Gonadotropin-Releasing Hormone Agonist Versus Human Chorionic Gonadotropin for Ovulation Induction in Polycystic Ovary Syndrome Patients Undergoing Intrauterine Insemination: A Randomised Controlled Trial

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ABSTRACT

Background: Gonadotropins have been recommended to improve ovulation, pregnancy and live birth rates in polycystic ovary syndrome (PCOS) patients with anovulatory infertility and clomiphene citrate (CC) resistance. However, this could increase the risk of ovarian hyperstimulation syndrome (OHSS). Gonadotropin-releasing hormone agonist (GnRHa) triggering could significantly reduce the risk of OHSS in patients undergoing in vitro fertilisation. However, data on the use of GnRHa in intrauterine insemination (IUI) is limited. This study compared the effectiveness of GnRHa and human chorionic gonadotropin (hCG) for ovulation induction in PCOS patients undergoing IUI.

Methods: This non-inferiority, single-centre, randomised controlled trial was conducted at IVFMD, My Duc Hospital, Ho Chi Minh City, Vietnam between April 2016 and May 2018. PCOS patients aged 18–37 years with CC resistance and ≤ 3 developing (≥ 16 mm) follicles on trigger day after stimulation with gonadotropins were eligible. Those with uterine abnormalities or tubal damage or inseminated with frozen semen were excluded. Triptorelin 0.1 mg or hCG 5000 IU was used when there was ≥ 1 follicle of ≥ 17 mm. IUI was performed at 36 hours after triggering. Primary outcome was ongoing pregnancy. Secondary outcomes were clinical pregnancy, multiple pregnancy, miscarriage and OHSS.

Results: A total of 380 patients were randomised (190 per group). Treatment groups had similar characteristics at baseline. Ongoing pregnancy rate was 23.7% in the GnRHa group versus 25.3% in the hCG group (Relative risk 0.94; 95% confidence interval, 0.66–1.34; $p = 0.81$). Secondary outcome parameters were also not significantly different between the two groups. There were two cases of mild OHSS in the hCG group and none in the GnRHa group.

Conclusion: 0.1 mg triptorelin was non-inferior to 5000 IU hCG IU in PCOS patients undergoing ovulation induction by hMG followed by IUI with respect to pregnancy outcomes.

Keywords: Ovulation Induction; Intrauterine Insemination; Gonadotropin-Releasing Hormone Agonist; Human Chorionic Gonadotropin; Ongoing Pregnancy.

TÓM TẮT

(ABSTRACT IN VIETNAMESE)

Đặt vấn đề: Gonadotropins được sử dụng để cải thiện tình trạng phóng noãn, tỷ lệ thai và sinh sống ở những bệnh nhân hiếm muộn có hội chứng buồng trứng đa nang (PCOS) có rối loạn phóng noãn và đề kháng với clomiphene citrate. Tuy nhiên, sử dụng gonadotrophins có thể làm tăng nguy cơ quá kích buồng trứng (QKBT). Trong những chu kỳ làm thụ tinh trong ống nghiệm, khởi động trưởng thành noãn bằng GnRH đồng vận có thể làm giảm nguy cơ QKBT. Tuy nhiên, ở các chu kỳ điều trị bằng phương pháp gây phóng noãn bằng gonadotrophins, dữ liệu về việc sử dụng GnRH đồng vận vẫn còn hạn chế. Nghiên cứu này được tiến hành với mục

tiêu so sánh hiệu quả của việc khởi động trường thành noãn của GnRH đồng vận và human chorionic gonadotropin (hCG) ở bệnh nhân PCOS điều trị bằng bơm tinh trùng vào buồng tử cung.

