A comparison between GnRH agonist and antagonist analogs for controlled ovarian stimulation in overweight/obese women with PCOS after ICSI

Una comparación de los efectos de los análogos agonista y antagonista de GnRH para la estimulación ovárica controlada en mujeres con SOP con sobrepeso/obesas después de la ICSI

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Abstract

Background: polycystic ovary syndrome (PCOS) is the most common endocrine disorder of reproductive age females with a prevalence of 10%. Obesity is one of its characteristic association with a prevalence of 40-60%, usually leads to reduce fertility, lower pregnancy potential and increase pregnancy loss. **Aim of the study:** to decide the better gonadotropin releasing hormone (GnRH) analogues down regulation protocol for overweight/obese PCOS women by studying ICSI outcome in form of ovarian response, embryos' quality, pregnancy rate and OHSS development. **Material & methods:** Forty sub-fertile women with PCOS whom their body mass index (BMI) ≥ 26 were included in the study. Their male partners had mild to moderate impairment in semen quality. All are subjected to COS by GnRH analogues and separated into 2 groups; group 1: down regulated by GnRH antagonist (n=14) and group 2: down regulated by GnRH agonist (n=26). **Results:** not significant difference between both groups concerning ovarian response. Pregnancy rate was greater and the rate of developing OHSS was lower in GnRH antagonist group with non-significant statistical difference 57.1% vs 38.5% and 0% vs 7.7% respectively. **Conclusions:** both GnRH antagonist and agonist had the same efficacy when used during COS/ICSI for overweight/obese PCOS, but had lower safety in favor of GnRH antagonist protocol.

Keywords: GnRH analogues, ovarian stimulation, overweight/obese, PCOS, ICSI

Resumen

Antecedentes: el síndrome de ovario poliquístico (SOP) es el trastorno endocrino más frecuente en mujeres en edad reproductiva con una prevalencia del 10%. La obesidad es una de sus características asociadas con una prevalencia del 40-60%, por lo general conduce a reducir la fertilidad, disminuir el potencial de embarazo y aumentar las pérdidas de embarazo. Objetivo del estudio: decidir el mejor protocolo de regulación descendente de análogos de hormona liberadora de gonadotropina (GnRH) para mujeres con SOP con sobrepeso/obesidad mediante el estudio de los resultados de ICSI en forma de respuesta ovárica, calidad de los embriones, tasa de embarazo y desarrollo de OHSS. Material y métodos: Cuarenta mujeres subfértiles con SOPQ cuyo índice de masa corporal (IMC) ≥ 26 se incluyeron en el estudio. Sus parejas masculinas tenían un deterioro de leve a moderado en la calidad del semen. Todos se someten a COS por análogos de GnRH y se separan en 2 grupos; grupo 1: regulado negativamente por el antagonista de GnRH (n=14) y grupo 2: regulado negativamente por el agonista de GnRH (n=26). Resultados: no hubo diferencia significativa entre ambos grupos en cuanto a la respuesta ovárica. La tasa de embarazo fue mayor y la tasa de desarrollo de SHEO fue menor en el grupo de antagonistas de la GnRH con una diferencia estadística no significativa del 57,1 % frente al 38,5 % y del 0 % frente al 7,7 %, respectivamente. Conclusiones: tanto el antagonista como el agonista de la GnRH tuvieron la misma eficacia cuando se usaron durante la COS/ICSI para el SOP con sobrepeso/obesidad, pero tuvieron menor seguridad a favor del protocolo del antagonista de la GnRH.

Palabras clave: análogos de GnRH, estimulación ovárica, sobrepeso/obesidad, SOP, ICSI

Introduction

The most common endocrine condition among women of reproductive age is polycystic ovarian syndrome (PCOS)[1]. Obesity, oligo- or amenorrhea, hormonal abnormalities, and infertility are all common symptoms of PCOS[2]. PCOS is a condition that causes both metabolic and reproductive problems, when two of the following criteria are met, the patient should be diagnosed with PCOS, according to Rotterdam criteria: oligoovulation that lasts for a long time or anovulation, hyperandrogenism (clinical or biochemical) and polycystic ovaries on ultrasound[3]. Obesity and insulin resistance are two frequent symptoms of PCOS, according to estimates more than 50% of females with PCOs are overweight or obese[4]. Obesity is a common phenotype in PCOS, and it's virtually always linked to insulin resistance[5]. As a result of obesity, women are more likely to experience difficulties during pregnancy, including maternal mortality, stillbirth, neonatal and infant death, large-for-gestational-age babies and fetal deformities thus obese women with PCOS are more likely to experience infertility and pregnancy difficulties[1]. When it comes to ovulation initiation or controlled ovarian stimulus. Increase secretion of luteinizing hormone (LH) and hyperandrogenemia are associated with lesser oocyte class, reduced fertilization, lesser implantation, and icrease miscarriage rates[6]. There is a possible advantage to using GnRH equivalents in controlled ovarian stimulus cycles, mainly in PCOS patients. GnRH agonists use before or during ovarian motivation decreases the occurrence LH surges and cycle deletion, consequential in a greater success rate[7]. Furthermore, in controlled ovarian stimulation (COS) cycles, this regimen is unable to minimize the incidence of ovarian hyperstimulation syndrome (OHSS)[7]. In comparison to GnRH agonists, GnRH antagonists for COS have some advantages including shorter analog treatment, shorter the FSH stimulation, decrease stimulation of ovary[8]. One benefit is ability to start ovulation with a spike of short endogenous luteinizing hormone induced by GnRH agonist management rather than induced by human chorionic gonadotropin (hCG)[9]. We hypothesize that GnRH antagonist cycles will result in better In vitro fertilization (IVF) consequences. The aim of this study was to compare the GnRH antagonist to the GnRH agonist long procedure in PCOs females with overweight and obesity.

