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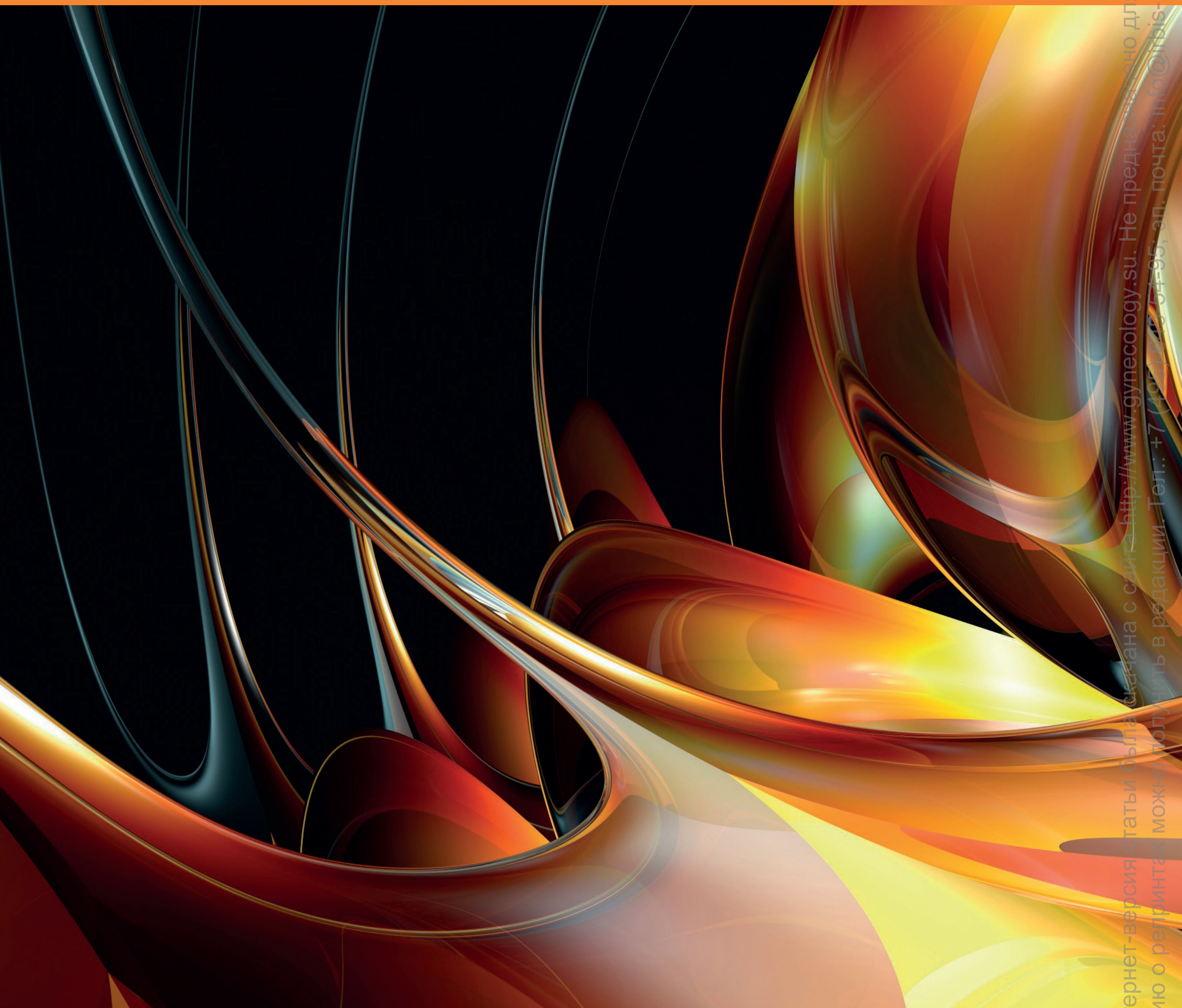

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The efficacy of GnRH agonist trigger followed by hCG add-back in normal responders for fresh embryo transfer: a case-control analysis from Vietnam

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Abstract

Aim: to assess the effects of a dual trigger by gonadotrophin-releasing hormone (GnRH) agonist and low-dose human chorionic gonadotropin (hCG) on in vitro fertilization (IVF) outcomes in women with normal ovarian response.

Materials and Methods. This case-control analysis comprised 118 patients who responded normally to ovarian stimulation with a GnRH antagonist protocol at Hue Center for Reproductive Endocrinology and Infertility, Vietnam, between January 2018 and October 2019. Recruitment was achieved through case-control matching: a case (with Dual trigger – group A) was paired with control (with hCG trigger – group B) in a 1:1 ratio. The primary markers of success were the retrieval of oocytes and embryological data, the pregnancy rate, and the incidence of ovarian hyperstimulation syndrome (OHSS).

