Gonadotropin releasing hormone agonist (GnRHa) versus human chorionic gonadotropin (HCG) for triggering of ovulation in ovarian stimulation cycles in polycystic ovarian syndrome (PCOS) women

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Abstract

Objective: To assess the efficacy and safety of gonadotropin releasing hormone agonist (GnRHa) as an alternative to conventional human chorionic gonadotropin (HCG) for triggering of ovulation in patients with polycystic ovarian syndrome (PCOS) undergoing sequential minimal ovarian stimulation followed timed intercourse.

Methods: A randomized controlled study that was conducted on PCOS patients subjected to sequential minimal ovarian stimulation followed by timed intercourse. All participants were randomly allocated at time of triggering of ovulation into 2 groups; GnRHa group in which ovulation was triggered by single SC injection of 0.2 mg of triptorelin, and HCG group in which ovulation was triggered by single IM injection of 5000 IU of urinary HCG. The main study's outcome measures included ovulation rate, clinical pregnancy rate and incidence of early ovarian hyperstimulation syndrome (OHSS).

Results: Final analysis was performed for data of 47 participants in the GnRHa group and 46 participants in the HCG group. There was no significant difference between the GnRHa and the HCG groups in the ovulation rate (95.7% vs 93.5%; P = 0.628) and clinical pregnancy rate (23.4% vs 21.7%; P = 0.848). There was no cases of OHSS in the GnRHa group and just one case in the HCG group, with no significant difference in the incidence of OHSS between the 2 groups (P = 0.495).

Conclusion: The GnRHa could be an effective and safe alternative to the traditional HCG in ovulation triggering after sequential minimal ovarian stimulation in PCOS patients without affecting ovulation and clinical pregnancy rates.

Keywords: PCOS, GnRHa, HCG, OHSS.

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Introduction

The polycystic ovarian syndrome (PCOS) is a condition affecting 5-20% of women in the child bearing period worldwide, and it is the commonest cause of

oligomenorrhea. Many of PCOS women are subfertile, however, only a small percentage require fertility treatment and most of them require long time to become pregnant naturally. There are different phenotypes of PCOS women, based on the definition of PCOS. Many possible treatment options are suggested for management of subfertility in PCOS women. The success and morbidity of these treatment options could be affected by the PCOS phenotype (1).

A class of medications known as aromatase inhibitors was first introduced in 2001 to induce ovulation in subfertile women, both in ovulatory and anovulatory cycles (2). Letrozole is the most popular aromatase inhibitor used for induction of ovulation, and is administered in a typical dose of 5 mg every day for 5 days (3). When used for induction of ovulation with timed intercourse, letrozole was found to have higher pregnancy rates and similar ovarian hyperstimulation syndrome (OHSS) rate, compared to clomiphene citrate (CC) (4). Sequential minimal ovarian stimulation protocol consists of administration of CC or letrozole, followed by low dose of gonadotropins. This protocol was used in both assisted reductive technology (ART) and non-ART treatment of subfertility with comparable safety and efficacy in comparison to other ovarian stimulation regimens (5-8).

Gonadotropin releasing hormone (GnRH) is a hormone secreted from the hypothalamus in pulses. It binds to surface receptors on the gonadotrophs of the anterior pituitary, and this results in secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) into peripheral circulation. Within the ovary, FSH binds to receptors on granulosa cell, while LH binds to receptors on theca cell, and this simulates folliculogenesis and ovarian steroidogenesis. At the midcycle, estrogen level rises rapidly resulting in LH surge which is responsible for final oocyte maturation (completion of the first meiotic division then progression to the metaphase stage of the second meiotic division). Ovulation occurs approximately 36-40 hours after LH surge (9).

Human chorionic gonadotropin (HCG) is usually used as a substitute for endogenous LH surge to trigger final oocyte maturation and ovulation at the end of the ovarian stimulation. The main disadvantage of HCG is its longer half-life than LH, which results in a prolonged luteotropic effect and as a result increases the risk of OHSS especially in high risk cases that have large number of preovulatory follicles (10).

In in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) cycles that use the GnRH antagonist protocol, triggering of final oocyte maturation could be achieve by a single injection of a GnRH agonist (GnRHa) preparation (11). Because GnRHa acts by inducing the endogenous LH (mimics the normal physiological mechanism), it was found that single injection of a GnRHa preparation may be useful in reducing the risk of occurrence of OHSS when compared to HCG (12). In IVF/ICSI cycles, HCG is used in doses of 5000-10000 IU, while GnRHa is used in variable doses with the most commonly used drug is triptorelin in a dose of 0.2 mg subcutaneously (13).

