aged from 28 years to 40 years at a tertiary fertility center in Taiwan. By means of chart review, we assessed the pregnancy outcome and OHSS incidence in high responders receiving GnRHa trigger plus individualized low-dose hCG support. The main outcomes were measured by ongoing pregnancy rate and OHSS incidence (SPSS), in which statistical significance was determined by Chi-square test.
Results: Moderate to severe OHSS did not develop in any patient receiving GnRHa trigger plus individualized low-dose hCG support. In fact, a satisfactory ongoing pregnancy rate (46.9%) was noted in patients receiving GnRHa trigger plus individualized low-dose hCG support.
Conclusion: Our study suggested that GnRHa trigger combined with individualized low-dose hCG support appears to be a safe approach with a satisfactory pregnancy outcome.

Keywords: agonist trigger; high responders; human chorionic gonadotropin (hCG); *in vitro* fertilization (IVF); ovarian hyperstimulation syndrome (OHSS)

1. Introduction

Ovarian hyperstimulation syndrome (OHSS) remains the most challenging complication in assisted reproductive technology, which potentially puts the patient into life-threatening danger.[1] Conventional use of human chorionic gonadotropin (hCG) for triggering, due to its sustained and considerably more powerful luteotropic activity, increases the risk of OHSS.[1,2] Previous studies have proposed replacing hCG with gonadotropin-releasing hormone agonist (GnRHa) to induce a surge of luteinizing hormone (LH),[3,4] by which OHSS risk can be eliminated.[5] Although the GnRHa-induced LH surge effectively stimulates final oocyte maturation,[4,6] due to the short duration of LH secretion and the status of pituitary desensitization, luteolysis occurs more rapidly compared to the natural cycles.[5,7] More and more evidence including that from the Cochrane Review has corroborated that GnRHa trigger in antagonist protocols did prevent OHSS[5,6,8] but led to unfavorable rates of ongoing pregnancy and live birth,[6,8,9] which mainly stemmed from defective corpus luteal function.[10,11] Therefore, adequate luteal phase support is essential to maintain a successful pregnancy in GnRHa-triggered cycles.

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Hsin-Yang Li, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: lihy@vghtpe.gov.tw (H.-Y. Li).

http://dx.doi.org/10.1016/j.jcma.2016.02.006

Respected scholars have developed various means of modified luteal phase support to enhance reproductive outcomes. Engmann et al[12] reported an ongoing pregnancy rate of 53.3% in GnRHa-triggered cycles that are supported by intramuscular (IM), progesterone (P), and transdermal estradiol (E_2) in the luteal phase. As described by Shapiro et al,[13] "dual trigger", in which a reduced dose (1000–2500 IU) of hCG was administered along with the triggering agonist, was also associated with excellent reproductive outcome. By contrast, Humaidan et al[14] suggested that 1500 IU of hCG could be given 35 hours after GnRHa trigger to rescue the corpus luteum. To the best of our knowledge, there seems to be a lack of consensus regarding the most effective and safest protocol for high responders.

Inspired by the aforementioned literature, we developed an individualized low-dose hCG support, in which the patients were dually triggered with GnRHa and an even lower dose (500–1000 IU) of hCG followed by luteal phase support with IM, P, and oral E_2 in combination with or without an extra rescue dose (300 IU) of hCG (depending on E_2 level in the luteal phase). The purpose of this present study was to compare the reproductive outcomes and OHSS incidence in high responders that were divided into four groups: (1) triggered with hCG under downregulation protocol, (2) triggered with hCG under GnRH antagonist protocol, (3) triggered with GnRHa alone under GnRH antagonist protocol, and (4) receiving GnRHa-triggered GnRH antagonist protocol with "individualized low-dose hCG support", i.e., dually triggered by GnRHa and 500–1000 IU of hCG with or without a rescue dose (300 IU) of hCG in the luteal phase.

