Comparative Study between Gnrh Agonists versus Antagonists Protocols for Super Ovulation in Persumed Normal Responders Undergoing Icsi

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Abstract: Objective: To evaluate the effectiveness and safety of gonadotrophin-releasing hormone (GnRH) antagonists compared with the GnRH agonists for controlled ovarian hyperstimulation in assisted conception cycle and its effect on pregnancy rates. **Methods:** A prospective randomized study over 300 women, being evaluated as normal responders recruited from clinic, patients have been divided into 2 groups as they received one of the two ovarian stimulation protocols, Group I: It included 150 women received GnRH agonist long protocol for their controlled ovarian hyper stimulation program, Group II: It included 150 patients received flexible GnRH antagonistic protocol. All patients were counseled and signed written informed consents before inclusion In the study. **Results:** There was no statistical difference between both groups as regard pregnancy rate, fertilization rate, good quality oocytes, clinical pregnancy, multiple pregnancy or incidence of miscarriage. How ever there was high statistical difference regarding duration of treatment, number of HCG ampules, follicular numbers detected by U/S, oocytes retrieved and incidence of OHSS in group I. But regard cost effectiveness there was high statistical difference in group II than group I patients. **Conclusion:** The use of GnRH antagonists is effective and safe comparable to the use of GnRH agonists. It results in shorter duration of stimulation, and reduction of HMG use. There no difference in pregnancy rate, fertilization rates or good quality oocytes compared to GnRH agonist protocol, However, the use of GnRH agonists is more cost effective whether in cost/cycle or cost/pregnancy.
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1. Introduction:

Controlled ovarian hyperstimulation (COH) is an essential part of the treatment of subfertility. For many years, gonadotropin-releasing hormone (GnRH) agonists have been used to inhibit the luteinizing hormone surge; prolonged treatment causes down regulation of the pituitary receptors and reversibly blocks gonadotropin secretion. Gonadotropin-releasing hormone agonists, however, are associated with a number of side effects, including a hypoestrogenic state and ovarian hyperstimulation syndrome**, (Gilliam, 2011).**

More recently, GnRH antagonists have been developed. These agents work at the level of the pituitary gland by competitively blocking the receptor in a dose-dependent fashion without the hypo-estrogenic side effects flare-up, or long down-regulation period associated with agonists **(Gilliam, 2011).**

2. Patients and Methods:

A prospective randomized study conducted in outpatient clinic of the International Islamic Center for Population Studies and Research; (Al-Azhar university) and are prepared for ICSI cycles during the period from September 2013 to October 2015. The Ethical approval for the study was obtained from the local ethical committee of Faculty of Medicine for girls.

The recruited patients have been divided into 2 groups as they received one of the two ovarian stimulation protocols:

Group I: It included 150 women received GnRH agonist long protocol for their controlled ovarian hyperstimulation programm.

Group II: It included 150 patients received flexible GnRH antagonistic protocol.

Inclusion Criteria: All patients selected fulfilled the following criteria:

Age: <35 years.
Body mass index (BMI): < 30 kg/m².
Hormonal profile:
FSH < 10 mIU/ml.
FSH/LH ratio > 2/1.
Normal prolactin level.
Estradiol< 80 pg/Ml.
women undergo their first IVF/ ICSI treatment.
U/S criteria:
Normal sized and appearance of both ovaries.
AFC: more than 8(2–10 mm) in size.

Exclusion criteria:

Age >35 years.

Hormonal profile:

FSH >10 mIU/ml.

FSH/LH ratio not 2/1.

- Hyperprolactinaemia.
- PCO patients diagnosed by clinical symptoms and signs, U/S and hormonal profile
- Abnormal semen analysis.
- Any endocrinological disorders.
- Previous gynecological operations.

The long GnRH agonist protocol consisted of daily subcutaneous injections of Triptorelin or leuprolide acetate, daily or depot injection on day 21 of the cycle. Adequacy of down regulation will be confirmed on the second day of bleeding following GnRH agonist administration by fall in the serum level of E2 (< 50 pg/ml), followed by gonadotropin stimulation.

In the GnRH antagonist group, exogenous gonadotropins will start on cycle day 2, and 0.25 mg, cetrorelix (Cetrotide; EMD Serono, Inc) will be added when the lead follicle reach 12- 14 mm in diameter. Cetrorelix will be continued until the day of hCG administration.

In both protocols, starting dose of HMG was 150–300 IU per day according to patient's age, body weight and antral follicles count by ultrasound assessment, such as (Merional, Fostimon 75 IU, from IBSA or Menogon, Ferring Germany). given deeply IM route at a fixed dose regimen. With individual adjustments according to ovarian response as measured by serial ultrasound scans and serum E2 levels from day 6-8 of gonadotrophin stimulation.