Material and methods

This is a prospective cohort study that was conducted at Al-Sadr Medical City/ IVF Center/Al- Najaf AL-Ashraf/Iraq. Forty sub-fertile couples, whom the females were diagnosed as PCOS according to Rotterdams' criteria and have a BMI ≥ 26 (overweight and obese) were involved in this study and all of them were involved in intra cytoplasmic sperm injection (ICSI) program The mean age of females partners was 29.3±3.4 years old. The infertile couples were separated in 2 groups: Group 1 females whom down regulated by GnRH antagonist and Group 2 females whom down regulated by GnRH agonist. Male partners had mild-moderate male factor infertility. Normal ovulatory females, anovulation other than PCOS, male partners with sever impairment of semen quality (astheno-terato-zoospermia) and frozen sperms had been excluded from this study. Male and female partners of both groups had been evaluated by urologists and gynecologists. Females of both groups had been subjected to pituitary down regulation using either GnRH antagonist; Cetrotide 0.25 mg (Serona) from day 6 (fixed protocol) or agonist; Decapeptyle 0.1 mg (Serona) from the second day of cycle which is indivisiualized according to each couples' then controlled ovarian hyper stimulation by recombinant FSH (r-FSH); Follitrope 75*2 IU (Merck) which was done under a close supervision by serial trans-vaginal ultrasound (TVUS) and hormonal assay for 10-14 days. Ovulation trigger was done either by HCG; Pregnyl 5000 IU*2 (Merck) injection when the total number of the follicles and their size are adequate (7-12 follicles of more than 16 mm size). Oocytes pickup was done by the gynecologist under general anesthesia using trans-vaginal approach. The maturity of oocytes was assessed microscopically. Only mature oocytes that resume their first meiosis (MI) and reaching second meiosis (MII) are appropriate for ICSI. Fertilization was assessed 16-18 hr afterward injection, assessment of the embryo eminence dependent on blastomere amount, shape, fairness, mono-nucleation, ratio of disintegrations. Embryos were categorized in to; good quality (grade I & II) "4 cells at 48 hr". Anything else were categorized as poor quality embryos (grade III & IV). Luteal phase support in form of vaginal progesterone suppositories commenced from the day of oocyte retrieval. Fresh embryo transfer was done using three good quality embryos, Assessment of chemical pregnancy 14 days following the transmission by determining human chorionic gonadotropin (Beta-HCG) level in the serum of women was done followed by calculation of pregnancy rate by dividing the total number of females with a positive pregnancy test of women that embryos were transferred to their uterus. Data were analyzed using SPSS, version 4.0. For continuous data, mean ±SD was calculated and for categorical data, percentage was calculated with a comparison by t-test or Chi-square respectively depending on P-value of ≤0.05.

Results

The antagonist and agonist groups were comparable in terms of patient characteristics such as age, duration of infertility, type of infertility and cycle day 2 hormonal levels. There was no significant difference between both protocols as shown in table1.

Table 1. Demographic characteristics of both groups

Parameters	GnRH Antagonist N=14 Mean±SD	GnRH Agonist N=26 Mean±SD	P-value
Age (years)	29.3 ±3.4	29.4 ±2.8	0.94
Duration of infertility (years)	7.07 ±4.3	9.03 ±4.08	0.16
Type of infertility Total no.			
Primary	11	15	0.18
Secondary	3	11	
Total	14	26	
Cycle day 2 hormones Mean±SD			
E2 (Pg/dl)	38.26± 16.8	35.4 ±15.7	0.61
LH (IU/ml)	7.4 ±4.7	2.8 ±0.94	0.11
FSH (IU/ml)	7.7 ±2.7	5.01± 155	0.15

Table 2 shows entire number of recovered oocyte, total number of mature and immature oocyte, total number of embryos and total dose of gonadotropin. The total no. of retrieved oocyte was similar between both groups (7.57± 3.9 vs7.72±5.1 p= 0.92). Total no. of mature oocytes (6.4 ±3.5 vs 6.5 ±4.9 p=0.93), total no. of immature oocytes(1.07± 2.3 vs1.16± 2.05p=0.90), total embryos(4.07 ±2.4 vs 4.9 ±4.6 p=0.51) and total dose of gonadotropin(1759.64 ±743.5 vs 1641.34 ±467.3 p=0.54) were not significantly differed.