2. Methods

2.1. Patients

A retrospective study was conducted at the Center for Reproductive Medicine in Taipei Veterans General Hospital, Taipei, Taiwan, and undertaken by means of chart review. From January 2009 to September 2011, we applied GnRHa trigger combined with individualized low-dose hCG support in 34 cycles, and GnRHa trigger alone in 23 cycles, to potential high responders with polycystic ovarian morphology (PCOM), polycystic ovarian syndrome (PCOS), or previous OHSS. In the aforementioned cycles, the serum level of E_2 on the day of trigger, i.e., peak E_2, ranged between 2500 pg/mL and 13478 pg/mL. To recruit matching cases triggered by hCG with comparable peak E_2, cycles with peak $E_2 \geq 2500$ pg/mL were enrolled. We excluded patients with one of the following conditions: (1) older than 40 years, (2) endometriosis, (3) hypogonadotropic hypogonadism, (4) freezing cycles, and (5) uterine abnormalities. In the study period, a total of 155 cycles were included in this retrospective study. As the study was merely performed via chart review, which included only analysis of data from routine clinical practice, it did not require submission to our Institutional Review Board. Informed consent was obtained from each patient who was included in the study.

2.2. Treatment protocols

Ovarian stimulation was performed with recombinant follicle-stimulating hormone (rFSH), with the starting dose determined by the patient's age, body mass index (BMI), basal FSH level, and antral follicle count. During stimulation, the dose of rFSH was adjusted by ovarian response monitored every other day from the 4th day of stimulation. A simplified schematic description of the four treatment protocols is shown in Fig. 1. Patients receiving protocol A were downregulated with daily leuprolide 0.5 mg subcutaneously (sc) from the preceding midluteal phase, and the dose of leuprolide was lowered to 0.25 mg from the starting day of rFSH stimulation. In Groups B–D, daily cotreatment with antagonist cetrorelix 0.25 mg sc was initiated either once the leading follicle had reached a size of 14 mm or no later than the 6th day of rFSH stimulation. The patients were triggered when at least three leading follicles reached above 17 mm in diameter. Oocytes were retrieved 34–36 hours after trigger, followed by *in vitro* fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI) according to the condition of the sperm.

In Groups A and B, 10,000 IU of hCG was injected to trigger final oocyte maturation, followed by luteal phase support consisting of micronized progesterone vaginally (90 mg/d; Crinone; Merck Serono, Geneva, Switzerland) and oral estradiol valerate (6 mg/d). In Group C, triptorelin (Decapeptyl; Ferring Pharmaceuticals, Saint-Prex, Switzerland) 0.2 mg was sc administered for triggering, and IM progesterone injection (100 mg/d) along with oral estradiol valerate (6 mg/d) was prescribed for luteal support. Patients in Group D were dually triggered by triptorelin 0.2 mg and hCG with a dose depending on the serum level of E_2 and the number of follicles $\geq$ 11 mm on trigger day (500 IU for cycles with peak $E_2 > 5000$ pg/mL or follicle number $\geq$ 25,750 IU for cycles with peak E_2 3500–5000 pg/mL and follicle number < 25, and 1000 IU for

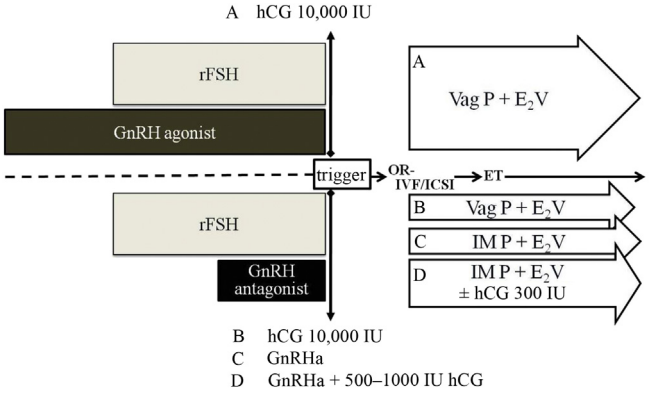

Fig. 1. Treatment protocols. Group A, downregulation protocol with hCG trigger; Group B, GnRH antagonist protocol with hCG trigger; Group C, GnRH antagonist protocol with GnRHa trigger; and Group D, GnRH antagonist protocol with GnRHa trigger combined with individualized low-dose hCG support (Please refer to Fig. 2A for the detail of individualization in Group D.). E_2V = estradiol valerate; ET = embryo transfer; IM P = intramuscular progesterone; IVF/ICSI = *in vitro* fertilization and/or intracytoplasmic sperm injection; OR = oocyte retrieval; rFSH = recombinant follicle-stimulating hormone; Vag P = vaginal-route micronized progesterone (Crinone).