Human chorionic gonadotropin (hCG), (Choriomon, IBSA), at a dose of 5,000-10,000 IU had been given intamuscullary when at least two follicles ≥18mm diameter were visualized by the ultrasound scan. Peak E2 Level will be measured on the same day.

Cycle monitoring: In ART unit Al-Azhar University, the ovarian response is monitored by vaginal ultrasound measurements of follicular growth and serum level of E2. The monitoring will identify those who have not responded adequately or to detect women at risk of OHSS, aiming to find the optimal time for triggering ovulation with hCG. At each scan the size and number of follicles were determined and recorded. Ovulation was triggered by administration of HCG (10,000 IU), intramuscularly, when at least 4 follicles reached 18 mm in diameter.

During the course of ovarian stimulation, patients were considered at actual risk of developing OHSS when they had: large number of follicles >20 on both ovaries, with the majority being small (<10 mm in mean diameter) and E2 < 3000 pg/ml, they were monitored daily and managed by coasting where gonadotropins were withheld while administration of the GnRH analogues were continued and these cases were excluded from the study.

Oocyte retrieval: 34-36 hours later after hCG administration, Transvaginal ultrasound-ditected Oocyte recovery is performed in the operating theater under full aseptic technique.

ICSI procedure: Oocyte identification, Assessment and grading of oocyte maturation after oocyte pick up. The ICSI procedure involves the injection of a single motile spermatozoon after semen preparation into the oocyte.

Fertilization and embryo cleavage after ICSI: The cleaving embryos are scored according to equality of blastomeric size and proportion of nucleate fragments.

Most patients performed embryo transfers on day 3 or day 5 after oocyte retrieval. At that time, the embryos were eight-cell stage, the embryonic genome at this stage is fully activated.

Two to Three embryos were placed into the uterus in most cases. Higher pregnancy rates can be obtained when selective transfer of two or three embryos is possible**.**

Luteal phase progesterone was then self-administered vaginally from day before embryo transfer for14 days and continuing for another 6–8 weeks in cases in which a pregnancy was achieved.

Two weeks after embryo transfer, serum hCG will be measured for confirmation of pregnancy, and a diagnosis of clinical pregnancy was made after visualization of fetal heart pulsation four weeks later by transvaginal sonography.

3. Results:

The Results of the study were as follows:

Table (1): Comparison between both groups as regard patient characteristics.

Patient charchetristics		Groups		T-test	
		Group I	Group II	t	P-value
Age	Range	19 : 35	23 : 35	2.672	0.008*
	Mean±SD	27.15 ± 3.87	28.23 ± 3.04		
BMI	Range	18 : 30	18 : 30	2.667	0.008*
	Mean±SD	26.10 ± 2.70	25.20 ± 3.17		
Periods of infertility	Range	1 : 8	2 : 6	0.053	0.958

Patient charchetristics		Groups		T-test	
		Group I	Group II	t	P-value
	Mean±SD	3.49 ± 1.42	3.48 ± 1.42		
	Mean±SD	13.17 ± 4.34	12.96 ± 4.52		
Type of infertility	1ry	136(90.67%)	141(94%)	X^2 1.186	0.276
	2ry	14(9.33%)	9(6%)		

Table (2): Comparison between both groups as regard basal hormonal profile.

Patient charchetristics		Groups		T-test	
		Group I	Group II	t	P-value
LH	Range	1.2 : 5	1 : 4.5	2.153	0.122
	Mean±SD	2.95 ± 0.98	2.65 ± 0.89		
FSH	Range	2.5 : 9.9	2 : 9.1	1.441	0.151
	Mean±SD	5.52 ± 1.50	5.22 ± 1.62		
E2	Range	10 : 50	17 : 65	2.208	0.029*
	Mean±SD	31.40 ± 9.91	35.78 ± 9.24		
PRL	Range	1 : 23	1 : 2	0.405	0.686

Regarding patient charchetristics there were statistical significant difference between the patients in the two studied groups regarding the age, being higher in group 1 than group 2, and BMI being higher in the antagonist group than agonist group. no statistical difference regarding duration of infertility, serum PRL, Basal LH and basal FSH. However basal E2 was significantly higher in Group2 than in group 1 patients.