Phương pháp: Đây là một thử nghiệm lâm sàng ngẫu nhiên có nhóm chứng, đơn trung tâm được thực hiện tại IVFMD, Bệnh viện Mỹ Đức, Thành phố Hồ Chí Minh, Việt Nam trong khoảng thời gian từ tháng 4/2016 đến tháng 5/2018. Bệnh nhân PCOS tuổi từ 18–37, đề kháng với CC và có ≤ 3 phát triển (≥ 16 mm) vào ngày tiêm khởi động trường thành noãn sau khi kích thích buồng trứng bằng gonadotropins được nhận vào nghiên cứu. Những bệnh nhân có bất thường tử cung hoặc có bằng chứng tổn thương ống dẫn trứng hoặc sử dụng tinh trùng trữ không được tham gia nghiên cứu. Triptorelin 0.1 mg hoặc hCG 5000 IU được sử dụng khi có ít nhất 1 nang ≥ 17 mm. IUI được thực hiện 36 tiếng sau đó. Kết cục chính là thai diễn tiến. Các kết cục phụ bao gồm thai lâm sàng, đa thai, sảy thai và HCQKBT.

Kết quả: Tổng cộng có 380 bệnh nhân được nhận vào nghiên cứu (190 mỗi nhóm). Đặc điểm cơ bản bệnh nhân và đặc điểm chu kỳ KTBT tương tự giữa hai nhóm. Tỷ lệ thai diễn tiến là 23.7% ở nhóm bệnh nhân sử dụng GnRH đồng vận so với 25.3% ở nhóm sử dụng hCG (Relative risk 0.94; khoảng tin cậy 95%, 0.66–1.34; $p = 0.81$). Không có sự khác biệt có ý nghĩa thống kê về các kết cục phụ. Tuy nhiên, có hai trường hợp QKBT mức độ nhẹ được ghi nhận ở nhóm sử dụng hCG và không có trường hợp nào xảy ra ở nhóm GnRH đồng vận.

Kết luận: Kết quả nghiên cứu cho thấy có thể sử dụng GnRH đồng vận thay thế cho hCG trong các chu kỳ IUI ở đối tượng phụ nữ HCBDTN sau khi kích thích buồng trứng bằng gonadotropins để dự phòng HCQKBT.

Từ khóa: gây phóng noãn; khởi động trường thành noãn; bơm tinh trùng vào buồng tử cung; hội chứng buồng trứng đa nang; GnRH đồng vận.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting women of reproductive age, with a prevalence of 8–13% depending on the population studied and definitions used (Teede et al., 2010; Azziz et al., 2016). For infertile couples with PCOS with no other factors contributing to infertility who have failed first-line oral ovulation induction therapy and are anovulatory, gonadotropins could be used as second-line pharmacological agents (Teede et al., 2018).

Human chorionic gonadotropin (hCG) has been widely used for mimicking the endogenous LH surge to induce luteinisation of the granulosa cells, final oocyte maturation and ovulation. However, the prolonged half-life of hCG compared with natural LH promotes supraphysiological luteal steroid levels and the development of multiple corpora lutea, resulting in a potential increased risk of ovarian hyperstimulation syndrome (OHSS). Therefore, the use of alternate modalities to induce oocyte maturation to prevent OHSS, such as gonadotropin releasing hormone agonists (GnRHa), has been the focus of research for years. The latest meta-analysis showed that in women undergoing fresh autologous cycles, GnRHa were associated with a lower incidence of mild, moderate or severe OHSS compared with hCG (Youssef et al., 2014).

While the use of GnRHa in IVF has been well documented, the use of these agents in intrauterine insemination (IUI) is still limited (Farag et al., 2015).

This randomised controlled clinical trial compared with the effectiveness of GnRHa and hCG for ovulation induction in PCOS patients undergoing IUI by gonadotropins.

METHODS

Study design

This was a non-inferiority, single-center, randomised controlled trial. The study protocol was approved by the hospital ethics committee (09/MD-HĐĐĐ) and conducted according to Good Clinical Practice and Declaration of Helsinki 2002 principles. Written and signed informed consents were obtained from all of the participants prior to inclusion in the study.

Infertile women with PCOS (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004), aged 18–37 years, clomiphene citrate resistance (failure to ovulate or to conceive after receiving 150 mg CC for at least three cycles), undergoing

ovulation induction with gonadotropins followed by IUI and having ≤ 3 follicles at ≥ 16 mm on the day of trigger were eligible. Patients with uterine abnormalities (submucosal fibroids, polyps in the uterine cavity, bicornuate uterus and synechiae of the uterine cavity), tubal damage, male factor infertility or using frozen semen were excluded.