cycles with peak E_2 < 3500 pg/mL and follicle number < 25). Luteal support for cycles in Group D included IM progesterone (100 mg/d), oral estradiol valerate (6 mg/d) and an additional 300 IU of hCG, which was administered if the serum E_2 dropped to below 800 pg/mL during close monitoring from the 2nd day to the 6th day after retrieval. For patients whose serum E_2 had never dropped below 800 pg/mL before Day 6 post retrieval, this rescue dose was not given (Fig. 2A).

Embryos were transferred on the 3rd day or the 5th day after retrieval depending on the number of good quality embryos available. In protocol D, if serum E_2 on Day 5 post retrieval became even higher than those on Day 2–4 post retrieval, under ethical considerations, all blastocysts were vitrified. Three patients in protocol A, two patients in protocol B, zero patients in protocol C, and one patient in protocol D underwent "freeze-all" strategy during the study period and were excluded from analyses. A total of 155 cycles were finally recruited, among which 74 cycles were triggered with hCG under downregulation protocol (Group A), 25 cycles were triggered with hCG under the GnRH antagonist protocol (Group B), 23 cycles were triggered with GnRHa alone (Group C), and 33 cycles received GnRHa trigger combined with individualized low-dose hCG support (Group D). Patients in all groups received luteal phase support from the day after oocyte retrieval to either 10 weeks of gestation or confirmed failure of pregnancy.

2.3. Outcome measures

Demographic variables recorded for each cycle included the following items: age, BMI, basal FSH and LH, PCOM or not, PCOS or not, previous OHSS or not, severe male factor requiring ICSI or not, primary infertility or not, the number of previous IVF attempts, and parity. Parameters in terms of ovarian stimulation, oocytes, embryos, and cycle outcomes were noted as follows: total gonadotropin dose, peak E_2 levels, the number of follicles on trigger day, oocyte number and maturity, fertilization rate, cleavage rate, the number of good available embryos, implantation rate, chemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate, the rate of early pregnancy loss, the serum level of E_2 and P on the 14th day after retrieval, and the rate of moderate/severe OHSS.

A good available embryo was defined as a six to eight cell embryo on the 3rd day after retrieval with a grade of I or II, according to criteria described elsewhere.[15] The implantation rate was calculated as the number of beating fetal hearts divided by the number of embryos transferred per patient. Positive pregnancy test was defined by the rising serum beta subunit of human chorionic gonadotropin titers above 10 IU/L on the 14th day after retrieval. Clinical pregnancy was counted if any intrauterine fetal heart beat was detected by transvaginal ultrasound 3 weeks after a positive chemical pregnancy test. Ongoing pregnancies had surviving fetuses at 12 weeks' gestation. Early pregnancy losses meant chemical pregnancies that failed in developing to ongoing pregnancies. The diagnosis of moderate-to-severe OHSS was made according to the criteria by Golan et al.[16]

