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Long Protocol of Gonadotrophin Releasing Hormone Agonist Versus Gonadotrophin Releasing Hormone Antagonist for ICSI Protocol as Regard Clinical Pregnant Rate

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Abstract

The administration of GnRH analogues requires ovarian stimulation to be controlled by exogenous FSH and suppresses a mid-cycle LH spike. These analogues are synthetic copies of native GnRH and are available as either agonists or antagonists. GnRH-an improvement in affinity to the GnRH receptor and allow OPU to be postponed for the weekends (so-called' programming') without having any adverse impact on the IVF result. GnRH antagonists gain rapid and dose-dependent inhibition of LH through competition.

This research was performed to equate GnRH antagonist vs. long GnRH agonist regimen in ovarian stimulation for ICSI-planned patients. The present research involved a retrospective examination of women between twenty and forty years of age, with a total of 70 patients completing ICSI periods. Both participants were subject to complete history, full analysis, and inquiry.

1) Group I (long protocol of GnRH-a)

Received Decapeptyl 0.1 mg/day beginning on day 20 or 21 of the prev period for 10 days till menses then decrease GnRH-a dose to half with start ovulation induction by 225-300 I.U of HMG/day depends on age and BMI, then the dose was adjusted according to individual endocrine and ovarian ultrasonic response till the day of HCG injection.

2) Group II (GnRH-ant)

HMG from day 2 or 3 of the cycle (3amp/day) then received Cetrorelix (Cetrotide) single dose 3mg S.C on cycle day 7 or 8 adjusted dose until day of HCG injection, HCG was given in dose 10,000 IU administered 34-36 h before the scheduled time of oocyte retrieval.

Sperm collection and OPU done in the same day and ET done after 2-3 day after fertilization. Then B-HCG done later after 14 days. Clinical pregnancy was diagnosed 3 weeks after a positive examination, with fetal echoes and ultrasound pulsations in the gestational sac.

The findings of the present analysis indicate no statistically relevant ova count, embryo transfer count, implantation rate, and pregnancy rate. However, the current study reported a statistically higher fertilisation rate in GII (GnRH antagonist) compared with GI (long GnRH agonist).

Conclusion

The current study indicates no statistically relevant variations between the GnRH antagonist and the long regimen of the GnRH agonist in ovarian stimulation for the patient planned to have ICSI according to era, BMI and husband's age, period of infertility, causes of infertility, form of infertility, retrieved ova count, implantation rate. However, the current study reported a statistically higher fertilisation rate in GII (GnRH antagonist) relative to GI (long GnRH agonist).

Introduction

Today, In vitro fertilisation (IVF) is a worldwide procedure that has given birth to over four million children. IVF is known to be a reliable and successful therapy for people suffering infertility [1].

The aim of IVF is to develop healthy embryos in vitro to be transferred to the uterine cavity. The ovaries are stimulated to develop multiple mature oocytes to be fertilised by sperm in the laboratory. Stimulation enables the collection of embryos to be transfused [2].

The first IVF therapy has been done in a normal cycle. Gonadothropines are given to stimulate multiple follicular growth and Gonadotropin-Releasing Hormone (GnRH) analogues are used to inhibit premature Luteinizing Hormone (LH) spikes in IVF. LH surges occur in about 20 percent of stimulated IVF patients. Avoiding LH surges with GnRH analogues increases the oocyte produced with more embryos, makes for improved selection and leads to an increase in pregnancy rates [3].

Subfertility affects 5-15 per cent of women globally and 50 per cent of infected women seek medical attention. Aided reproductive technology (ART) is an important technique for infertile couples. During controlled ovarian stimulation (COS) processes, pituitary suppression decreases the risk of premature LH. Early ovulation ends in the cancellation or retrieval of oocytes of low consistency (which adversely affect pregnancy rates) [4].