On the second day of a spontaneous or progestogen-induced withdrawal bleeding, all patients received a daily intramuscular injection of human menopausal gonadotropin (hMG; IVF M 75 IU, LG Life Sciences, Korea) for 7 days, with a starting dose of 75 IU/day. Patients were asked to come back for the first ultrasound scan on day eight of stimulation. The dose of hMG was maintained for 3 days if there was no follicle >12 mm on ultrasonography scan. After that, follicular monitoring was performed every three days for dose adjustment. If there was no follicle >12 mm after 12 days of stimulation, the hMG dose was increased by 75 IU/day for 7 days up to a maximum dose of 225 IU/day. Criteria for triggering was the presence of at least one leading follicle of 17 mm in diameter. If there were more than three follicles ≥ 16 mm on the day of triggering, the cycle was cancelled to reduce the risk of multiple pregnancy and OHSS. Intrauterine insemination was done using fresh semen obtained from the husband. All semen samples were prepared using the gradient method. Insemination was performed once, at 36 hours after triggering. Luteal phase support with vaginal progesterone 400 mg (Cyclogest®; Actavis, United Kingdom) was started one day after IUI and continued until the seventh week of gestation.

Randomisation and treatment

Potentially eligible couples were given the information sheet about the study on the second day of the women's menstrual cycle (about 2 weeks before randomisation). Screening for eligibility was performed by treating physicians on the day of triggering. Eligible participants were invited to a full discussion with investigators about the study and were given the informed consent form. Couples had about an hour to decide whether they agreed to participate in the study or not. Written informed consent was obtained by the investigators from all couples prior to enrolment. Participants were randomised into two groups in a 1:1 ratio by using a computer-generated random list (with a block size of 2, 4, or 8). Patients in the GnRHa group were given Triptorelin (Diphereline 0.1 mg, Ipsen Beaufour, France) 0.1 mg subcutaneously and those in the hCG group were given hCG

(Pregnyl 5000 IU, MSD, Netherlands) 5000 IU intramuscularly. Due to the nature of interventions, this study was only blinded to physicians who performed IUI and embryologists who performed sperm preparation.

Outcomes

The primary outcome was ongoing pregnancy rate. Ongoing pregnancy was defined as pregnancy with a detectable heart rate after 12 weeks of gestation. Secondary outcomes were rates of clinical pregnancy, multiple pregnancy, miscarriage and moderate or severe OHSS.

Statistical analysis

The ongoing pregnancy rate after IUI using hCG trigger at IVFMD was 16.5%. We performed a non-inferiority study in which the maximal acceptable difference between hCG trigger and GnRHa trigger was set at 13%. Given a power of 90%, two-sided alpha of 5% and a loss to follow-up or protocol deviation rate of 10%, the total number of participants required was calculated to be 380 (190 per group).

Data analysis was performed on an intention-to-treat basis. Between-group differences in categorical variables were assessed using the Fisher’s exact test. For continuous variables, results were given as mean ± standard deviation (SD) and between-group differences were assessed using Student’s *t*-test. For dichotomous endpoints, relative risk (RR) and 95% confidence interval (CI) values were calculated; *p*-values < 0.05 were considered statistically significant. All analyses were conducted using statistical software R, version 2.15.1 (R Foundation for Statistical Computing).

RESULTS

Between April 2016 and May 2018, 1997 women were screened for eligibility, 380 of whom were randomly assigned to the GnRHa or hCG group (190 patients per group). No patients were lost to follow-up (Fig. 1).

Baseline characteristics were comparable between the two groups. All patients in the study had a normal BMI (Table 1). The duration of stimulation and total dose of hMG used were higher in GnRHa group compared with the hCG group. However, these differences were not statistically significant (Table 2). The primary

Table 1. Patient characteristics at baseline.