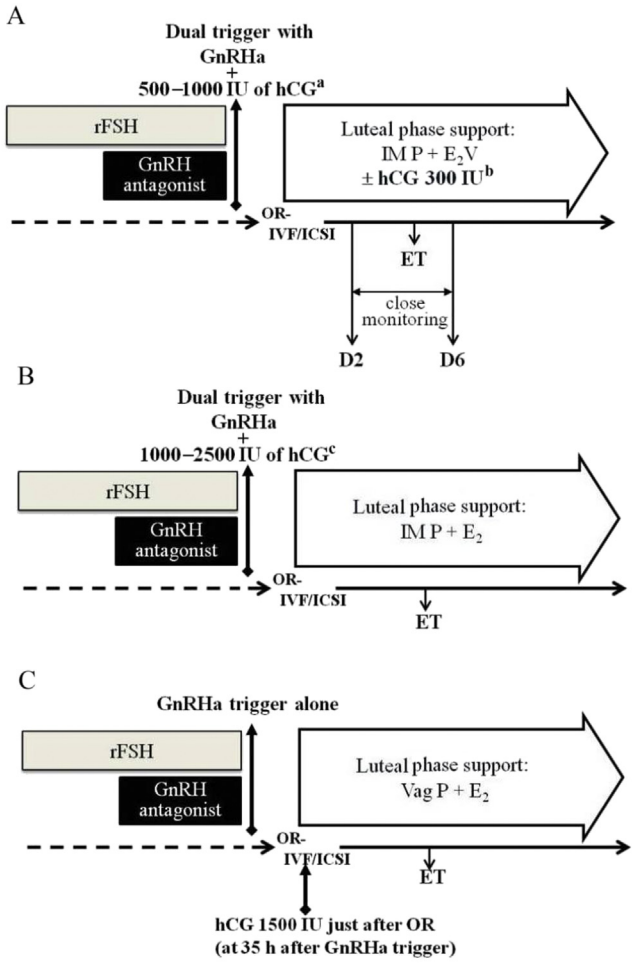

Fig. 2. Comparisons among different protocols of low-dose hCG supplementation in GnRHa-triggered IVF/ICSI cycles. A, Individualized low-dose hCG support in our study. B, Dual trigger developed by Shapiro et al.[13] C, Corpus luteum rescue at oocyte retrieval raised by Humaidan.[19] A fixed dose of 1500 IU hCG is administered shortly after the oocyte retrieval to rescue the function of corpus lutea. [a] The dosage of hCG (500–1000 IU) in dual trigger depends on peak E_2 and the number of follicles ≥ 11 mm on trigger day: 500 IU for cycles with peak E_2 >5000 pg/mL or follicle number ≥ 25; 750 IU for cycles with peak E_2 3500-5000 pg/mL and follicle number < 25; and 1000 IU for cycles with peak E_2 <3500 pg/mL and follicle number < 25. [b] The additional shot of hCG 300 IU for rescue in luteal phase support: administered if serum E_2 drops to below 800 pg/mL during close monitoring from Day 2 to Day 6 after retrieval. Otherwise, this rescue dose is not given. [c] 1000–2500 IU of concomitant hCG: varied according to weight and OHSS risk factors. Patients with > 25 follicles receive an average of 23.1 IU/kg, whereas those with ≤ 25 receive an average of 29.9 IU/kg. D2 = Day 2 after oocyte retrieval; D6 = Day 6 after oocyte retrieval; E_2V = estradiol valerate; ET = embryo transfer; h = hours; IM P = intramuscular progesterone; IVF/ICSI = *in vitro* fertilization and/or intracytoplasmic sperm injection; OR = oocyte retrieval; rFSH = recombinant follicle-stimulating hormone; Vag P = vaginal-route micronized progesterone (Crinone).

2.4. Statistical analyses

Chi-square tests were used for comparisons of nominal variables in all four groups; Fisher's exact test was used for adjusting the expected count less than five when dealing with 2 × 2 tables. Continuous parameters were analyzed with ANOVA test followed by Tukey's HSD post-hoc examinations.

The SPSS statistical package (version 17; SPSS Inc., Chicago, IL, USA) was used for analysis, and a p value < 0.05 was considered to be statistically significant.

3. Results

With regards to demographic data, age, BMI, basal FSH and LH levels, the proportion of ICSI, primary infertility and parity were comparable among the groups (Table 1). The proportion of patients with previous IVF attempts was significantly higher in Group D than that in Group A.

The overall dose of gonadotropin used in Group D was lower than that in Groups A and B (Table 2). Serum level of E_2 on the day of trigger was significantly lower in Group B than that in Groups A and D. Patients in Group D had more follicles on the day of trigger and more oocytes retrieved than those in Groups A and B. There was no significant difference among the groups associated with the percentage of mature or metaphase of second meiosis oocytes. Additionally, the fertilization rate in Group D was higher than that in Group C. There was no significant difference in cleavage rate among groups. The number of good available embryos in Group D was higher than that in Groups A and B.