Table 2. Response to controlled ovarian stimulation in both groups.

parameters	Gnrh Antagonist N=14 Mean±SD	GnRH Agonist n=26 Mean±SD	P-value
Total no. of retrieved oocytes	7.57± 3.9	7.72 ±5.1	0.92
Total no. of mature oocytes	6.4 ±3.5	6.5 ±4.9	0.93
Total no. of immature oocytes	1.07± 2.3	1.16± 2.05	0.90
Total embryos	4.07 ±2.4	4.9 ±4.6	0.51
Good	3.7 ±2.08	4.4 ±4.1	0.6
Bad	0.29± 0.61	0.56 ±1.22	0.4
Total dose of gonadotropin	1759.64 ±743.5	1641.34 ±467.3	0.54

Table 3 shows pregnancy rate and OHSS among both protocols. Pregnancy rates was not significantly differed but higher rate of pregnancy occurred with antagonist protocol (57.1 vs 38.5% p = 0.25). In GnRH antagonist, risk of OHSS was lower compared to agonist group but insignificant (0% vs7.7% p = 0.28).

Table 3. Stimulated cycle characteristics of both groups

Parameters	GnRH Antagonist N=14 Total no./ %	GnRH Agonist n=26 Total no./ %	P-value
Pregnant	57.1%	38.5%	0.25
Not pregnant	42.9%	61.5%	
OHSS	0%	7.7%	0.28
No OHSS	100%	92.3%	

Discussion

The modification between agonist and antagonist procedures for non-PCOS patients managed with IVF/ICSI has been demonstrated in numerous studies In this study, we investigated the effectiveness of GnRH antagonist and GnRH agonist procedures for pituitary downregulation during ICSI cycle management in PCOS patients who were overweight or obese. PCOS is the utmost predominant cause of "oligo-ovulation and anovulation" in females who are feeling infertility[10]. The GnRH agonist protocol is a traditional protocol that is still widely used around the world. It allows for increase no. of pre-ovulatory follicles of recovered oocytes and lead to embryos obtainable for transmission, resulting in improved IVF outcome[11,12]. In clinical practice, GnRH antagonists have provided another choice for ovarian induction in IVF. The usage of GnRH antagonist in helped reproductive skills to prevent LH surge appeared to pave the way for a more "pleasant" IVF procedure[12,13]. In the current study found that ovarian response in form of entire dose of gonadotropins, entire number of retrieved oocytes, oocyte maturity and embryos' quality were similar in two protocols which was similar to the results of previous studies[14,15]. Whereas some researchers found that total dose of gonadotropin and duration of stimulation were lower and number of oocyte retrieved was higher in antagonist than agonist protocols[12,16,17]. When aggressively stimulated with exogenous gonadotropins, obese women with polycystic ovary syndrome are at an increased risk of developing ovarian hyperstimulation[18]. Although together agonists and antagonists can defeat raised bloodstream LH level, the lesser follicular assistance to decrease the danger of ovarian hyperstimulation in females with POS[19]. The current research analyzes the risk of OHSS and pregnancy rates in GnRH antagonist and GnRH agonist protocols. We find no significant difference in pregnancy rate and the incidence of OHSS in both protocols but lower rate of OHSS and higher pregnancy rate in antagonist protocol than agonist. This outcome was alike to prior study that stated no significant difference in pregnancy rate among together group[20]. Two previous studies demonstrate same result regarding lower rate of OHSS[21,22]. In the setting of avoiding OHSS, one benefit is the capability to activate ovulation with a little endogenous luteinizing hormone surge encouraged by GnRH agonist direction more than the protracted LH action encouraged by hCG[12,23]. The GnRH antagonist regimen is still being debated

as to whether it can lower the occurrence of OHSS. When compared to the GnRH agonist protocol, a large body of published evidence demonstrates that the GnRH antagonist regimen can minimize the incidence of mild and moderate OHSS[24]. However, a meta-analysis of five randomized controlled studies found that the kind of analogue had no effect on the risk of severe OHSS[25-30].

Conclusion

Both GnRH antagonist and agonist had the same efficacy when used during COS/ICSI for overweight/obese PCOS. Furthermore a GnRH antagonist can help to minimize the occurrence of OHSS. These findings imply that in PCOS patients, a GnRH antagonist is more effective and safe.

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