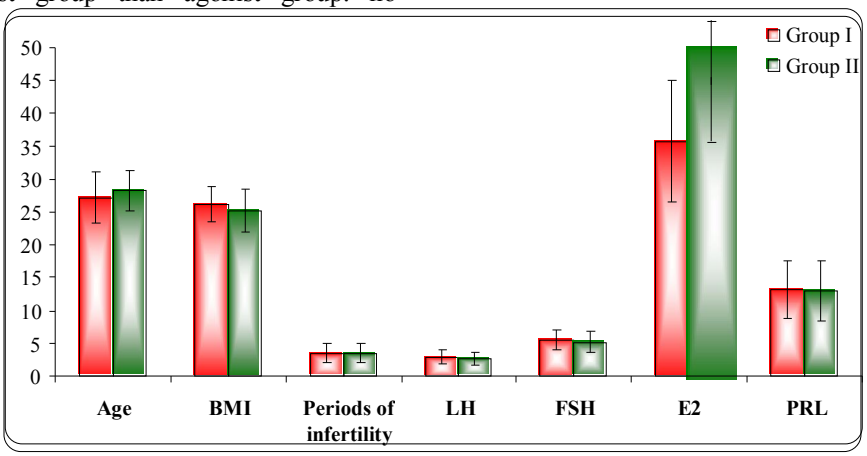

Fig. (1): Comparison between the Studied Groups regarding patients' characteristics and basal hormonal profile.

Table (3): Comparison between the Studied Groups regarding the stimulation characteristics of the cycle.

		Groups		T-test	
		Group I	Group II	t	P-value
Days of cycle	Range	22 : 28	8 : 16	80.007	0.000*
	Mean±SD	25.08 ± 1.25	12.08 ± 1.55		
	Range	16 : 70	18 : 45	10.460	0.000*
	Mean±SD	38.43 ± 7.25	30.36 ± 6.06		
n. of HMG ampules	Range	7 : 13	7 : 12.5	-0.832	0.406
	Mean±SD	11.19 ± 1.44	11.32 ± 1.33		
End.th	Range	690 : 8100	600 : 6123	4.735	0.000*
	Mean±SD	2612.46 ± 1184.21	2015.47 ± 990.93		
E2 at triggering day	Range	3 : 17	2 : 15	7.300	0.000*
	Mean±SD	9.00 ± 2.52	6.87 ± 2.53		
follicular count					

Regarding charter of the cycle there was high statistical difference between both groups regarding days of stimulation, number of HMG ampules, follicular count detected in U/S and the level of E2 at the day of HCG administration being higher in patients treated with agonist protocol (group1). How ever there was no statistical difference between both groups regarding endometrial thickness.

Table (4): Comparison between the Studied Groups regarding the embryology lab characteristics.

		Groups						T-test	
		Group I			Group II			t	P-value
Number of retrieved oocytes	Range	2:13			1:10				
	Mean±SD	7.12	±1.97		5.81	±2.10		5.582	000*
M2	Range	1	:	5	1	:	4	1.409	0.160
	Mean±SD	3.31	±	1.34	3.07	±	1.60		
Total number of Fertilized oocytes	Range	2	:	8	1	:	8	4.976	0.000*
	Mean±SD	4.82	±	1.45	3.93	±	1.65		
Feilization rate	Range	30	:	100	33	:	100	1.885	0.0604
	Mean±SD	72.70	±	17.93	69.13	±	14.72		
Total number of embryos transferred	Range	1	:	3	1	:	3	4.767	0.000*
	Mean±SD	2.55	±	0.63	2.17	±	0.75		
implantation rate	Range	0	:	100	0	:	100	-0.016	0.987
	Mean±SD	14.64	±	21.12	14.68	±	21.94		

Between the two studied groups, there were high statistical difference in the number of retrieved oocytes and total number of fertilized oocytes as well as total number of embryos transferred being higher in group 1 patients, but there were no statistical difference regarding –mk,0'. jjjjmgood quality oocytes represented by M2 oocyte, fertilization rate or implantation rate.

Table (5): Comparison between the Studied Groups regarding the Pregnancy Rates.

Outcome		Groups		
		Group I	Group II	Total
Negative pregnancy test	N	90	99	189
	%	60.00	66.00	63.00
Positive pregnancy test	N	63	51	111
	%	40.00	34.00	37.00
Total	N	150	150	300
	%	100.00	100.00	100.00
Chi-square	X^2	1.159		
	P-value	0.282		

Pregnancy rate was insignicantly lower in group 2 (antagonist group) than group 1(agonist group).

Table (6): Comparison of two groups as regard pregnancy outcome.

