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ORIGINAL ARTICLE

Gonadotropin Releasing Hormone Agonist versus Human Chorionic Gonadotropin in Patients with PCOS as Trigger of Ovulation

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ABSTRACT

Background: Many patients develop excessive response for gonadotropin stimulation through controlled ovarian stimulation (COS) cycle over the years, there was an increase in incidence of ovarian hyperstimulation syndrome (OHSS) which represents an important medical problem for the clinicians. **Objectives**: to compare GnRHa and hCG as ovulation trigger in patients with PCOS after controlled ovarian stimulation by estimation of ovulation rate and rate of clinical pregnancy in studied group and detect efficacy in preventing or reducing incidence of OHSS. **Patients & Methods:** This prospective study was carried out in the unit of Cytogenetic and Endoscopy in department of Obstetrics and Gynecology in Zagazig university hospital during the period from September 2017 to January 2018 where 52 subfertile women with anovulatory PCOS. **Results**: showed that there is no significant difference in the overall ovulation rate. The average rate of ovulation was 38 (33.04%) and 30 (26.06 %) in GnRHa and hCG groups. The OHSS incidence was higher in hCG group than the GnRHa group. **Conclusions**: hCG was the gold standard for complete oocyte maturation, the new agent seems to be GnRHa with its potential advantages over hCG trigger in OHSS reduction.

Keywords: Gonadotropin ; PCOS ; Trigger of Ovulation.

INTRODUCTION

Many patients develop excessive response for gonadotropin stimulation through controlled ovarian stimulation (COS) cycle over the years, there has been an increase in incidence of ovarian hyperstimulation syndrome (OHSS) posing an important medical problem for the clinicians [1]. Most of them are mild with no adverse consequences to the patient [2].

However, when (OHSS) is severe, it is associated with morbidity, the consequences may be lethal and fatalities have also been reported and this is increase in high-risk population of polycystic ovary syndrome (PCOS) so practitioner seek balance between optimal ovarian stimulation and treatment success to improve reproductive outcome with minimal rate of severe ovarian hyperstimulation or to prevent its occurrence [3].

Exogenous human chorionic gonadotropin (hCG) was used for infertility treatment and ovulation disorder. Since 1790s, .to achieve final oocyte maturation was by exogenous hCG as it typically administered to act as substitute for utilizing hormone surged, it has been considered the golden standard for granulosa cell and complete oocyte maturation. Due to its similarity to (LH) it binds to and activate the receptor for LH/hCG receptors, where it has long half-life when compared with natural LH [4].

There are important difference between the LH and hCG half life where in LH about 60 minutes and for hCG increased 24 hours [5]. Consequently leading to its long lasting strong influence of ovarian function to prolonged stimulation effect on multiple corpora luteal which responsible for entire cascade of OHSS through the vascular endothelial growth factor [6].

The activity of the sustained luteotropic which produced by hCG is prone to cause bad effects and most worrying ovarian stimulation side-effects and known as the ovarian hyperstimulation syndrome (OHSS). So when hCG used as trigger after ovulation induction or use for synchronizing the timing of ovulation with sexual intercourse mostly OHSS continue for 3-4 days after the administration of hCG in patients and this is first onset or through early pregnancy after administration during (12-17 days) (second onset) [7].

With holding the consequence of canceled cycles, we used the early severe climate OHSS. Although this cancellation showing patient frustration and is related with money and time consuming, another methods aimed for OHSS prevention and maintain the outcome reproductive [8].

It has been proposed that the gonadotropin - releasing hormone agonist (GnRHa) administration instead of hCG for the induction of maturation oocyte can decrease the OHSS risk significantly [2].

GnRHa trigger stimulate FSH surges in the mid cycle which begin to rise after 12 hours and remain activated for 24 to36 hours, LH begins to rise after 4 hours of GnRHa trigger and affect the oocyte maturation and more expansion in the cumulus cell which surround the oocyte and releasing the proteolytic enzyme which included in the process of ovulation [2].