None of the patients in Groups C and D developed moderate/severe OHSS. By contrast, 33.8% (25/74) of the patients in Group A and 24.0% (6/25) in Group B suffered from OHSS (Table 3). There was a tendency toward a better outcome in Group D than in Group C in terms of higher implantation rate (22.5 ± 5.2% vs. 5.8 ± 2.8%), clinical pregnancy rate (48.5% vs. 17.4%) and ongoing pregnancy rate (46.9% vs. 17.4%) as well as lower miscarriage rate (16.7% vs. 50.0%); but probably due to the limited case number, it did not reach statistical significance (Table 3). With regards to the serum levels of E_2 and P on the 14th day after retrieval, there was no statistically significant difference among the groups. However, a statistically significant difference emerged when we compared serum E_2 levels exclusively in cycles with positive pregnancies tests. On the 14th day after retrieval, serum E_2 level in patients with positive pregnancy tests was significantly higher in Group B as compared with that in Groups C and D. Both E_2 and P levels of patients with positive pregnancy tests on the 14th day after retrieval seemed to be higher, although not statistically significant, in Group D than in Group C (Table 3).

4. Discussion

Early luteolysis associated with GnRHa triggering is the key to the prevention of OHSS, but at the same time it leads to an increased rate of early pregnancy loss.[17,18] To provide adequate luteal phase support in GnRHa triggered cycles, scientists have reported better pregnancy outcomes by supplementation of exogenous intramuscular progesterone and transdermal estradiol[12] or administration of low-dose hCG as a dual trigger[13] (Fig. 2B) or as a luteal rescue[19] (Fig. 2C). In our retrospective study, we found that low-dose hCG given in GnRHa triggered cycles was associated with improved reproductive outcome as compared with intramuscular progesterone without hCG. However, the use of hCG in GnRHa triggered cycles is not without risk, especially in patients at a high risk for OHSS. Shapiro et al[20] reported that even with an hCG dose of 650 IU in combination with GnRHa trigger, OHSS still developed in one patient among 182 high responders. The rescue dose of 1500 IU hCG given at retrieval was associated with one case of moderate OHSS in 12 high-risk patients in one report,[19] and one case of severe OHSS in 71 women with high OHSS risk in another study.[21]

The rationale for the individualized low-dose hCG we administered in GnRHa-triggered cycles was the idea of

Table 1
Demographic data.

Characteristics of patients	Group A (hCG trigger in downregulation protocol)	Group B (hCG trigger in antagonist protocol)	Group C (GnRHa trigger in antagonist protocol)	Group D (GnRHa trigger + individualized hCG in antagonist protocol)	p
Patients, n	74	25	23	33	
Age (y)	32.3 ± 3.1	33.8 ± 3.3	32.6 ± 3.1	33.5 ± 4.1	0.153
BMI (kg/m^2)	21.3 ± 2.9	22.9 ± 4.3	22.0 ± 3.0	22.1 ± 4.3	0.259
Basal FSH (IU/L)	5.8 ± 2.2	6.3 ± 2.8	6.6 ± 1.8	6.5 ± 1.7	0.330
Basal LH (IU/L)	7.2 ± 4.2	7.5 ± 7.2	8.2 ± 3.3	9.2 ± 7.2	0.363
PCOM	37 (50)[a]	11 (47.8)[a]	18 (78.3)[ab]	28 (84.8)[b]	0.002*
PCOS	16 (21.6)[a]	9 (36.0)[ab]	5 (21.7)[a]	20 (60.6)[b]	0.001*
Previous OHSS	7 (9.5)[a]	4 (16.7)[ab]	7 (30.4)[ab]	15 (45.5)[b]	<0.001*
Severe male factor requiring ICSI	39 (52.7)	8 (32.0)	11 (55.0)	15 (45.5)	0.296
Primary infertility	44 (61.1)	13 (54.2)	17 (73.9)	20 (60.6)	0.561
Previous IVF attempts					
0	52 (73.2)	16 (64.0)	16 (69.6)	14 (43.8)	0.034*
≥1	19 (26.8)[a]	9 (36.0)[ab]	7 (30.4)[ab]	18 (56.3)[b]	
Parity					
0	65 (87.8)	22 (88.0)	20 (87.0)	26 (78.8)	0.635
≥1	9 (12.2)	3 (12.0)	3 (13.0)	7 (21.2)	

Data are presented as n (%) or mean ± standard deviation.
* Values in groups without the same letter are statistically different.

Table 2
Stimulation characteristics and data of oocytes and embryos.