		Group I		Group II		Total		Chi-square	
		N	%	N	%	N	%	X^2	P-value
Outcome	Negative pregnancy test	87	60	99	66	189	63	1.159	0.282
	Positive pregnancy test	63	40	51	34	111	37		
multiple pregnancy	Negative	142	94.67	143	95.33	285	95	0.070	0.791
	Positive	8	5.33	7	4.67	15	5		
Abortion	Negative	147	98.67	148	98.00	145	48.33	0.000	1.000
	Positive	3	1.33	2	2.00	5	1.67		

clinical pregnancy		Groups		
		Group I	Group II	Total
Negative	N	97	99	195
	%	64.3	66.00	65.00
Positive	N	60	49	112
	%	40	32.60	36.00
Total	N	150	150	300
	%	100.00	100.00	100.00
Chi-square	X^2	0.132		
	P-value	0.716		

There is no statistical difference as regard pregnancy rate clinical pregnancy, incidence of multiple pregnancy or miscarriage.

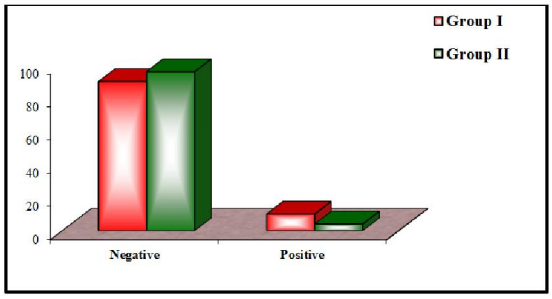

Table (7): Comparison between the two studied groups as regard incidence of OHSS

OHSS		Groups		
		Group I	Group II	Total
Negative	N	135	144	279
	%	90.00	96.00	93.00
Positive	N	15	6	21
	%	10.00	4.00	7.00
Total	N	150	150	300
	%	100.00	100.00	100.00
Chi-square	X^2	4.275		
	P-value	0.039*		

The incidence of OHSS in group 2(antagonist group) was signicantly lower than group 1 (agonist group)

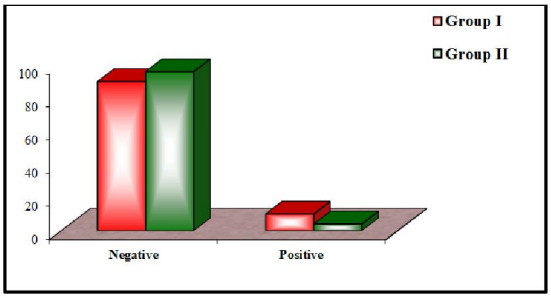

Fig 3: Incidence of OHSS among studied groups

The patients presented 72 hours after embryo transfer with abdominal discomfort, pain, nausea, and abdominal distention. On examination there was no evidence of ascites, but ultrasonic evidence of ascites was present as well as enlarged ovaries. Both patients had normal hematological and biological profiles. They were managed on outpatient basis and were instructed to maintain a schedule of only light physical activity (to avoid the risk of ovarian torsion). Strict bed rest, on the other hand was not instructed (to avoid the risk of thromboembolic complication). They were advised to drink at least 1L of fluid per day. The condition resolved gradually and neither of them developed severe OHSS.

Table (8): Correlation between both groups as regard E2 Level at the day of HCG

E2 at triggering day		
	r	P-value
follicular count	0.864	.000*
Retrieved oocytes	0.768	.000*
M2	0.606	.000*
Total Fertilized eggs	0.677	.000*
Fertilization	0.205	.000*
Total embryo transferred	0.524	.000*

There was +ve correlation between E2 level and follicular count, retrieved oocytes, good quality oocytes represented by M2 oocytes, total number of fertilized eggs, fertilization rate and total embryo transferred.

Table (9): Criteria of pregnant patients

	pregnancy test				T-test	
	Negative		Positive			
	Mean	± SD	Mean	± SD	t	P-value
Age	28.00	± 3.69	27.16	± 3.13	2.004	0.046*
LH	2.92	± 1.04	2.78	± 0.86	1.058	0.291
FSH	5.51	± 1.56	5.30	± 1.52	1.031	0.303
BMI	26.03	± 2.97	25.00	± 2.88	2.959	0.003*
Number of HMG ampules	34.48	± 7.94	34.26	± 7.59	0.230	0.818
Duration of cycles	18.14	± 6.71	19.33	± 6.55	-1.504	0.134
Endomtrial thickness	11.05	± 1.45	11.61	± 1.21	-3.425	<0.001*
E2 at triggering day	1995.10	± 1070.34	2856.90	± 1021.04	-6.848	<0.001*
follicular count	7.01	± 2.55	9.51	± 2.28	-8.522	<0.001*
Retrieved oocytes	5.60	± 1.98	7.93	± 1.51	-10.673	<0.001*
M2	2.39	± 0.97	4.57	± 1.14	-17.602	<0.001*
Total number of Fertilized eggs	3.58	± 1.25	5.72	± 1.23	-14.390	<0.001*
Fertilization rate	65.48	± 16.67	80.02	± 12.58	-7.944	<0.001*
Total number of transferred embryos	2.11	± 0.74	2.78	± 0.41	-8.908	<0.001*
implantation rate	0.00	± 0.00	39.71	± 15.99	-34.088	<0.001*