The amplitude of the LH surge after the agonist trigger is similar to that seen in natural cycle [2]. Many studies reported that the use of GnRH agonist in the final oocyte maturation as compared with hCG trigger gave similar or good results to the injection of hCG which increase the level of LH more than with GnRHa trigger[9].

There were some concerns for the GnRHa effectiveness for production of maximum mature oocyte yield which may lead to decrease its normal use in PCOS for prevention or decrease incidence of OHSS like other clinicians. We were reluctant to use GnRHa in place of hCG as trigger in PCOS patients undergo ovulation induction cycle [8].

AIM OF THE WORK

The aim of this work was to compare GnRHa and hCG as ovulation trigger in patients with PCOS after controlled ovarian stimulation by estimation rate of ovulation and rate of clinical pregnancy in each group and detect efficacy in preventing or reducing incidence of OHSS.

PATIENTS AND METHODS

This prospective study was carried in the unit of Cytogenetic and Endoscopy in Obstetrics and Gynecology department in Zagazig university hospital during during the period from September 2017 to January 2018 where 52 subfertile women with anovulatory PCOS were included in this study where ovulation trigger was attempted after ovulation induction. Patients included in this study were induced for ovulation by clomiphene citrate tablets with sequential HMG injection before the leading follicles reach 18-20 mm in diameter .

Written informal consent was obtained from all subjects and the study was carried according to the research ethical committee of Faculty of Medicine, Zagazig University. This study was carried according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Patients were randomized into two groups using a computer-generated sequence and the randomization list was held in a secure box and the participants were assigned to their group using sequentially-numbered opaque sealed envelopes that were opened at the start of the study; GnRH agonist group (1) and hCG group (2).

Group(1): GnRH agonist group which received single dose of 2 ampules Triptoline (Decapeptyl injection 0.1 mg/ml subcutaneously) with prefilled syringe, (Ferring-Switzerland).

Group(2): hCG group which received single dose hCG (Choriomon , 5000 iu vials, IBSA, Switzerland) of 2 vails (10000 iu) intramusculary.

Inclusion criteria:

- Patients were diagnosed as PCOS according to the Criteria of ESHRE/ASRM Rotterdam (2003), as the following :

1- Anovulation or Oligo.

2- Hyperandrogenism with Clinical and/or biochemical symptoms

3- ovaries with Polycys on Ultrasonography (more than 12 follicles with 2 – 10mm diameter, or the ovarian volume > 10 ml^3).

- Age, 18 – 35 years. I
- nfertility less than 2 years.
- Type of infertility (primary or secondary).
- Patent Fallopian tube diagnosed by Hystrosalpingogram, Laparoscopy or Hydrosonography.
- Normal basal day 2 hormonal profile, Estradiol (E2), Luteinizing hormone (LH), follicle stimulating hormone (FSH), Prolactin serum level and thyroid stimulation hormone (TSH).
- Normal basal ultrasound on day 2 of cycle.
- Body mass index (BMI more than 18 and less than 30 Kg/m^2).

Exclusion criteria:

- Patient with male infertility (abnormal semen analysis) , normal semen according to WHO criteria 2010. Contraindication of ovulation induction, (Multiple ovarian cysts or allergy to inducing agent " Clomid"). Patients with any tubal pathology or uterine pathology.Known or suspected pelvic infection (PID).

The following procedures were done to every patient on admission:

1) Counsel patients about the nature of drug, route of administration, health benefits and side effects were clearly explained to each patient.
2) Careful and detailed history was taken from the patient who included Personal history (name, age, special habits, occupation and address).
3) Menstrual history included, First day of last menstrual period (LMP), Regularity: rhythm of the menstrual cycles, duration and amount.
4) Obstetric history included, Gravidity, mode of previous deliveries or abortions.
5) Past history included, (history of diabetes mellitus, hypertension disorder, Cardiac problems, Renal troubles, Chest troubles , Bleeding tendency, Blood diseases) and previous history of ovarian hyper stimulation.
6) Surgical history included, previous uterine scars.
7) Abdominal examination to detect Presence of scars of previous operations.
8) **2 D base Transvaginal ultrasound scan.**
9) **The following investigations were done:**
   a) Day2 or Day3; FSH, LH, Prolactin, Estradiol (E2) and TSH.
   b) E2 in day of trigger.
   c) LH 12 hours after trigger.
   d) Mid luteal Progesterone serum level in day 21 of the cycle.
   e) Pregnancy test 2 weeks after trigger.