Pulsatile release of GnRH from the hypothalamus induces the production and secretion of follicle stimulating hormone (FSH and LH from the anterior pituitary gland. Pituitary suppression during ART cycles enables the ovarian stimulation to be regulated by exogenous FSH and suppresses the mid-cycle LH surge. This is done by the administration of GnRH analogues in western reproductive medicine. These analogues are synthetic copies of the native GnRH and are available as agonists or antagonists [5].

Aim of The Work

To compare between GnRH antagonist vs long protocol of GnRH agonist in ovarian stimulation for patient planned to ICSI.

Patients and methods

The present research involved a retrospective review of women between the ages of twenty and forty years with a total of 70 patients completing ICSI periods in two special ICSI centres from May2018 to May 2020.

The eligibility criteria included a female age between 20 and 40 years of age with a typical hormonal profile and no pelvic pathology. We included women undergoing the first ICSI trial (or previous trial with good response). The exclusion conditions are those of a patient over forty or below twenty. Ethical approval was taken and informed and written consent from all patients.

All participants were subjected to:

1) History taking:
2) Examination:
3) Investigation:

-Male: semen analysis, ABO, Rh.
-Female: hormonal profile was done.

1)Group I (long protocol of GnRH-a)
Received Decapeptyl 0.1mg/day starting on day 20 or 21of the previous cycle for 10 days till menses.
Criteria of suppression:
Hormonal: - E2 <50 pg/ml
- Progesterone < 1ng/m
- LH <5 IU
US: No ovarian cysts and Endometrial thickness <6 mm predicts down regulation in 95% of cases. Then decrease GnRH-a dose to half with start ovulation induction by 225-300 I.U of HMG/day depends on age and BMI mostly started by 3 amp/day in average weight women between 25-35 years, then the dose was adjusted according to individual endocrine and ovarian ultrasonic response till the day of HCG injection. Poor responder should receive high dose of HMG started by (400-450 I.U/day)

2)Group II (GnRH-ant)
HMG from day 2 or 3 of the cycle (3amp/day) then received Cetrorelix (Cetrotide) single dose 3mg S.C on cycle day 7 or 8 then the adjusted according to endocrine and ovarian ultrasonic response till the HCG injection.
HCG was given in dose 10,000 IU administered 34-36 h before the scheduled time of oocyte retrieval using the same criteria in both groups which are:

- At least 3 follicle > 18 mm.
- E2: 150 pg/ml per >15mm follicles.
- Endometrial thickness is > 8 mm, Triple line.

Day of OPU:

- Sperm collection:

On the day of egg collection, the male partner must send a sperm sample of the semen to be extracted after three or four days of sexual activity. Masturbation is the favoured form of selection in a clinic. Upon completion of the collection, the sample is sent to the laboratory where it is prepared for IVF. The sperm is separated from other elements in the semen and activated to fertilise mature oocytes.

- Oocyte retrieval:

Done in the operating room under general anaesthesia and conducted under transvaginal ultrasound supervision on day 0, 36 hours after injection of HCG. In compliance with published protocols, both patients underwent ICSI. Embryo transfer was done on day 2 or 3 after OPU using a Wallace catheter or a Cook catheter if the Wallace catheter could not be inserted; fertilisation tests are performed by embryologists. The first symptoms of fertilisation are given by two pronuclei appearing within the egg.

A B-HCG serum test was performed to confirm pregnancy two weeks after embryo transfer. Clinical pregnancy was diagnosed 3 weeks after positive result of foetal echoes and ultrasound pulsations in the gestational sac. The outcomes of two stimulation procedures were correlated with the number of follicles greater than 17 mm, the number of oocytes recovered and fertilised, the rate of fertilisation per oocyte, the number of embryos transferred and the rate of conception per activation period.

Statistical analysis: Data were entered using Epi-Info version 6 and SPP for Windows version 8

Results

Table 1 indicates no statistically significant variations between the era, BMI and marital age groups studied. No statistically significant differences between the groups studied in terms of length of infertility, cause of infertility and form of infertility. Table 2 indicates no statistically significant variations between the groups studied in the recovered ova count. There are no statistically significant differences between the groups studied in the co-transferred embryos. Table 3 indicates no statistically important variations in the implantation rate between the groups tested. GII had a slightly higher rate of fertilization compared to GI. Table 4 indicates no statistically important variations in fertility rates between the groups analyzed.