Results. 59 patients in group A and 59 women in group B were recruited. Two groups had comparable patient characteristics and ovarian reserve. The initial dose, total dose, duration of gonadotropin administration, and peak of estradiol level were not statistically different across groups. The number of recovered oocytes (10.3 ± 4.2 vs. 10.0 ± 3.3; p = 0.663), mature oocytes (8.6 ± 3.7 vs. 8.1 ± 2.8; p = 0.346), and high-quality embryos (56.2 ± 28.9 vs. 59.8 ± 35.9; p = 0.555) was equivalent. Fertilization, clinical pregnancy, and live birth rates were comparable between the dual trigger and hCG groups. In neither group were any occurrences of OHSS seen.

Conclusion. Dual trigger may substitute hCG for final oocyte maturation and fresh embryo transfer in patients with normal responses to GnRH antagonist protocol-induced ovarian stimulation without compromising IVF outcomes.

Keywords: dual trigger, gonadotrophin-releasing hormone (GnRH) agonist, GnRH antagonist, normal responder, ovarian hyperstimulation syndrome, OHSS

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Эффективность триггера овуляции агониста ГнРГ с последующим добавлением ХГЧ у нормальных респондеров при переносе свежих эмбрионов: Вьетнамское исследование «случай–контроль»

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Резюме

Цель: оценить влияние двойного триггера овуляции агониста гонадотропин-рилизинг-гормона (ГнРГ) и низких доз хорионического гонадотропина человека (ХГЧ) на исходы экстракорпорального оплодотворения (ЭКО) у женщин с нормальным овариальным ответом.

Материалы и методы. В исследование «случай–контроль» были включены 118 пациенток с нормальным ответом на стимуляцию яичников с применением протокола с антагонистом ГнРГ. Исследование проводилось в Центре репродуктивной эндокринологии и бесплодия Хюэ (Вьетнам) в период с января 2018 г. по октябрь 2019 г. Набор пациенток проводился путем сопоставления «случай–контроль»: случай (применение двойного триггера – группа А) сопоставлялся с контролем (применение триггера ХГЧ – группа Б) в соотношении 1:1. Основными маркерами успеха были: получение ооцитов и эмбриологические характеристики, частота наступления беременности и частота синдрома гиперстимуляции яичников (СГЯ).

Результаты. В исследование были включены 59 пациенток из группы А и 59 женщин из группы Б с сопоставимыми характеристиками и овариальным резервом. Между группами не отмечено статистических отличий в начальной дозе, общей дозе, продолжительности введения гонадотропина и пиковом уровне эстрадиола. Количество сформированных ооцитов (10,3 ± 4,2 против 10,0 ± 3,3; p = 0,663), зрелых ооцитов (8,6 ± 3,7 против 8,1 ± 2,8; p = 0,346) и эмбрионов высшего качества (56,2 ± 28,9 против 59,8 ± 35,9; p = 0,555) были сходными в обеих группах. Также между группами были сопоставимы показатели фертилизации, наступления клинической беременности и частоты живорождения, случаи СГЯ в обеих группах не наблюдались.

Заключение. Двойной триггер овуляции может заменить ХГЧ для окончательного созревания ооцитов при переносе свежих эмбрионов у пациенток с нормальным ответом на стимуляцию яичников в протоколе с применением антагонистов ГнРГ, без влияния на исход ЭКО.

Ключевые слова: двойной триггер, агонист гонадотропин-рилизинг-гормона, ГнРГ, антагонист ГнРГ, нормальный респондер, синдром гиперстимуляции яичников, СГЯ

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Introduction / Введение

In vitro fertilization (IVF) cycles require final maturation to harvest mature oocytes from preovulatory follicles in controlled ovarian stimulation (COH) [1]. Human chorionic gonadotropin (hCG) is widely used as a surrogate Luteinizing hormone (LH) surge to stimulate final oocyte maturation and restart of meiosis following COH [1]. This protocol has been the gold standard for IVF cycles [1, 2]. However, the comparatively long serum half-life of hCG leads to a prolonged and potent luteotropic action, which increases the risk of ovarian hyperstimulation syndrome (OHSS) in high-risk individuals [3].