Statistical analysis

Data were collected, tabulated and analyzed by SPSS 20 software. The significance level was considered at $P < 0.05$.

RESULTS

Table (1), showed that there was no significant statistical difference regarding stimulation cycle characters among both groups in all 3 cycles. Table (2), showed that there was a significant statistical significant difference regarding LH 12 hr only among the biochemical markers in all cycles where it is higher in GnRHa group. Table (3), showed that

the incidence of OHSS were high in hCG group in all the three cycles, which is statistically significant while the multiple pregnancy were high in hCG group but did not reach the significance level. The rate of clinical pregnancy was similar in the studied groups. Regarding OHSS there was 4 cases of OHSS in hCG group and 1 case in GnRHa group in the 1st cycle, all were mild OHSS, 1 case of OHSS in hCG group with no OHSS cases in GnRHa group in the 2nd cycle and 1 case of severe OHSS in hCG group and 1 case of mild OHSS in GnRHa group in the 3rd cycle. **Table (4),** showed that the Comparison between over all ovulation, pregnancy rate and abortion rate in both treated studied groups showed no significant statistical difference. **Table (5),** showed that LH 12 hrs after trigger, mid-luteal serum Progesterone, low basal LH and ovulation rate were considered good predictors for pregnancy while infertility type , age, duration of infertility , E2, endometrial thickness, day 2 FSH, prolactin, TSH and trigger modalities were not considered good predictors for pregnancy. **Table (6),** showed that the mid luteal progesterone was significantly higher in pregnancy.

Table (1): comparison between stimulation cycle character in the 3 cycles

	Group (I) GnRHa	Group (II) hCG	P value
First cycle	Patient NO. = 23	Patient NO. = 23	
No. of DF (>=18-20mm)	2.087 ±5.599 (2 – 5)	2.087 ±4.044 (2 – 6)	0.610
No. of IMF (12-14mm)	22 ±7 (12-14)	22 ±8 (13-14)	0.617
Endometrial thickness mm	10.174 ±1.749 (7 – 11)	10.913 ±2.065 (8 – 10)	0.197
Duration of stimulation/days	11.478 ±1.806 (9 – 14)	11.696 ±1.636 (9 – 14)	0.671
Total dose of HMG (IU)	656.521 ±169.762 (375 –675)	739.130 ±184.610 (300 – 750)	0.121
No. of Ovulation / patient	17/23 (73.9%)	14/23 (60.9%)	0.387
Second cycle	Patient NO. = 20	Patient NO. = 18	
No. of DF (>=18-20mm)	5 ±5.3 (4-5)	5.34 ±4.33 (5-8)	0.491
No. of IMF (12-14mm)	21 ±7 (11-14)	21 ±6 (12-14)	0.617
Endometrial thickness mm	10.4 ±1.7 (8-10)	11.4 ±2.06 (7-10)	0.197
Duration of stimulation/days	11.4 ±0.2 (9-12)	11.4 ±0.1 (9-13)	0.671
Total dose of HMG (IU)	622.515 ±176.21 (625-900)	714.1 ±193.6 (750-975)	0.121
No. of Ovulation / patient	15/20 (75.0%)	12/18 (66.66%)	0.39
Third cycle	Patient NO. = 18	Patient NO. = 15	
No. of DF (>=18-20mm)	7.8 ±5.1 (4-7)	8.11 ±4.30 (6-8)	0.491
No. of IMF (12-14mm)	19 ±6.9 (10-18)	21 ±2 (11-19)	0.617
Endometrial thickness mm	10.6 ±1.68 (8-11)	10.39±2.07 (7-9)	0.197
Duration of stimulation/days	10.99 ±0.21 (8-11)	11.1 ±0.2 (9-12)	0.671
Total dose of HMG (IU)	666.5 ±166.1 (750-1125)	711.1 ±189.4 (975-1350)	0.121
No. of Ovulation / patient	6/18 (33.33%)	4/15 (26.66%)	0.432

Table (2): comparison between biochemical markers regarding stimulation characters of GnRHa and hCG in all three cycles.