Characteristic	GnRHa (n = 190)	hCG (n = 190)
Age, year	28.8 ± 3.1	28.5 ± 3.1
BMI, kg/m ²	21.4 ± 2.3	21.4 ± 3.0
Duration of infertility, months	21.0 ± 14.1	24.2 ± 17.3
Type of infertility, n (%)		
Primary	154 (81.1)	150 (78.9)
Secondary	36 (18.9)	40 (21.1)
AMH, ng/mL	8.7 ± 3.5	8.2 ± 3.4
LH, IU/L	13.7 ± 7.4	13.5 ± 7.1
Total testosterone, nmol/L	1.3 ± 0.7	1.3 ± 0.7
SHBG, nmol/L	53.5 ± 31.2	56.1 ± 35.0
FTI	3.4 ± 3.0	3.2 ± 2.6

Values are mean ± standard deviation or number of patients (%).

AMH, anti-Müllerian hormone; BMI, body mass index; FTI, free testosterone index; GnRHa, gonadotropin-releasing hormone agonist; hCG, human chorionic gonadotropin; LH, luteinising hormone; SHBG, sex hormone binding globulin.

Table 2. Characteristics of treatment cycles.

Characteristic	GnRHa (n = 190)	hCG (n = 190)	p-value
Duration of stimulation, days	13.40 ± 4.49	12.65 ± 4.36	0.098
Total dose of hMG, IU	1295.58 ± 645.38	1223.91 ± 688.58	0.296
No. of follicles ≥11 mm	4.18 ± 2.63	4.07 ± 2.58	0.680
Endometrial thickness, mm	11.65 ± 1.73	11.51 ± 1.81	0.436
Post-wash TPMSC, 10 ⁶	9.35 ± 3.92	9.16 ± 3.97	0.850

Values are mean ± standard deviation.

GnRHa, gonadotropin-releasing hormone agonist; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropins; TPMSC, total progressive motile sperm count.

endpoint, ongoing pregnancy, occurred in 45/190 patients (23.7%) in GnRHa group and 48/190 (25.3%) patients in the hCG group (RR 0.94; 95% CI, 0.66–1.34; $p = 0.81$) (Table 3). There were no statistically significant differences between the GnRHa and hCG groups in the positive pregnancy rate (34.7% vs. 30.5%, $p = 0.444$) and the clinical pregnancy rate (30% vs. 27.4%, $p = 0.65$). There were no cases of OHSS in the GnRHa group and two cases of mild OHSS (1.1%) in the hCG group ($p = 0.49$). Other secondary outcomes were also comparable between two groups (Table 3).

DISCUSSION

Our data showed that GnRHa triggering was non-inferior to hCG triggering in patients with PCOS undergoing ovulation induction with gonadotropins followed by IUI. Analysis of the primary endpoint (ongoing pregnancy) and secondary endpoints (clinical pregnancy, miscarriage, ectopic pregnancy, multiple pregnancy and OHSS) showed comparable results between the treatment groups.

Strengths of our study include its randomised design with the largest sample size to date, recruitment of the planned number of participants, and no loss to follow-up. There are also some limitations that need to be taken into account when interpreting our results. Firstly, the study was conducted at a single center in Asia. Although not common, ethnic differences might affect the response to gonadotropins as well as GnRH analogues due to receptor polymorphisms (Fatemi et al., 2014). Moreover, the majority of our PCOS patients were lean, which might compromise the external validity of the study. Secondly, the study had an unblinded design due to the nature of the interventions. Attempts to minimise bias included similar semen preparation protocol in both groups and insemination performed by specialists who were unaware of treatment allocation. Thirdly, we did not follow the patients until live birth. However, there are several arguments showing that ongoing pregnancy represents the best primary outcome measure in reproductive medicine trials (Braakhekke et al., 2014). Finally, we did not have data on the endocrine profiles of participants after administration of GnRHa because of the protocol for IUI in daily practice.