Variable	Group A (hCG trigger in downregulation protocol)	Group B (hCG trigger in antagonist protocol)	Group C (GnRHa trigger in antagonist protocol)	Group D (GnRHa trigger + individualized hCG in antagonist protocol)	*p*
Patients, *n*	74	25	23	33	
Total dose of gonadotropin (IU)	2790 ± 678[b]	3005 ± 567[b]	2469 ± 917[ab]	2357 ± 873[a]	0.008*
E_2 on day of trigger (pg/mL)	5182 ± 2113[b]	3893 ± 1673[a]	4663 ± 1545[ab]	5390 ± 2212[b]	0.024*
Follicles on trigger day	18.3 ± 5.5[a]	15.6 ± 7.1[a]	20.1 ± 5.7[ab]	22.7 ± 8.0[b]	0.001*
Oocytes	14.7 ± 6.4[a]	14.0 ± 8.6[a]	18.5 ± 7.1[ab]	23.4 ± 10.5[b]	<0.001*
Rate of mature oocytes,%	77.5 ± 20.1	79.9 ± 21.7	80.8 ± 18.5	74.6 ± 18.1	0.647
Rate of MII oocytes in ICSI cycles, %	70.4 ± 20.5	70.7 ± 19.4	70.5 ± 24.3	74.2 ± 19.7	0.941
Fertilization rate,%	75.4 ± 16.0[ab]	73.4 ± 19.1[ab]	68.5 ± 20.7[a]	82.2 ± 10.0[b]	0.022*
Cleavage rate, %	85.4 ± 15.3	79.7 ± 16.5	84.2 ± 16.3	82.7 ± 16.4	0.460
Good available embryos	3.2 ± 1.8[a]	2.5 ± 1.7[a]	3.4 ± 2.7[ab]	4.6 ± 2.6[b]	0.004*

Data are presented as mean ± standard deviation.
MII = metaphase of second meiosis.
* Values in groups without the same letter are statistically different.

Table 3
Cycle outcomes of all patients and serum E_2 and P levels on Day 14 after oocyte retrieval in patients with positive pregnancy tests.

Variable	Group A (hCG trigger in downregulation protocol)	Group B (hCG trigger in antagonist protocol)	Group C (GnRHa trigger in antagonist protocol)	Group D (GnRHa trigger + individualized hCG in antagonist protocol)	*p*
Patients, *n*	74	25	23	33	
Moderate-to-severe OHSS rate	25 (33.8)	6 (24.0)	0 (0)	0 (0)	<0.001
E_2 on Day 14 after oocyte retrieval (pg/mL)	2313 ± 2275	2387 ± 2340	1373 ± 708	1523 ± 1032	0.078
P on Day 14 after oocyte retrieval (ng/mL)	137.7 ± 153.3	145.9 ±163.0	65.0 ± 68.4	143.3 ± 147.9	0.215
Implantation rate (%)	17.0 ± 3.2	14.2 ± 4.8	5.8 ± 2.8	22.5 ± 5.2	0.129
Positive pregnancy test	32 (43.2)	10 (41.7)	8 (34.8)	19 (57.6)	0.351
Clinical pregnancy rate	26 (35.1)	8 (33.3)	4 (17.4)	16 (48.5)	0.122
Ongoing pregnancy rate	24 (32.9)	6 (27.3)	4 (17.4)	15 (46.9)	0.129
Early pregnancy loss	7 (22.6)	2 (25.0)	4 (50.0)	3 (16.7)	0.326
Patients with positive pregnancy tests, *n*	32	10	8	19	
E_2 on Day 14 after oocyte retrieval (pg/mL)	3343 ± 2295[ab]	4178 ± 2430[b]	1512 ± 833[a]	2120 ± 980[a]	0.006*
P on Day 14 after oocyte retrieval (ng/mL)	233.1 ± 173.9	287.3 ±161.9	77.8 ± 96.9	202.2 ± 173.0	0.063

Data are presented as *n* (%) or mean ± standard deviation.
* Values in groups without the same letter are statistically different.