Gonadotrophin-releasing hormone (GnRH) antagonists are supposed to be an optimal choice of therapy for women undergoing COH for IVF, and it has grown in favor during the past two decades [4, 5]. There are several theoretical advantages of GnRH antagonists over GnRH agonists, including immediate and rapid suppression of Gonadotrophin production, lack of flare-up effect, absence of menopausal-like symptoms, reduced risk of ovarian cyst formation, shorter duration of treatment, a significantly smaller dose of Gonadotropins per cycle, and a decreased OHSS risk [6, 7].

Furthermore, the GnRH agonist trigger may provide a more physiological surge of LH and Follicle Stimulating Hormone (FSH), stimulating an FSH surge comparable to the normal mid-cycle surge [8, 9]. However, compared to the hCG trigger, the GnRH agonist (GnRHa) trigger with conventional luteal phase support (LPS) had a greater miscarriage rate, lower implantation, ongoing pregnancy, and live birth rates [10, 11].

In recent years, the most prominent are the American and European ways of enhancing the luteal phase in response to GnRHa stimulation. The American technique used transdermal estradiol and intramuscular progesterone (Progesterone IM) for severe LPS therapy. As part of the European protocol, A. Alleyassin et al. advocated low-dose hCG supplementation on the day of oocyte extraction or early in the luteal phase, followed by standard LPS [12]. A dual trigger, a combination of GnRHa and low-dose hCG delivered at the time of triggering, may eliminate OHSS and increase the luteal phase without requiring further intensive LPS [13, 14].

Numerous studies have demonstrated the advantages of the European strategy. GnRH agonist trigger followed by a modest bolus of hCG and fresh embryo transfer might prevent high-risk women from suffering OHSS (an average of 25 follicles or less with 11 mm in diameter). In high responders (with an average of 17–18 oocytes), the predicted OHSS would decrease significantly when employing this method [15, 16]. However, up to date, the published research on the role of dual triggers in normal responders has been limited. Besides, it is necessary to

Highlights

What is already known about this subject?

- Human chorionic gonadotropin (hCG) is commonly used to stimulate the final maturation of oocytes and the resumption of meiosis after ovarian stimulation.
- In high ovarian responders, using gonadotrophin-releasing hormone agonist (GnRHa) in the last stages of oocyte maturation produced comparable results to the human chorionic gonadotropin (hCG) trigger.
- Dual triggering (GnRHa + 1000 IU hCG) resulted in higher implantation, clinical pregnancy, and live birth rates than hCG, but ovarian hyperstimulation syndrome (OHSS) still exists.

What are the new findings?

- In normal responders, GnRHa can produce comparable results to hCG in terms of the number of retrieved oocytes, mature oocytes, usable embryos, and number of high-quality embryos.
- Clinical pregnancy rates, live birth rates, and implantation rates did not statistically differ between GnRHa and traditional hCG groups in normal responders.
- GnRHa trigger in cases of normal responders showed no incidences of OHSS.

How might it impact on clinical practice in the foreseeable future?

- In normal responders, GnRHa can be substituted for as a safe and effective trigger following ovarian stimulation.
- After GnRHa stimulation, a tailored dose of hCG (500–1000 IU) may be recommended as a safe and effective technique for luteal phase support.

Основные моменты

Что уже известно об этой теме?

- Хорионический гонадотропин человека (ХГЧ) обычно используется для стимуляции окончательного созревания ооцитов и возобновления мейоза после стимуляции яичников.
- Использование агониста гонадотропин-рилизинг-гормона (аГнРГ) на последних стадиях созревания ооцитов у женщин с высоким уровнем ответа яичников дало результаты, сравнимые с применением ХГЧ в качестве триггера.
- По сравнению с ХГЧ, применение двойного триггера (аГнРГ + 1000 МЕ ХГЧ) приводило к более высокой частоте имплантации, клинической беременности и живорождения, но и к развитию синдрома гиперстимуляции яичников (СГЯ).

Что нового дает статья?

- У женщин с нормальным ответом применение аГнРГ может давать результаты, сравнимые с использованием ХГЧ, по количеству извлеченных ооцитов, зрелых ооцитов, пригодных для использования эмбрионов и количеству эмбрионов высшего качества.
- Между группами женщин с нормальным ответом, получающими аГнРГ и традиционный ХГЧ, частота наступления клинической беременности, живорождения и имплантации статистически не отличалась.
- У женщин с нормальным ответом при применении триггера аГнРГ не отмечалось СГЯ.

Как это может повлиять на клиническую практику в обозримом будущем?

- После стимуляции яичников у женщин с нормальным ответом аГнРГ можно использовать в качестве безопасного и эффективного триггера.
- После стимуляции аГнРГ можно рекомендовать применение ХГЧ в индивидуально подобранной дозировке (500–1000 МЕ) в качестве безопасной и эффективной поддержки лютеиновой фазы.

determine the maximum number of oocytes in which dual trigger should be recommended.