To the best of our knowledge, very few studies had evaluated the efficacy and safety of using GnRHa in comparison to HCG for triggering of ovulation in timed intercourse cycles stimulated by CC or letrozole (14, 15), or stimulated by sequential minimal ovarian stimulation protocol (16, 17). Therefore, we aimed in the current study to assess the efficacy (in terms of ovulation rate and clinical pregnancy rate) and safety (in terms of prevention of OHSS) of GnRHa as an alternative to conventional HCG for triggering of ovulation in patients with PCOS undergoing sequential minimal ovarian stimulation followed timed intercourse.

Patients and methods

Study design and population:

This was a randomized controlled trial that was conducted during the period from June 2021 through September 2022 in the Fertility Care Unit in Mansoura University Hospital, Egypt. The study protocol was reviewed and approved by the Mansoura Faculty of Medicine Institutional Research Board (Code No. MS.21.03.1399). Women selected for participation in the study were those with PCOS, diagnosed according to the Rotterdam Consensus 2004 (18), based on presence of at least two criteria of the following three criteria: 1) anovulation or oligo-ovulation; 2) clinical or biochemical evidence of hyperandrogenism; and 3) polycystic ovarian morphology on transvaginal sonography (TVS) assessment. All the possible participating women were interviewed, received sufficient information on the protocol of the study, and then counseled to be enrolled in the study.

The potential participants were then assessed for meeting the inclusion and exclusion criteria. The main inclusion criterion were PCOS women who were planned to be subjected to sequential minimal ovarian stimulation followed by timed intercourse. The exclusion criteria were: 1) age is > 35 or < 18 years; 2) body mass index (BMI) is ≥ 35 < 18.5 kg/m2; 3) abnormal hysterosalpingography (HSG); 4) pelvic adhesions with disturbance of the tubo-ovarian relationship diagnosed by laparoscopy; and 5) abnormal husband semen analysis according to WHO 2010 criteria (19).

Initial evaluation:

Complete history was taken from each participant, including personal history, menstrual history, obstetric history (gravidity and parity to clarify the type and duration of infertility), medical history, and surgical history. General examination was performed with recording of the patient's height in centimeter (cm) and weight in kilograms (kg) and calculation of the BMI. Basal serum FSH, LH, prolactin, thyroid stimulating hormone (TSH), and antimullerian hormone (AMH) levels were assessed for all participants.

Ovarian stimulation protocol:

The sequential minimal ovarian stimulation was started by giving letrozole (Femara®, Letrozole 2.5 mg, oral tablets, NOVARTIS, New Jersey, United States) in a dose of 5 mg every day for 5 days (from the 2nd day to the 6th day of the menstrual cycle) followed by a gonadotropin preparation (Gonapure®, Follitropin alpha 75 IU, IM/SC injection, MINA PHARM, Egypt) in a low dose (75 IU every day) from the 7th day to the 9th day of the menstrual cycle. Monitoring of growth of the follicles by TVS scanning (folliculometry) was started on the 10th day of the stimulation cycle. In women with at least one follicle ≥ 12 mm, the gonadotropin was continued without further increase in the dose and folliculometry was performed every 2-3 days, then ovulation was triggered when there was at least one follicle with a diameter ≥ 18 mm. Women who did not achieve mature follicle ≥ 18 mm were excluded from randomization.

At the time of ovulation triggering, the study's participants were randomly allocated into 2 groups; the GnRHa group and the HCG group. The randomization process was performed by a nurse using opaque, unlabeled, sealed envelopes containing computer-generated random numbers. The randomization was balanced (allocation ratio to each group was 1:1) and simple, and the study was an open label study (i.e. the participants, investigators and caregivers were aware of group allocation).

For participants in the GnRHa group, ovulation was triggered by single SC injection of 0.2 mg of a GnRHa preparation (Decapeptyl®, Triptorelin 0.1 mg, SC injection, Ferring, Germany) while for participants in the HCG group, ovulation was triggered by single IM injection of 5000 IU of urinary HCG (Choriomon®, HCG 5000 IU, IM injection, IBSA, Switzerland). All women were then

advised for a timed intercourse at the day of triggering of ovulation and the next day.