"installments", by which we demonstrated a satisfactory pregnancy outcome with no OHSS. This was achieved by means of low-dose hCG divided into 500−1000 IU for combined trigger and then 300 IU for rescuing corpus luteum if needed. We closely monitored serum E_2 level from the 2nd day to the 6th day after retrieval, in order to timely administer the rescue dose of 300 IU hCG if serum E_2 dropped to below 800 pg/mL. We tailored the timing to boost a bolus of low-dose hCG before Day 6 post retrieval. This timing referred to the length of the luteal phase documented after GnRHa trigger alone, which was around 4 days at the shortest, as referenced in the literature.[22] If serum E_2 was above 800 pg/mL on Day 6 post retrieval, the 300 IU rescue dose of hCG was not given in order to avoid OHSS, and the corpus luteum was expected to be partially rescued by implanted trophoblast-derived hCG from Day 9 of retrieval should pregnancy occur. We observed that 300 IU of hCG would offer 2−3 additional days of corpus luteum support. If serum E_2 on the 5th day after retrieval became even higher than those on Days 2−4 after retrieval (which occurred in only 1 patient receiving dual trigger during the study period), all blastocysts were cryopreserved to prevent late-onset OHSS. We believe that this approach will make the high responders much safer.

We intentionally applied the tailored approach with low-dose of hCG (Group D) and GnRHa trigger alone (Group C) for the high responders identified by the characteristics of PCOM, PCOS, or previous OHSS. When compared with Groups C and D, more high responders (enrolled by peak $E_2 \geq 2500$ pg/mL) in Groups A and B had no known predisposing factors and became apparent during ovarian stimulation. Owing to the study design and the inherent limitation in the nonrandomized retrospective study, some confounding factors were distributed unevenly in each group. Groups C and D had more patients with PCOM, PCOS, or previous OHSS (Table 1); however, no patient in Groups C and D experienced OHSS and an ongoing pregnancy rate of 46.9% was achieved in Group D. It was the good reproductive outcome with zero OHSS rate in an even higher percentage of high-risk

population that convinced us of the benefits of this protocol of GnRHa trigger with individualized low-dose hCG support.

A presumed advantage of concomitant hCG in GnRHa trigger is to aid in oocyte maturation, as well as its benefit to luteal support. Although there is no significant difference in the oocyte maturity among the four groups, our data revealed a higher fertilization rate in Group D (mean 82.2%), significantly when compared with Group C (mean 68.5%) and nonsignificantly when compared with Groups A (mean 75.4%) and B (mean 73.4%), respectively. Except for the fertilization rate of 62.8% in dual trigger reported by Shapiro et al[13] and the fertilization rate of 79.2% in dual trigger reported by Griffin et al,[23] there was limited data in reference to the fertilization rate in cycles triggered by GnRHa combined with hCG. As for GnRHa trigger alone versus hCG trigger, previous investigations showed similar fertilization rates.[9,14,24] The possible explanation for better fertilization in our combined trigger might be that low-dose of hCG could assist final maturation of oocytes in aspects not detectable by the morphology, which needs further validation via well-designed prospective trials. We assumed both the higher fertilization rate and superior luteal support contributed to a better pregnancy outcome as compared with the group receiving GnRH agonist trigger alone.

Although mean E_2 level on trigger day in group D reached 5390 pg/mL, an ongoing pregnancy rate of 46.9% was achieved. Extremely high level of peak E_2 in this group did not seem to impair the reproductive outcome, which conflicted with the previous concept that high E_2 level would impede implantation.[25,26] A possible explanation could be that the high responders per se produced plenty of oocytes to be fertilized, and further led to sufficient embryos to be selected. Thus, the resulting blastocysts transferred into the uterus might be "strong" enough to overcome the inferior environment. Whether this hypothesis is correct needs further investigation.