Aim: to assess the effects of a dual trigger by GnRH agonist and low-dose hCG on IVF outcomes in women with normal ovarian response.

Materials and Methods / Материалы и методы

Study design / Дизайн исследования

Between January 2018 and October 2019, infertile patients who had their first IVF/ICSI cycle with a normal response to COH utilizing the GnRH antagonist protocol at the Hue Center for Reproductive Endocrinology & Infertility, Hue University Hospital, Vietnam, were included in this case-control analysis.

Recruitment was accomplished by case-control matching: a case (with Dual trigger) was followed by a control (with hCG trigger) matched with a ratio of 1:1, according to the homogenized factors: age (± 2 years), anti-Mullerian hormone (AMH) ± 1.5 (ng/ml), and antral follicle count (± 2 follicles).

Inclusion and exclusion criteria / Критерии включения и исключения

The inclusion criteria for normal responders were as follows: at least 5 follicles ≥ 14 mm, no more than 25 follicles ≥ 12 mm, estradiol (E2) < 4000 pg/mL on the day of triggering, and no more than 20 oocytes retrieved [17, 18]. Women with polycystic ovary syndrome or endometrioma, ovarian cysts, or a history of ovarian surgery or ovarian failure were excluded from the study.

Treatment protocol / Протокол лечения

On day 2 of the cycle, the daily dose of recombinant FSH (rFSH) (follitropin alfa; Gonal F®, Merck KGaA, Germany) was initiated following an ultrasound to determine the antral follicles count (AFC) and rule out the existence of ovarian cysts. Depending on the patient's age, AMH, and AFC, the starting dosage of rFSH is either 150 IU or 225 IU per day. Transvaginal ultrasonography and serum estradiol levels were measured during the whole stimulation period and on the last day of oocyte maturation induction. GnRH-antagonist 0.25 mg/day (Cetrorelix, Cetrotide®, Merck KGaA, Germany) was begun

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on day 5 of stimulation according to a fixed protocol and continued until the day of triggering, as shown in **Figure 1**.

Patients were randomized to receive either a dual trigger (group A) with GnRHa (Fertilpeptil® 0.1 mg/ml, Triptorelin acetate, Ferring Pharmaceutical, Switzerland) and hCG 1500 IU (Pregnyl® 1500 IU, MSD, USA) plus hCG 1500 IU (Pregnyl® 1500 IU, MSD, USA) on the day (group B). On the day of the trigger, serum concentrations of estradiol (E2) and progesterone were tested. Thirty-six hours later, ultrasound-guided oocyte retrieval was performed.

Embryo quality was evaluated based on cleavage and morphological scores, as indicated by L.L. Veeck [19]. Fresh embryo transfer would be performed on day 3 following oocyte retrieval, and the number of embryos transferred would be determined based on the patient's age and embryo quality.

If moderate OHSS symptoms, according to criteria proposed by A. Golan et al., were present after oocyte retrieval until the day of transfer, the fresh embryo transfer would be canceled [20]. When patients exhibited abdominal distension with or without nausea, vomiting, or diarrhea, mild OHSS was identified. In addition to the characteristics of mild OHSS, the presence of ultrasonographic ascites distinguished moderate OHSS. Patients with severe OHSS exhibited moderate OHSS symptoms, including ascites, hydrothorax, hemoconcentration, coagulation problems, and/or renal/hepatic dysfunction.

Progesterone (Crinone gel 8 %, Merck KGaA, Germany) was administered vaginally twice daily to support the luteal phase from the day of oocyte retrieval until either the 10th week of gestation or a negative pregnancy test. Fourteen days after embryo transfer, serum β-hCG was evaluated. If the β-hCG result was greater than 50 mIU/mL (positive test), pregnant women were followed with serial ultrasound examinations, and four weeks following embryo transfer, the number of gestational sacs with fetal cardiac activity was assessed (clinical pregnancy). The implantation rate was calculated by dividing the number of gestational sacs identified at 6 weeks of pregnancy ultrasonography screening by the number of embryos implanted into the uterine cavity.

Outcome variables / Конечные точки

The primary outcomes were the clinical pregnancy rate. The secondary outcomes were MII, fertilization top-quality embryo rates, and the rate of OHSS.

Ethics aspects / Этические аспекты

This study was approved by the Ethics Committee of the University of Medicine and Pharmacy, Hue University (Approval Nr: H2023/020, signed in February, 2023).