Documentation of ovulation:

All participants were subjected for follow up 3 days after ovulation triggering by TVS scanning for detection of signs of ovulation including: 1) vanishing of the follicle or sudden reduction in its size; 2) presence of free fluid in the pelvis or Douglas pouch; 3) increased echogenicity of the follicle, indicating formation of corpus luteum; and 4) replacement of the triple line endometrial shape by the hyperechoic, homogenous luteinized endometrium.

Luteal phase support:

All participants were supplemented one day following triggering of ovulation with progesterone vaginal suppositories (Prontogest®, Progesterone 200 mg, vaginal or rectal pessaries, MARCYRL, Egypt) in a dose of 200 mg every 12 hours.

Documentation of pregnancy:

In women who missed a menstrual period for one week, quantitative serum beta-HCG (β-HCG) level was assessed using immunoassay and a serum β-HCG level > 10 mIU/ml was considered an indicator of biochemical pregnancy. Women with biochemical pregnancy were examined by TVS scanning at 6-8 weeks from the first day of the last menstrual period to diagnose clinical intrauterine pregnancy which was defined as the presence of at least one intrauterine gestational sac with fetal pole and cardiac pulsation on TVS scanning at 6-8 weeks of gestation.

Outcome measures:

The main study's outcome measures were:

- Ovulation rate: calculated by dividing the number of women with documented ovulation by the number of women received triggering of ovulation.
- Clinical pregnancy rate: calculated by dividing the number of women with clinical pregnancy by the number of women received triggering of ovulation.
- Incidence of early OHSS.

Statistical analysis:

The IBM® SPSS® Statistics, version 20.0 for Windows was used for tabulation and analysis of data. Quantitative variables were displayed as mean ± standard deviation (SD) and median (minimum and maximum) while qualitative variables were displayed as number and percentage. The Student t test and the Mann Whitney U test were used to compare between the 2 groups for normally and non-normally distributed quantitative variables, respectively after testing normality distribution using Kolmogorov-Smirnov and Shapiro-Wilk tests. The Chi-Square and Fischer's exact tests were used for comparison of the qualitative variables between the 2 groups as appropriate (Fischer's exact was used when > 25% of cells have count less than 5). The P values were considered statistically significant at level ≤ 0.05.

Results

As shown in the flow diagram of the study (Figure 1), 264 women were evaluated for eligibility to participate in the study; and 164 of these women were excluded (82 women did not meet the inclusion criteria of the study, 17 women refused to participate in the study, and 65 women did not achieve mature follicle ≥ 18 mm). The remaining 100 women were included in the study and were randomized into the 2 study groups. Out of the 100 participants who were randomized, 3 women in the GnRHa group and 4 women in the HCG group were lost to follow-up. Therefore, data of 47 participants in the GnRHa group and 46 participants in the HCG group were subjected to final analysis.

No significant difference between the 2 groups in the demographic, clinical and hormonal characteristics (tables 1 and 2). Regarding the cycle characteristics and outcomes (table 3), the number of follicles ≥ 18 mm and the

endometrial thickness were comparable among both groups. Also, there was no significant difference between the GnRHa group and the HCG group in ovulation rate (95.7% vs 93.5%; P = 0.628) and clinical pregnancy rate (23.4% vs 21.7%; P = 0.848). There was no cases of OHSS in the GnRHa group and only one case in the HCG group with no significant difference between both groups in the incidence of OHSS (P = 0.495).