	Group (I) GnRHa (N=23)	Group (II) hCG (N=23)	P value
E2 on day of trigger Pg/ml			
After first cycle	995.325 ±1014.7	938.130 ±1375.77	0.873
After second cycle	403±211	532±330	0.871
After third cycle	406±213	529±2.99	0.873
Mid-luteal p (ng/ml)			
After first cycle	26.639±19.697	26.639±19.697	0.752
After second cycle	27.639±19.23	29.641±19.235	0.734
After third cycl	29.82±18.20	30.66±18.17	0.733
LH 12 hrs after triggering (miu/ m)			
After first cycle	73.639 ± 08.7	13.9 ± 8.9	<00.1
After second cycle	65.8 ±7.7	14.7±7.61	<00.1
After third cycle	68.11±6.7	18.66±6.3	<00.1
hCG (pg/ml) Day 14 post trigger			
After First cycle	212.273±545.4	829.65±1885.4	0.139
After Second cycle	379±1365	645±1866.27	0.584
After Third cycle	186±454	791.3±1770	0.284

Table (3): Outcome measures in both studied groups in all three cycles.

	GnRHa		hCG		
OHSS	No	%	No	%	
After first cycle	1/23	4.33	4/23	17.39	< 0.05
After second cycle	0/20	0	1/18	5.55	
After third cycle	1/18	5.5	1/15	6.66	
Clinical pregnancy					
After first cycle	3/23	8.6	5/23	21.7	0.543
After second cycle	2/20	10	3/18	16.66	0.632
After third cycle	2/18	11.11	2/15	13.33	0.654
Multiple pregnancy					
After First cycle	0/23	0	1/23	4.33	0.875
After Second cycle	0/20	0	1/18	5.55	0.873
After Third cycle	0/18	0	2/15	13.33	0.876
Abortion					
After first cycle	1/23	4.33	0/23	0	0.493
After second cycle	1/20	5	0/18	0	0.493
After third cycle	0/18	0	1/15	6.66	0.618

Table (4) : Over all cycles stimulation and outcome characters:

Ovulation rate **Ovulation rate / patient** **Ovulation rate / cycle**	38 (32.7%) 38/61 (62.29%)	30 (25.6%) 30/56 (53.57%)	68 (58.11%) 68 (58.11%)
Pregnancy rate **Pregnancy rate / patient** **Pregnancy rate / cycle**	7 (5.98%) 7/61(11.47%)	10 (8.54%) 10/56 (17.85%)	17 (14.52%) 17/117(14.52)
Abortion rate **Abortion rate / patient** **Abortion rate / cycle**	2 (1.7%) 2/61(11.47%)	1 (0.85%) 10/56 (17.85%)	3 (2.56%) 17/117(14.52)

Table (5) shows multi-variant analysis for predictors of pregnancy:

AGE	28.4 + 2.77	29.99 + 3.82	0.087
BMI	23.521 + 5.31	24.75 + 5.26	0.532
Type of infertility			
Primary **Secondary**	8.0 9.0	10 19	0.533 0.416
Duration of infertility, yr	1 – 1.6 yrs	1.5 – 2 yrs	0.276
Total dose of HMG	656.5217	375.321	0.525
No. of mature follicles	71	13	0.96
Endometrial thickness mm	9.28 + 1.63	8.32 + 2.15	0.521
E2 on trigger day	959.315 + 104.4	375.130 + 111.7	0.873
LH 12 Hrs after trigger	70.633 + 13.12	12.9 + 8.9	< 0.005
Mid-luteal progesterone	25.391 + 10.69	8.613 + 19.6	< 0.005
Day 2 FSH	7.18±1.55	7.90 ±2.7	0.965
Basal LH	8.63 ±2.3	9.69 ±2.73	0.02
Prolactin	12.695±5.2	13.9±8.32	0.848
TSH	2.66±0.8	2.32±0.7	0.388
GnRHa **Trigger / pt. hCG**	7 / 61 (11.47%) 10 / 56 (17.85%)	54 / 61 (88.50%) 46 / 56 (82.14%)	0.532
Ovulation / pt	17 / 68 (17.35%)	51 / 68 (52.05%)	0.0002

Table (6) : Uni-variant analysis for predictors of pregnancy.

Ovulation / pt	17 / 68 17.35%	51 / 68 52.05%	0.0002
Basal LH	6.90 ±2.5	8.32 ±2.73	0.0 00
LH 12 Hrs after trigger	70.633 + 13.12	12.9 + 8.9	< 0.005
Mid luteal progesterone	25.391 + 10.69	8.613 + 19.6	< 0.002

DISCUSSION

This study showed that the there was no significant statistical difference in the rate of overall ovulation in the studied groups. The mean ovulation rate was 38(32.74%) in GnRHa group and 30(25.64%) in hCG group with (p value 0.491) and regards over all pregnancy rate also no significant difference between both groups where the GnRHa group was 7 (11.47%) and 10 (17.85%) in hCG group , (p value 0.63), these results were in agreement with study of **Badeea et al.** [10]. who reported that in a meta-analysis study compared the clinical efficacy and safety of GnRHa with hCG for ovulation trigger in women with PCOS; they concluded that there was no significant statistical difference between GnRHa group and hCG group regarding rate of pregnancy in women underwent HMG stimulation for IUI cycles.

The present study revealed that there was a statistical significant difference in post triggering LH levels increase, 12 hrs after GnRHa than hCG administration (73.639 + 8.7 vs.13.9 + 9.9) respectively . These results coincide with the results of **Badeea et al.** **(10)**, and **Deepika et al.** [11] where they mentioned that there was a marked LH increase in the GnRHa group, this may be due to the pituitary surge of LH hormone and the increasing careful in the hCG group was related with the high levels of circulating estradiol.

This study showed that the mean mid luteal serum progesterone was in the 1st cycle 26.639 ± 19.697 in GnRHa group and 26.639 + 19.696 in hCG group. There was no statistically significant difference between the studied groups, (P value = 0.752) , (0.734) in the 2nd cycle and (0.733) on the 3rd cycle. In agreement with our results, **Humaidan et al.** [2]. reported that the effect of GnRHa in luteal function was contraindicated during the previous studies, and the luteal function can be improved through pre-ovulation FSH surge by the effect of LH induction on granulosa cell in addition to maturation oocyte promotion and cumulus expansion.

In the current study there was a significant difference regarding prevention of severe early OHSS & OHSS incidence in high-risk patients. In GnRHa group, OHSS incidence was 4% in the first cycle , 0% in the 2nd cycle and 5.5% in the 3ed cycle while the incidence of OHSS was 17% in the first cycle, 0% in the second cycle and 5.5% in the third cycle. By comparison of the two groups the results showed the OHSS incidence in hCG group was significantly higher than the GnRHa group. **These results were in agreement with study of Anat and Adrian** [12] **who** concluded that the replacement of hCG instead of GnRHa triggering help to avoid OHSS and leading to new horizon of egg maturation.

On contrary, Youssef et al. [13]concluded that in women with high risk of OHSS , the utility of GnRHa as final oocyte maturation trigger in fresh autologous cycles should be evaluated in the content of effect versus safety (lower birth rate, lower ongoing pregnancy rate and high rate of miscarriage).

Conclusion: hCG was the gold standard for complete oocyte maturation, the new agent

seems to be GnRHa with its potential advantages over hCG trigger in OHSS reduction.