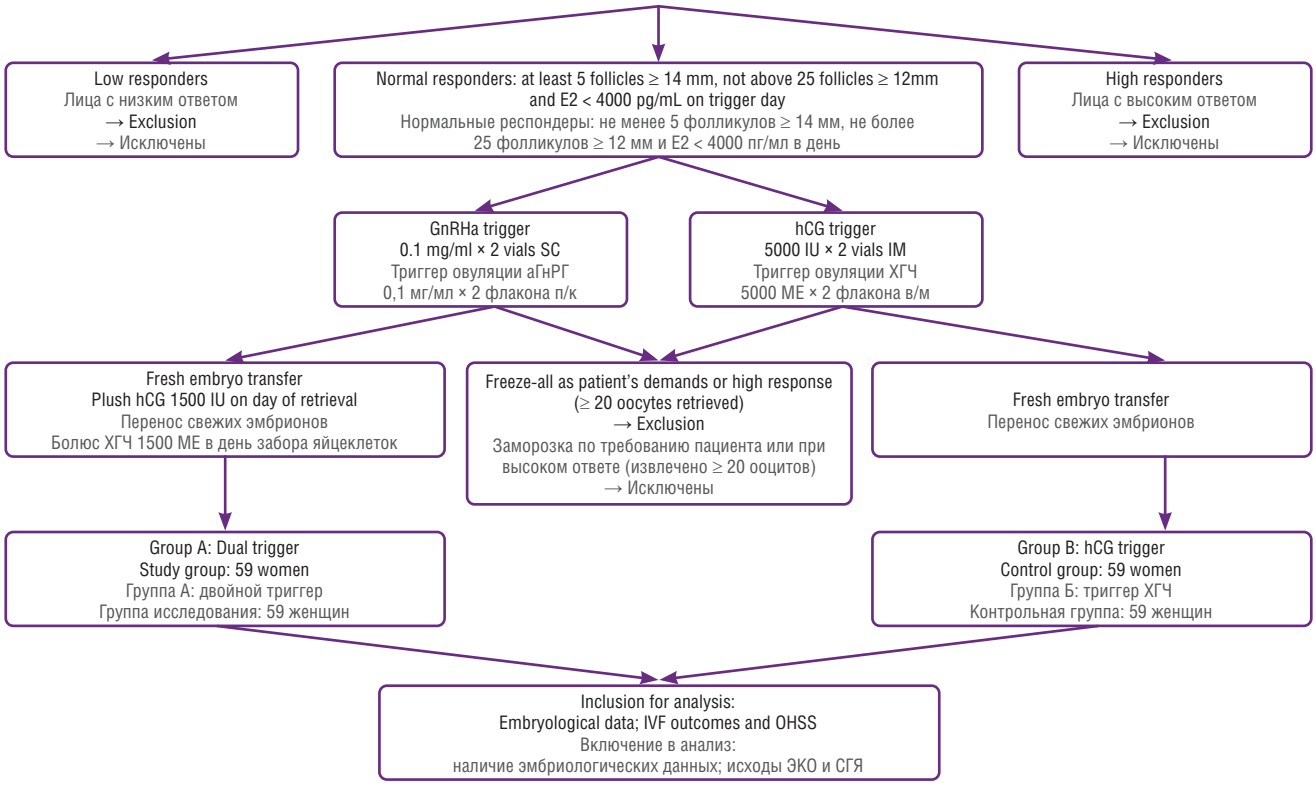

Figure 1. Algorithm for inclusion of study population.

Note: *E2 – estradiol; GnRHa – gonadotrophin-releasing hormone agonist; hCG – human chorionic gonadotropin; IM – intramuscular; SC – subcutaneous; IVF – in vitro fertilization; OHSS – ovarian hyperstimulation syndrome.*

Рисунок 1. Алгоритм включения в исследуемую когорту.

Примечание: *E2 – эстрадиол; аГнРГ – агонист гонадотропин-рилизинг-гормона; ХГЧ – хорионический гонадотропин человека; в/м – внутримышечно; п/к – подкожно; ЭКО – экстракорпоральное оплодотворение; СГЯ – синдром гиперстимуляции яичников.*

The present study was conducted in accordance with the Declaration of Helsinki. The informed consent form was obtained for all participants before participation in this study. All information and data were encrypted and confidential. All samples were handled and processed strictly, as an approved local review board protocol stipulated.

Statistical analysis / Статистический анализ

Statistical analysis was performed using SPSS 20.0 statistical software (IBM, USA). Data were presented as numbers, percentages, or Mean (M) ± SD. Chi-square or Fisher exact tests were used for categorical l variables, and the independent-sample t-test was used for continuous variables where appropriate. All analyses of significance were two-sided and tested at the 5 % level. A p-value of less than or equal to 0.05 was considered statistically significant.