Figure 1. Study flow diagram

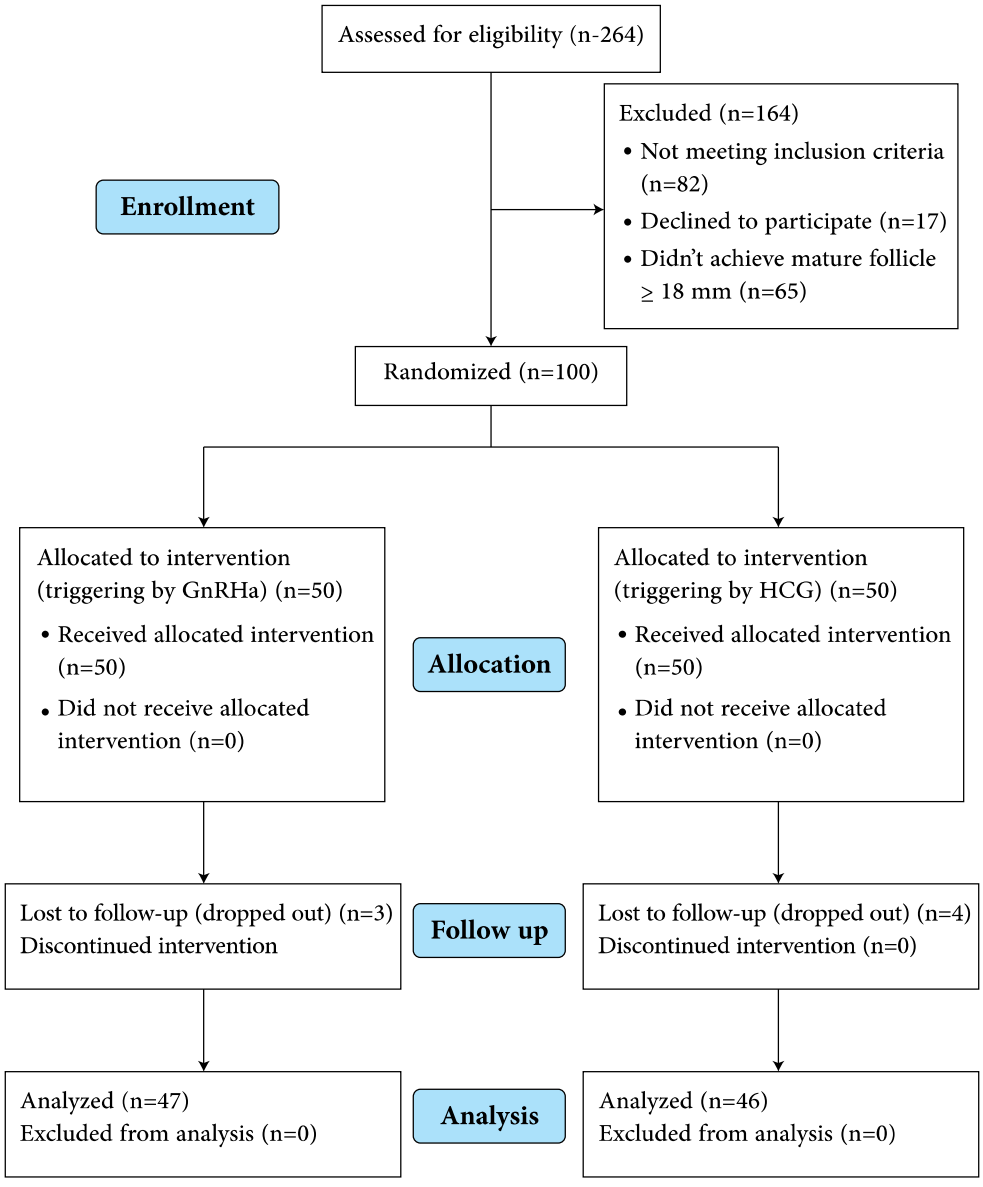

Table 1. Demographic and clinical characteristics among both groups

	GnRHa group (n = 47)	HCG group (n = 46)	P value
Age (years)			0.877
Mean ± SD	24.02 ± 3.25	24.11 ± 3.44	
Median (min-max)	24 (19-35)	24 (19-35)	
BMI (kg/m^2)			0.170
Mean ± SD	28.28 ±1.72	27.80 ± 1.61	
Median (min-max)	28.20 (24.84-32.37)	28.08 (24.84-31.21)	
Infertility type			0.508
Primary	34 (72.3%)	36 (78.3%)	
Secondary	13 (27.7%)	10 (21.7%)	
Duration of infertility (years)			0.555
Mean ± SD	1.74 ± 0.98	1.75 ± 1.17	
Median (min-max)	1.5 (1-5)	1.25 (1-5)	

Table 2. Hormonal characteristics among both groups

	GnRHa group (n = 47)	HCG group (n = 46)	P value
Serum AMH (ng/ml)			0.570
Mean ± SD	4.88 ± 1.70	4.69 ± 1.38	
Median (min-max)	4.25 (3.17-11.50)	4.19 (3.21-10.60)	
Basal serum FSH (mIU/ml)			0.899
Mean ± SD	6.52 ± 1.76	6.56 ± 1.65	
Median (min-max)	6.36 (2.03-9.80)	6.27(2.80-9.90)	
Basal serum LH (mIU/ml)			0.356
Mean ± SD	5.98 ± 1.97	5.67 ± 2.07	
Median (min-max)	5.72 (2.60-9.83)	5.15 (2.03-9.70)	
Serum prolactin (ng/ml)			0.996
Mean ± SD	13.64 ± 4.73	13.63 ± 5.33	
Median (min-max)	12.77 (5.60-21.61)	13.20 (0.66-21.70)	
Serum TSH (mIU/ml)			0.730
Mean ± SD	1.82 ± 0.82	1.77 ± 0.78	
Median (min-max)	1.77 (0.38-3.40)	1.62 (0.38-3.15)	