In view of the implantation rate (22.5% vs. 5.8%), clinical pregnancy rate (48.5% vs. 17.4%), and ongoing pregnancy rate (46.9% vs. 17.4%) for Group D versus Group C, there was a tendency toward a better outcome in the group of agonist plus individualized low-dose hCG support (Group D) versus agonist trigger alone (Group C). The rate of early pregnancy loss (16.7% and 50.0% for Groups D and C, respectively) seems to be higher in the group of agonist trigger alone. Probably due to the limited case number, it did not reach statistical significance. In Group D, there was a trend toward higher serum E_2 (1523 pg/mL vs. 1373 pg/mL for Group D vs. Group C) and P (143.3 ng/mL vs. 65.0 ng/mL for Group D vs. Group C) levels on the 14^{th} day after oocyte retrieval as compared with Group C, although statistical significance was not reached. If we focused on the population with positive pregnancy tests (Table 3), serum E_2 level on the 14^{th} day after oocyte retrieval in Group D (2120 pg/mL) was significantly lower than that in Group B (hCG trigger in antagonist cycles, 4178 pg/mL), and slightly higher (nonsignificantly) than that in Group C (1512 pg/mL). Regarding the P level on the14^{th} day after oocyte retrieval in the population with positive pregnancy tests, there was a similar tendency, i.e., the P level in Group D was lower than that in Group B and higher than that in Group C (Group B, 287.3 ng/mL; Group C, 77.8 ng/mL; and Group D, 202.2 ng/mL), although statistical significance was not reached. This status was what we managed to achieve: to rescue only a small portion of the corpus lutea awaiting subsequent endogenous hCG to sustain it, merely satisfying pregnancy maintenance, but not to the level toward OHSS.

To date, conclusions from the existing meta-analyses for GnRHa trigger were the results of either analyzing data from studies recruiting normo-ovulatory women[9] or pooling data from studies enrolling normal and high responders.[8,18] The authors in Kolibianakis et al[27] have proposed a view of examining the various surveys on GnRHa trigger in two categories: patients at a normal risk for OHSS and those with a high risk of OHSS. With this view, we reviewed and summarized investigations involving GnRHa triggering combined with supplementation of low-dose hCG, as described below. In patients at a normal risk for OHSS, low-dose hCG resulted in comparable pregnancy outcomes in GnRHa-triggered groups as compared with hCG-triggered groups. However, no difference could be concluded regarding OHSS incidence after GnRHa triggering versus conventional hCG triggering, because either no cases of OHSS were reported in either group[28] or the study was not powered to detect differences in OHSS rate.[14,29] As for high responders receiving GnRHa triggering, low-dose hCG administration either on the day of oocyte retrieval[19,21] or in the form of dual trigger,[20] can provide good pregnancy rates with a low but not zero rate of OHSS. A retrospective study conducted by Griffin et al[23] used a dual trigger with GnRHa and 1000 IU of hCG in selected patients at risk of OHSS with peak $E_2 < 4000$ pg/mL, reporting a significantly higher pregnancy rate as compared with GnRHa trigger alone, as well as only one case of mild OHSS in 34 patients receiving dual trigger. In our present study with the tailored approach, none of the 33 patients in Group D with mean peak E_2 exceeding 5000 pg/mL experienced OHSS. Therefore, hCG is like a double-edged sword from which patients cannot benefit until we find not only the predicting parameters to select the most appropriate population but also the optimal way to tailor the dose individually. Moreover, individualized low-dose hCG supplementation may provide a more patient-friendly way of luteal support instead of painful progesterone injection. A preliminary report from Kol et al[30] suggested that two boluses of 1500 IU hCG, without any additional luteal support containing progesterone, could revert the luteolysis after a GnRHa trigger in the normal responders. Thus, we can anticipate that once the optimal dose-tailoring approach is confirmed, the patients would be freed from painful intramuscular P injection and achieve good pregnancy outcomes without experiencing OHSS.

In conclusion, GnRHa trigger in combination with tailored low-dose hCG support seems to be a safe approach with a satisfactory pregnancy outcome for high responders, in contrast to high OHSS rate in hCG-triggered cycles and low pregnancy rate in GnRHa-triggered cycles without hCG. Further larger randomized controlled trials should be pursued to refine this protocol so that a patient-friendly regimen can be finalized to obtain excellent reproductive outcome and to almost completely avoid OHSS.

Acknowledgments

The authors thank Dr. Shang-Liang Wu at Biostatistics Task Force, and Dr. Chi-Mou Juang at the Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, for their statistical advice. This work has been supported, in part, by the National Science Council, Taiwan (NSC 98-2314-B-075-032-MY3) and the Taipei Veterans General Hospital (V101C-140 and V101B-046).

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