Results / Результаты

A total of 118 participants were included in the research, with 59 patients receiving dual triggers and 59 patients receiving standard hCG triggers (**Fig. 1**). Several baseline characteristics of patients in the two groups were compared: age, location, type of infertility, length of infertility, body mass index (BMI), waist, waist-hip ratio, waist-height ratio, and level of basal hormones (FSH, LH, and AMH). The two groups had no statistically significant difference in the general features (**Table 1**).

In bivariate analysis, as shown in **Table 2**, there was no statistically significant difference between the two

Table 1. Patient's general characteristics and ovarian reserve.

Таблица 1. Общие характеристики и овариальный резерв пациенток.

Characteristics Характеристика	Dual trigger group Группа с двойным триггером n = 59	hCG trigger group Группа с триггером ХГЧ n = 59	p
Age, years / Возраст, лет, M ± SD	32.0 ± 4.4	31.9 ± 4.0	0.878
≥ 35 years / ≥ 35 лет, n (%)	17 (54.8)	14 (45.2)	0.530
< 35 years / < 35 лет, n (%)	42 (48.3)	45 (51.7)	
Geography / География:			
urban / городской житель, n (%)	25 (49.0)	26 (51.0)	0.853
non-urban / сельский житель, n (%)	34 (50.7)	33 (49.3)	
Type of infertility / Вид бесплодия:			
primary / первичное, n (%)	40 (50.6)	39 (49.4)	0.845
secondary / вторичное, n (%)	19 (48.7)	20 (51.3)	
Duration of infertility, years, M ± SD Длительность бесплодия, лет, M ± SD	5.5 ± 3.0	4.9 ± 2.5	0.293
BMI, kg/m^2, ИМТ, кг/м^2, M ± SD	20.4 ± 1.8	20.3 ± 2.1	0.761
≥ 18.5, n (%)	50 (51.5)	47 (48.5)	0.470
< 18.5, n (%)	9 (42.9)	12 (57.1)	
Waist, cm, M ± SD Окружность талии, см, M ± SD	70.7 ± 6.8	69.5 ± 5.8	0.284
≥ 80, n (%)	7 (70.0)	3 (30.0)	0,186
< 80, n (%)	52 (48.1)	56 (51.9)	
Waist-Hip ratio, M ± SD Отношение окружности талии к окружности бедер, M ± SD	0.80 ± 0.06	0.79 ± 0.06	0.242
≥ 0.85, n (%)	12 (54.5)	10 (45.5)	0.636
< 0.85, n (%)	47 (49.0)	49 (51.0)	
Waist-Height ratio, M ± SD Отношение окружности талии к росту, M ± SD	0.46 ± 0.05	0.44 ± 0.04	0.101
Basal FSH, mIU/mL, M ± SD Исходный ФСГ, мМЕ/мл, M ± SD	6.77 ± 2.69	6.84 ± 1.70	0.861
Basal LH, mIU/mL, M ± SD Исходный ЛГ, мМЕ/мл, M ± SD	5.35 ± 2.08	5.16 ± 2.93	0.680
AMH, ng/mL, M ± SD АМГ, нг/мл, M ± SD	3.23 ± 1.97	3.29 ± 1.93	0.854

Note: *hCG – human chorionic gonadotropin; BMI – body mass index; FSH – follicular stimulating hormone; LH – luteinizing hormone; AMH – anti-Mullerian hormone.*

Примечание: *ХГЧ – хорионический гонадотропин человека; ИМТ – индекс массы тела; ФСГ – фолликулостимулирующий гормон; ЛГ – лютеинизирующий гормон; АМГ – антимюллеров гормон.*

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Table 2. Controlled ovarian stimulation cycles and embryological data of two patient's groups.

Таблица 2. Циклы контролируемой стимуляции яичников и эмбриологические данные в группах обследованных пациенток.