Table 3. Cycle characteristics and outcomes among both groups

	GnRHa group (n = 47)	HCG group (n = 46)	P value
No. of follicles ≥ 18 mm	2 (1-6)	1 (1-5)	0.148
Endometrial thickness (mm)			0.706
Mean ± SD	11.06 ±1.94	10.91 ± 1.99	
Median (min-max)	11 (8-14)	11 8-14)	
Ovulation	45 (95.7%)	43 (93.5%)	0.628
Clinical pregnancy	11 (23.4%)	10 (21.7%)	0.848
OHSS	0 (0.0%)	1 (2.2%)	0.495

Discussion

Many treatment options are available for subfertile women with PCOS, including: 1) weight reduction and lifestyle modification in obese women; 2) metformin and/or inositol administration for several months; 3) induction of ovulation with CC or letrozole; 3) low-dose gonadotropin stimulation or laparoscopic ovarian drilling in case of resistance to CC and/or letrozole; and 4) IVF/ICSI in case of failure of the other management option (20). Sequential minimal ovarian stimulation, consisting of administration of CC or letrozole followed by low dose of gonadotropins, has been used for induction of ovulation in PCOS women with comparable safety and efficacy to other ovarian stimulation regimens (7). Ovulation triggering is a crucial step in infertility treatments, both in natural and stimulated cycles (21, 22).

Both LH and HCG have biological and structural similarities and therefore, they can bind to and stimulate the same receptor but HCG has much longer half-life (24 hours) than LH (1 hour). For several decades, HCG has been the traditional method used, as a substitute for LH surge, for triggering of ovulation but due to its longer half-life than LH, HCG exerts a continuous stimulation of ovarian steroid hormones production for up to 5 days, and thus predisposes to OHSS. Moreover, there were reported negative effects of HCG on oocyte quality and endometrial receptivity (23).

Administration of a GnRHa preparation can activate the GnRH receptor in the pituitary, resulting in LH surge that mimic the natural LH surge. This GnRHa-induced LH surge can efficiently trigger oocyte maturation and ovulation. The natural LH surge consists of 3 phases, with a duration of 48 hours while the GnRHa-induced LH surge is composed of 2 phases, with a total duration of 24-36 hours. Therefore, the amount of gonadotropins secreted from the pituitary are lower with using GnRHa for ovulation triggering (24, 25).

Triggering of ovulation with GnRHa instead of HCG has the advantage of being more physiological as it acts by inducing the endogenous LH surge and it is well known that LH has a shorter half-life than HCG. Not only that but also, GnRHa stimulates the midcycle FSH surge which was shown to up regulate the LH receptors on granulosa cells. However, the main drawback of using GnRHa for triggering of ovulation is early corpus luteum degeneration that results in reduction of the serum progesterone level which is known as a luteal phase deficiency, which lowers the chance of pregnancy and increase the pregnancy loss rate. Thus, adequate luteal phase support is required

when using GnRHa as an ovulation trigger (26).

Many studies have evaluated the efficacy and safety of GnRHa as an ovulation triggering agent in comparison to HCG in IVF/ICSI treatment (27-30), however, to the best of our knowledge, very limited number of studies had evaluated both types of trigger in stimulated intrauterine insemination cycles (31, 32), and in timed intercourse cycles stimulated by CC or letrozole (14, 15), or by sequential minimal ovarian stimulation protocol (16, 17). Therefore, the current study was conducted to assess the efficacy and safety of GnRHa as an alternative to HCG for triggering of ovulation in PCOS women undergoing sequential minimal ovarian stimulation followed by timed intercourse.

Concerning demographic, clinical and hormonal characteristics in the current study, no significant difference was found between the GnRHa group and the HCG group in these parameters. Also, the number of mature dominant follicles and the endometrial thickness on the triggering day were comparable between both groups. These findings agree with what was reported in other studies (14-17, 31, 32), and indicate that adequate randomization was conducted in the current study, and also, refute any bias that might have slanted the results in favor of one group rather than the other.