Table1: Comparison between the studied groups regarding the demographic data and infertility parameters.

	GI n=35	**GII n=35**	**Student t test**	
			t	**P**
Age	28.51 ± 4.7	28.51 ± 5.2	-0.025	0.97
BMI	28.11 ± 3.41	26.71 ± 2.51	0.25	0.79
Husband age	33.31 ± 5.7	32.31 ± 6.3	0.59	0.55
	GI n=35	**GII n=35**	**Student t test**	
			t	**P**
Duration of infertility (years)	4.71 ± 2.8	4.11 ± 3.5	0.72	0.46
			Chi-square test	
Causes of infertility			X2	P
• **Unexplained**	4	1	7.0	0.071
• **Male**	20	25		
• **Tubal**	2	4		
• **Ovarian**	4	-		
Type of Infertility				
• **Primary**	27	27	0.0	1.0
• **Secondary**	8	8		

Table 2: Comparison between the studied groups regarding retrieved ova count and transferred embryos count.

		GI n=35	GII n=35	Student t test	
				T	P
Retrieved ova	Range	5.0 – 22.0	4.0 – 22.0	-0.21	0.83
	Mean ± SD	11.8 ± 4.3	12.0 ± 5.3		
		GI n=35	GII n=35	Student t test	
				T	P
Transferred embroys	Range	1.0 – 3.0	1.0 – 3.0	1.2	0.25
	Mean ± SD	2.0 ± 0.41	1.9 ± 0.48		

Table 3: Comparison between the studied groups regarding implantation rate and Fertilization rate.

		GI n=35	GII n=35	Student t test	
				T	p
Implantation rate	Range	33.0 – 100.0	33.0 – 100.0	-1.24	0.22
	Mean ± SD	51.7 ± 14.1	57.2 ± 19.9		
		GI n=35	GII n=35	Student t test	
				T	p
Fertilization rate	Range	33.0 – 78.0	50.0 – 83.0	-3.6	0.001*
	Mean ± SD	58.4 ± 10.3	67.6 ± 9.2		

Table 4: Comparison between the studied groups regarding Clinical Pregnancy rate.

		GI n=35	GII n=35	Chi-square test	
				X2	P
Pregnancy rate	Pregnant	14	12	0.27	0.6
	Not pregnant	16	18		

Discussion

There was a chance of inhibiting the early release of LH by GnRH-ant administration. GnRH – induces direct and rapid hypophysical suppression, which is the opposite of agonists needing protracted administration to achieve the same effect. As a result, antagonists can be prescribed shortly before the predicted LH peak and only a few days of therapy are required. Most studies say GnRH-administration starting on the sixth day of ovarian stimulation [6].

In the Cochrane review compared the GnRH-ant to the agonist long regimen, slightly less births occurred in the antagonist group. However, through the usage of antagonists, there has been a substantial decrease in the occurrence of ovarian hyperstimulation, cycle length, and gonadotrophin specifications [7].

The present research was intended to equate GnRH-ant with the long GnRH-ant regimen in ovarian stimulation for the patient planned to have ICSI. Patients involved in the analysis were divided into two 30 groups of patients: Group I (long GNRH-a protocol) received Decapeptyl 0.1 mg/day beginning on day 20 or 21 of the previous cycle before day of HCG injection, while Group II (GNRH-ant) received Cetrorelix (Cetrotide) 3 mg on day 7 or 8 of the cycle; 225-300 I.U. of HMG/day was confirmed after control.

In the present research, no statistically significant variations were reported between the era, BMI, and marital age groups examined. This means that the variations in the findings of the analysis are due to the protocols used. In addition, there were no statistically meaningful variations between the groups analysed in length of infertility, cause of infertility and type of infertility.