Parameters **Показатель** **M ± SD**	**Dual trigger group** **Группа с двойным триггером** **n = 59**	**hCG trigger group** **Группа с триггером ХГЧ** **n = 59**	**p**
Antral follicle count / Количество антральных фолликулов	10.2 ± 3.0	9.7 ± 3.2	0.371
Starting dose of Gonadotropin Начальная доза гонадотропина	232.6 ± 28.0	236.4 ± 30.6	0.481
Duration of Gonadotropin Длительность применения гонадотропина	8.0 ± 0.8	8.3 ± 1.1	0.057
Total dose of Gonadotropin / Общая доза гонадотропина	1853.8 ± 297.6	1972.0 ± 417.0	0.079
Peak E2 level, pg/ml / Пик уровня Е2, пг/мл	2094.3 ± 687.8	2061.1 ± 765.1	0.805
Number of oocytes retrieval Количество извлеченных ооцитов	10.3 ± 4.2	10.0 ± 3.3	0.663
Number of mature oocytes / Количество зрелых ооцитов	8.6 ± 3.7	8.1 ± 2.8	0.346
Number of zygotes / Количество зигот	7.0 ± 3.2	6.1 ± 2.5	0.100
Number of usable embryos, A+B Количество пригодных для использования эмбрионов, A+B	5.4 ± 2.9	4.9 ± 2.8	0.364
Number of good embryos, A Количество хороших эмбрионов, A	3.3 ± 2.4	2.9 ± 2.3	0.455
Fertilization rate, % / Частота оплодотворения, %	81.2 ± 15.2	75.5 ± 16.9	0.053
Usable embryo rate, % Частота использования пригодных эмбрионов, %	78.6 ± 24.4	79.7 ± 30.7	0.831
Good embryo rate, % Частота использования хороших эмбрионов, %	56.2 ± 28.9	59.8 ± 35.9	0.555

Note: *E2 – estradiol; hCG – human chorionic gonadotropin.*

Примечание: *Е2 – эстрадиол; ХГЧ – хорионический гонадотропин человека.*

methods in terms of starting dose, total dose, duration of gonadotropin, peak E2 level, AFC, number of retrieved oocytes, number of mature oocytes, and number of usable embryos, as well as fertilization rate, usable embryo rate, and good embryo rate ($p > 0.05$).

In this investigation, OHSS was not observed in either group. As indicated in **Table 3**, the clinical pregnancy rate was decreased but not statistically significant in the dual trigger group compared to the hCG group (27.1 % versus 32.2 %; $p = 0.545$). Among 59 patients with GnRH

Table 3. Fresh embryo transferred cycles and in vitro fertilization outcome of two patient's groups.

Таблица 3. Циклы переноса свежих эмбрионов и результаты экстракорпорального оплодотворения в группах обследованных пациенток.

Parameters **Показатели**	**Dual trigger group** **Группа с двойным триггером** **n = 59**	**hCG trigger group** **Группа с триггером ХГЧ** **n = 59**	**p**
Endometrial thickness, mm, M ± SD Толщина эндометрия, мм, M ± SD	10.0 ± 1.6	9.8 ± 1.7	0.458
Number of embryos transferred, M ± SD Количество перенесенных эмбрионов, M± SD	2.4 ± 0.6	2.5 ± 0.5	0.405
Number of good embryos transferred, M ± SD Количество перенесенных хороших эмбрионов, M± SD	1.9 ± 0.9	1.8 ± 1.0	0.515
Implantation rate / Частота имплантации эмбриона	51.9 ± 26.1	46.0 ± 29.3	0.520
Clinical pregnancy / Клиническая беременность: Yes / Да, n (%) No / Нет, n (%)	 16 (27.1) 43 (72.9)	 19 (32.2) 40 (67.8)	0.545
Live birth / Живорождение: Yes / Да, n (%) No / Нет, n (%)	 11 (18.6) 48 (81.4)	 15 (25.4) 44 (74.6)	0.374

Note: *hCG – human chorionic gonadotropin.*

Примечание: *ХГЧ – хорионический гонадотропин человека.*

agonist treatment, the implantation rate was 51.9 % per 100 embryos transferred. In other groups, consisting of 59 patients using the hCG trigger, the rate was 46,0 per 100 embryos transferred, and the difference between the two groups was not statistically significant (p = 0.520). Similar to the live birth rate, these two groups did not differ substantially (p = 0.374).

Discussion / Обсуждение

Earlier research revealed that using GnRH agonists in the last stages of oocyte maturation yielded comparable or superior results to the hCG trigger [21, 22]. GnRH agonist trigger also induced an endogenous FSH surge, promoted the growth of cumulus cells around the oocyte, and released proteolytic enzymes [23, 24]. However, the initial investigations conducted in IVF donor cycles revealed that the luteal phase length was significantly shorter (4.16 ± 0.70 days vs. 13.63 ± 2.20 days) in donors ovulated with the agonist compared to donors in whom ovulation was induced with hCG [21, 22].

Cochrane analysis of 17 randomized controlled trials, including 1817 women, concluded that GnRH agonist triggers reduced the likelihood of conception and increased the probability of early miscarriages in fresh autologous IVF treatment cycles compared to hCG [25]. After the GnRH agonist trigger, several modifications of normal LPS supplementation were performed, including injection of a modest bolus of hCG or recombinant LH to rescue the luteal phase or intense LPS with estradiol and progesterone, resulting in decreased OHSS and a high rate of ongoing pregnancy [26–28].