In the current study, the used GnRHa preparation was triptorelin in a dose of 0.2 mg SC and the used HCG preparation was urinary HCG (uHCG) in a dose of 5000 IU IM. Similar to the current study, Li et al used the same triptorelin and uHCG doses (32). On the other hand, some authors used the same triptorelin dose (0.2 mg) and a higher uHCG dose (10000 IU) in their studied (15-17). Bathwal et al used a lower triptorelin dose (0.1 mg) and the same uHCG dose (5000 IU) (31), and Shalev et al used a lower triptorelin dose (0.1 mg) and a higher uHCG dose (10000 IU) (14).

Ovulation was assessed in our study by TVS scanning for detection of signs of ovulation. The ovulation rate was high in both groups but without significant difference (95.7% in the GnRHa group vs 93.5% in the HCG group, P = 0.628). Similar to our study, Le and his colleagues (32) and Bathwal and his colleagues (31) have assessed ovulation by TVS scanning for detection of ovulation signs and they did not find significant difference in the ovulation rate between both groups. In other studies, ovulation was assessed by midluteal measurement of serum progesterone level, however, in agreement with our results, the ovulation rate was comparable between the GnRHa and the HCG groups (14, 15).

In our study, we provided luteal phase support to all patients in the form of progesterone vaginal suppositories in a dose of 200 mg every 12 hours. Likewise, luteal phase support was provided in some studies (17, 31, 32), however, in contrast, Ammar and his colleagues (15) and Shalev and his colleagues (14) did not provide luteal phase support.

Our results revealed clinical pregnancy rate of 23.4% (11 cases) in the GnRHa group and 21.7% (10 cases) in the HCG group without significant difference between both groups (P = 0.848). These results were keeping with Ammar and his colleagues who did not find significant difference in the clinical pregnancy rate between the GnRH group and the HCG group (21.6% vs 22.6%, P = 0.87) (15). In the same line, Shalev et al. reported similar pregnancy rates in their GnRH and HCG groups, however, their reported clinical pregnancy rates were lower than what was reported in the current study (12% in the GnRHa group and 12.6% in the HCG group) (14). In contrast to our findings, Elmahdy and Elsharkawy have found a significantly higher pregnancy rate in the HCG group than in the GnRHa group (30.5% vs 21.1%, P = 0.049) (17). On the other hand, Bathwal and his colleagues disagreed with Elmahdy

and Elsharkawy by finding a significantly higher clinical pregnancy rate in favor of the GnRHa group (10.33% in the GnRHa group vs 4.96% in the HCG group, P = 0.026) (31).

In the current study, no recorded cases of OHSS in the GnRHa group while only one case of mild OHSS was detected in the HCG group. This OHSS developed 3 days following trigger and the patient was candidate for conservative management. In the same line, Elmahdy and Elsharkawy found one case of moderate OHSS in the HCG group, and there were no such cases in the GnRHa group (17). Also, Ammar et al reported 3 case of mild OHSS in the HCG group, and they did not report any case of OHSS in the GnRHa group (15). Moreover, no reported cases of OHSS in either groups in the study by Shalev and his colleagues (14). In contrast, BuTalag and his colleagues reported a significantly higher OHSS rate in the HCG group than in the GnRHa group after one cycle of ovarian stimulation (17.39% vs 4.33%, P < 0.05) (16). This could be attributed to the use of high HCG dose (10000 IU) in a high risk group of patient (PCOS patients) having different phenotypes that could affect the morbidity of treatment (1).

The main strength point in the current study came from the fact that it was a randomized study with adequate randomization that appeared in absence of significant difference between the two groups regarding any demographic, clinical or hormonal parameter. Another strength point in our study is that, to the best of our knowledge, this is one of the very limited number of studies that assessed the efficacy and safety of GnRHa as an alternative to HCG for triggering of ovulation in PCOS women undergoing sequential minimal ovarian stimulation followed by timed intercourse. A limitation of the current study lies in the lack of blinding of participants and assessors. Another limitation is the small sample size which may have limited the study's power to detect significant differences in the outcomes measures.

In conclusion, the GnRHa could be an effective and safe alternative to the traditional HCG in ovulation triggering after sequential minimal ovarian stimulation in PCOS patients without affecting ovulation and clinical pregnancy rates. Using GnRHa for triggering of ovulation could avoid the occurrence of OHSS, which is one of the nightmares in patients with PCOS undergoing fertility treatment.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

Ethical considerations: This paper has been adapted from the MSc. thesis written by Mr. Ammar Hesham Dorra.

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