In the current study, male factor was the commonest reported etiology of infertility (66.0 %) followed by ovarian factor (15.5 %), tubal factor (9.5 %) and unexplained infertility (9.0 %). This is like the findings of the study of (8). In this reserech, rconfirmed that male factor was most commonly reported factor in their study.

In our sample, there were no statistically important variations in the ova count between the groups tested. This is in agreement with the report (Panchal, et al 2012) (9). The object of the research was to equate the efficacy of GnRH-ant with the administration of luteal phase estradiol with GnRH-a long-term protocol. 55 IVF-ICSI patients obtained oestradiol in the luteal step of the cycle prior to the GnRH-ant cycle. Fifty-five patients submitted to IVF-ICSI using agonist were allocated, the primary result was the amount of oocytes restored. In terms of clinical features, patients were identical. No variations were observed in the number of oocytes recovered (Study Group, 8.1 +/-4.7; Control Group, 7.4 +/-4.5) or in oocyte efficiency.

In addition, the analysis of (Orvieto, et al 2012) (10) aimed to investigate if progesterone regulation in the late follicular process varies when GnRH-ant is used relative to GnRH-a and if so, to what degree the increase in progesterone affects the probability of pregnancy. In their study a total of 190 patients were randomised: 94 in the GnRH-a group and 96 in the GnRH-ant group. GnRH-a long protocol began with intranasal buserelin on Day 21 of the corresponding cycle (600 mg per day). The GnRH-ant protocol begins on Day 6 of stimulation with ganirelix or cetrorelix (each 0.25 mg). No major variations were established between the two protocols with respect to the number of oocytes recovered.

However, the authors measured the therapeutic applicability of GnRH-ant. For ovarian enhancement in young people undergoing ICSI, where only three oocytes can be fertilised. In their analysis, patients treated with GnRH-a protocol had slightly higher recovered oocytes counts relative to patients treated with GnRH-ant protocol [11].

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There were no statistically important variations between the groups examined in relation to the transferred embryo count. This is consistent with the research of who compared the effectiveness of GnRH-a and GnRH-antagonist in a retrospective study of IVF/ICSI carried out in a tertiary teaching hospital. The study identified no major variations between the groups analyzed in the number of embryos transferred [12]

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In our research, there were no statistically important variations between the groups analysed regarding the implantation rate. This is in line with the study of the effectiveness of GnRH-ant in IVF/ICSI periods. Fifty-two women undergoing antagonistic protocol were studied, and information on patient background, treatment parameters (total gonadotrophin dosage) was obtained. Duration of care and oocyte yield and results in terms of embryological parameters (cleavage rate, implantation rate) and clinical pregnancy. These criteria were compared to 121 women under the traditional long protocol. The study found no statistically important variations in the implantation rate between the two protocols [13]

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However, the current study documented a statistically higher GII fertilisation rate compared to GI. That's in compliance with the assertion mentioned study of (Merviel, et al 2015) [13].

Finally, the current research did not identify statistically relevant variations between the clinical pregnancy rate groups analysed in line with the (Lin, et al 2014) [14] meta-analysis of the existing RCTs assessing the outcomes of the IVF/ICSI use of GnRH-ant for ovarian stimulation in PCOS patients relative to the classical luteal long agonist protocols. In the study, nine RCTs investigated PCOS patients undergoing IVF/ICSI, including 588 women undergoing long agonist protocols and 554 women who underwent GnRH-ant protocols have been included. As for the clinical pregnancy rate (CPR), the GnRH-a protocol is similar to the GnRH-a long protocol.

Conclusion

The current study showed no statistically relevant discrepancies between the GnRH antagonist and the long regimen of the GnRH agonist in ovarian stimulation for the patient planned to have ICSI according to age, BMI and marital age, period of infertility, causes of infertility, type of infertility, retrieved ova count, implantation rate. However, the current study reported a statistically higher fertilisation rate for GII (GnRH antagonist) compared to GI (long GnRH agonist).

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