In high ovarian responders, dual triggering (GnRHa + 1000 IU hCG) had greater implantation, clinical pregnancy, and live birth rates than the conventional hCG group [13, 29]. A recent retrospective analysis reported that dual trigger in GnRH-antagonist protocols (defined as an Estradiol level greater than 4000 pg/mL on the day of triggering or as the number of retrieved oocytes 20) was capable of averting severe OHSS while maintaining an exceptional embryo rate of good quality [30]. However, the lack of analysis of pregnancy rates constituted a weakness of this study.

In normal responders, our data showed the duration of gonadotropin, total dose of gonadotropin, peak E2 level, number of retrieved oocytes, number of mature oocytes, number of useable embryos, and number of healthy embryos did not differ substantially between the two approaches. These outcomes are comparable to D. Bodri et al. study on oocyte donor cycles [22]. In addition, clinical pregnancy rates, live birth rates, and implantation rates did not differ statistically between GnRH agonist and conventional hCG groups.

Regarding OHSS, no cases were recorded in this investigation. B.S. Shapiro et al. also observed that the incidence of OHSS was extremely low (under 1 %) in patients with a high risk of OHSS (Estradiol level > 4,700 pg/ml and ≥ 27 follicles on trigger day) who underwent final maturation utilizing a dual trigger [30]. In individuals with an Estradiol level under 4000 pg/ml to receive GnRH agonist paired with low-dose hCG on the day of hCG administration, D. Griffin et al. observed just one case of OHSS per 103 cycles [13]. K.E. O'Neill et al., however, found that dual trigger was associated with a significantly increased risk of severe OHSS compared to GnRH agonist alone. In fact, the COH patients in their study included individuals with poor, normal, and high responses and those at high risk for OHSS [31].

This study excluded patients with an estrogen level above 4000 pg/ml or fewer than 20 retrieved oocytes. Enormous discrepancies in inclusion criteria include the cutoff level of serum estradiol, number of mature follicles or follicles exceeding 11–12 mm in diameter, or variation in dosage of low-dose hCG (1000–1500 IU) in the trials mentioned above contributed to the varied outcomes. In addition, ethnicity may contribute to disparities in the efficacy and response to LPS or triggering regimens. More extensive prospective randomized controlled studies utilizing the same methodology and inclusion criteria are required to evaluate the effectiveness of dual trigger protocol in preventing OHSS and the optimal dosage of hCG to be administered with GnRH agonist trigger to maintain the success of assisted reproductive technology. A tailored dosage of hCG (500–1000 IU) should be suggested as a safe and effective method for achieving satisfactory results in individuals at high risk of OHSS while utilizing GnRH antagonist regimens in COH.

Conclusion / Заключение

In conclusion, the current investigation indicated that dual triggers could substitute hCG for oocyte maturation in normal responders without compromising IVF outcomes or raising the risk of OHSS. To increase pregnancy rates and reduce the risk of OHSS, larger RCTs are necessary to determine the population-specific cutoff level for the number of mature oocytes and maximum peak estrogen level on the triggering day.

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Le M.T., Tran N.Q.T. – data collection, formal analysis, original draft, review, and editing; Le N.S.V., Nguyen Q.H.V., Cao T.N. – original draft, review, and editing;	Ле М.Т., Тран Н.К.Т. – сбор и анализ данных, исходная концепция, обзор литературы и редактирование текста; Ле Н.С.В., Нгуен К.Х.В., Као Т.Н. – исходная концепция, обзор литературы и редактирование текста.
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The lack of focus on a specific group of subjects is a linitation of the study. More extensive prospective randomized controlled studies utilizing the same methodology and inclusion criteria are required to evaluate the efficacy of the dual trigger protocol in preventing OHSS and the optimal dose of hCG to be administered with the GnRH agonist trigger in order to maintain the success of assisted reproductive technology.	Ограничением настоящего исследования является изучение определенной группы пациентов. Необходимы более обширные проспективные рандомизированные контролируемые исследования с использованием той же методологии и критериев включения для оценки эффективности протокола применения двойного триггера овуляции в отношении предотвращения СГЯ и использования оптимальной дозы ХГЧ, которую следует вводить с агонистом ГнРГ для успешности проведения вспомогательных репродуктивных технологий.
Patient consent	**Согласие пациентов**
Obtained.	Получено.
Ethics approval	**Одобрение этического комитет**
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