Triptorelin is a decapeptide and potent long-acting GnRHa commonly used for GnRHa trigger. Although GnRHa preparations may vary in their relative potencies, evidence suggests that all types and administration forms of GnRHa trigger sufficiently induce ovulation and that there are no significant differences in pregnancy rate in ovulation induction cycles between the different forms and types (Parneix et al., 2001). In IVF settings, triptorelin 0.2 mg has been shown to be as effective as doses of 0.3 and 0.4 mg in terms of number of mature oocytes and top quality embryos (Vuong et al., 2016). In IUI cycles, triptorelin 0.5 mg has been used for trigger in 12 IUI patients at risk of OHSS, resulting in six pregnancies and no cases of OHSS (Shalev et al., 1994). The same group, in a trial involved in 24 IUI cycles, suggested that a single dose of triptorelin 0.1 mg was sufficient to induce ovulation and the results of a dose-response study lead them to conclude that triptorelin 0.1 mg was superior to doses of 0.05 and 0.5 mg for ovulation trigger (Shalev et al., 1995; Shalev, 1995). These findings were supported by the results of our randomised controlled

Table 3. Treatment outcomes.

Outcome	GnRHa (n = 190)	hCG (n = 190)	RR (95% CI)	p-value
Ongoing pregnancy, n (%)	45 (23.7)	48 (25.3)	0.94 (0.66–1.34)	0.811
Positive pregnancy test, n (%)	66 (34.7)	58 (30.5)	1.14 (0.85–1.52)	0.444
Clinical pregnancy, n (%)	57 (30.0)	52 (27.4)	1.10 (0.80–1.51)	0.650
Miscarriage, n (%)	17 (8.9)	8 (4.2)	2.12 (0.94–4.81)	0.098
Ectopic pregnancy, n (%)	5 (2.6)	2 (1.1)	2.50 (0.49–12.73)	0.449
Multiple pregnancy, n (%)				
Twin	11 (6.0)	4 (2.2)	2.51 (0.80–7.87)	0.114
Triplet	2 (1.1)	2 (1.1)	1.00 (0.14–7.03)	0.999
OHSS, n (%)	0 (0.0)	2 (1.1)	—	0.499

CI, confidence interval; OHSS, ovarian hyperstimulation syndrome; RR, relative risk.

trial, which showed that triptorelin 0.1 mg was non-inferior to hCG 5000 IU in terms of pregnancy outcomes in PCOS patients.

The rationale behind using GnRHa for triggering ovulation, instead of hCG for ovulation induction, is to induce a short duration surge of endogenous gonadotropins (duration 24–36 hours), resembling the mid-cycle surge of the natural cycle (Fauser et al., 2002), thus reducing the risk of OHSS. In our study, there was no cases of OHSS in the GnRHa group compared with two cases of mild OHSS in the hCG group. However, it should be noted that we excluded patients with more than three follicles at 16 mm on the day of triggering for ethics reasons. Thus, our results may underestimate the benefit of GnRHa for the prevention of OHSS.

It has well known that the luteal phase after GnRHa trigger is impaired in IVF cycles, making it essential to use intensive luteal phase support after fresh embryo transfer (Dosouto et al., 2017). However, data on the quality of the luteal phase and progesterone concentrations throughout the luteal phase after GnRHa administration for triggering ovulation remain controversial (Emperaire et al., 2004). In a prospective cohort study, involved in 194 patients undergoing ovulation induction with hMG and triggered by GnRHa, data showed that luteal phase defects do not occur at random after agonist-triggered ovulation in classic stimulated cycles or in a particular indication for ovarian stimulation, but rather represent an individual characteristic. The authors concluded that such an individual reaction might be related to personal differences in GnRHa interaction and/or pharmacodynamics at the pituitary or ovarian level. This could be prevented by vaginal progesterone or low-dose hCG (Emperaire et al., 2004).

In summary, results of our study showed that 0.1 mg triptorelin was non-inferior to 5000 IU hCG in PCOS patients undergoing ovulation induction by hMG followed by IUI with respect to pregnancy outcomes. Therefore, GnRHa might be used as an alternative method for triggering to prevent OHSS in this high-risk population without compromised the pregnancy rates.

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