REFERENCES

1- Fatemi H.M., Popovic TB., Humaidan P., Kol S., Banker M., Devroey P. et al. Severe ovarian hyperstimulation syndrome after gonadotropin releasing hormone (GnRHa) agonist trigger and (freeze all) approach in GnRHa antagonist protocol. Fertile sterile **2014;**101:1008-1011.

2- Humaidan P, Polyzos N, Alsbjerg B, Erb K, Mikkelsen AL, Elbaek HO et al. GnRH trigger and individualized luteal phase HCG support according to ovarian response to stimulation tow prospective randomized controlled multi centre studies in IVF patientS. Hum. Report **2013**; 28(9):2511-2521.

3- Nistri CO, Teixeira DM, Moroni RM, Leitao VM and Martins WP Ovarian hyperstimulation syndrome pathophysiology. Staging, prediction and prevention ultrasound Obstet. Gynecol **2015**; 45:377- 393.

4- Kummer NE, Feinn RS, Griffin DW, Nulsen JC, Benadiva CA and Engmann LL Predicting successful induction of oocyte maturation after gonadotropin releasing hormone agonist (GnRHa) trigger. Hum Reprod. **2013**; 28:152-159.

5- Griesinger G., Schultz L., Bauer T., Broessner A, Frambach T. and Kissler S. Ovarian hyperstimulation syndrome prevention by gonadotropin releasing hormone agonist triggering of final oocyte maturation in gonadotropin releasing hormone antagonist protocol in combination with ((freeze all) strategy. Prospective multi-centric study. Fertile steril **2011**; 95: 2029-2033.

6- **Liu X, Zhang Y, Zheng SY, Lin R, Xie YJ, Chen H et al.** Efficacy of exenatide on weight loss, metabolic parameters and pregnancy in overweight/obese polycystic ovary syndrome. Clin Endocrinol (Oxf) **2017**; 87(6):767-774.

7- Shapiro B.S., Daneshmand S.T., Garner F.C., Aguirre M. and Thomas S. Gonadotropin-releasing hormone agonist combined with a reduced dose of human chorionic gonadotropin for final oocyte maturation in fresh analogous cycles of in vitro fertilization. Fertil Steril. **2008**; 90:231-233.

8- Damewood MD, Shen W, Zacur HA, Schlaff WD, Rock JA and Wallach EE. Disappearance of exogenously administered human chorionic gonadotropin. Fertil. steril. **1989;** 52:398-400.

9- Yen SS, Erena O, Little B and Pearson OH . Disappearance rates of endogenous luteinzing hormone and chorionic gonadotropin. clin Endocrinol metal.2010; 28:1763-1767.

10 Badeea S and Siam S . Pregnancy rate after ovulation triggering with gonadotrophin releasing hormone agonist versus human chorionic gonadotrophin in women undergoing controlled ovarian stimulation/ intrauterine insemination. Faculty of Medicine, Zagazig University, Egypt. Middle East Fertility Society Journal. **2014** ; 19: 262–267.

11- Deepika K, Dhoble S, Praneesh G, Rathore S, Upadhaya A and Rao K. Gonadotropin-releasing hormone agonist trigger is a better alternative than human chorionic gonadotropin in PCOS undergoing IVF cycles for an OHSS Free Clinic: A Randomized control trial . Journal of human reproductive sciences. **2016;** 9, (3) : 164-172 .

12- Anat HK and Adrian S . hCG Triggering in ART: An Evolutionary Concept. Int J Mol Sci **2017**; 18(5): 1075.

13- Youssef MA, Abou-Setta AM and Lam WS . Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles. 2016 Apr 23;4(4):CD003719.

BuTalag, I., Sarhan, A., Harira, M. Gonadotropin Releasing Hormone Agonist versus Human Chorionic Gonadotropin in Patients with PCOS as Trigger of Ovulation. *Zagazig University Medical Journal*, 2019; Jully. 2020 Volume 26 Issue 4 (574-581): -. doi: 10.21608/zumj.2019.13352.1239