In This study pregnant patients were signicantly lower in age and BMI, Higher in endometrial thickness, E2 level at triggering day, follicular count seen on us, retieved oocytes, total number of fertilized eggs, fertilization rate and implantation rate. Although there were no statistical differences in hormonal profile, number of HMG ampules or duration of stimulation.

Table (10): Criteria of OHSS patients in both groups

Patients characteristics (M)	group1	group2
Age/years	29	25
Infertility duration/years	3	4.5
BMI (kg/m^2)	27	21
Basal FSH (mIU/ml)	5	4.3
Total number of HMG ampoules	18	16
E2 level on day of hCG (pg/ml)	3670	3012
Total number of oocytes on u/s	20	14
Total number of oocytes retrieved	9	6
Total number of M II	7	4
Number of fertilized eggs	7	5
Number of embryos transferred	3	3
+ve Pregnancy test (N)	**7**	**3**

Table (11): Cost effectiveness for both groups

	Cost of drugs/ cycle	PR%	Difference
Group 1	2760EP	40%	46
Group 2	3240EP	33%	66
Difference	480EP	7%	43.6

Cost effectiveness per pregnancy for antagonist group was statistically higher than agonist group. It is noted that cost effectiveness per cycle is also higher in group 2 patients, as the total cost for group 2 were as follows:

3240(stimulation treatment) +200(investigations)+1400 (luteal phase support)+3000 (oocyte aspiration operation)=7840EP

For group 1: 2760+200+1400+3000=7360.

4. Discussion:

The long mid-luteal GnRH-a protocol in IVF entities comprises the initiation of treatment during the mid-luteal phase of the previous cycle (day 21-24 from the previous cycle). The length of the treatment period is increased because 2-3 weeks are usually needed to obtain desensitization, proved by serum estradiol level< 50 pg.ml, absence of follicular activityin U/S and endometrial thickness ≤ 6ml.

The recorded side effects of treatment are related to hormonal depletion (such as hot flashes, bleeding, and vaginal dryness). In addition, larger number of HMG ampoules is required for ovarian stimulation. This increases the cost of the procedure and the risk of ovarian hyperstimulation syndrome (OHSS), a rare but serious complication **(rizk & and Smitz, 1992).**

The use of gonadotrophin releasing hormone (GnRH) antagonists should overcome these disadvantages, because they cause immediate suppression of gonadotrophin secretion without the initial stimulatory effect. The ability of the GnRH antagonists, to inhibit the premature LH surge during ovarian stimulation has been reported. They suppress gonadotrophins by blocking the GnRH receptors, and thus treatment is restricted to those days when a premature LH surge is likely to occur **(Mekaru et al., 2011).** The anticipated advantages of GnRH-antagonist treatment in ovarian stimulation programs in our study are a reduction of the use of gonadotrophins, and a lower risk for developing OHSS

A baseline measurement of serum FSH concentration, usually on day 3 of the cycle, is a fairly good predictor of ovarian reserve. As the ovary fails, the FSH begins to rise in the follicular phase of the cycle. A fluctuating baseline FSH level is indicative of already compromised ovarian function **(Balen and Jacob, 2003).** Females in this study did day 3 basal FSH. Only patient with FSH levels <IOmIu/ml were included, as high levels of serum FSH, >12 or >15mIU/ml) on cycle day 2 or 3 is a prediction to a poor ovarian response **(Cameron et al., 1988, Scott at al., 1989 & Toner et al., 1991).**

In the presented work we have found that the duration of stimulation and number of HMG ampoules used were both significantly lower in the antagonist (group II). These findings correspond with the findings of other clinical trials **(Vlaisavljevic et al., 2003, Al-Anany and Abouighar, 2002- Albano et al., 1997, and North American Ganirelex: study group, 2001).** A likely explanation is that the agonist suppresses the natural cycle follicular recruitment initiated by inter cycle FSH rise so that longer treatment with gonadotropins is required which allows more follicles to enter the growing phase **(Andre et al., 2002).** And also the length of the treatment in long agonist group increased because the additional 2-3 weeks usually needed for desensitization.

As regard E2 level monitored in different opportunities during the stimulation cycle in both groups, we have found that there was no statistical difference in the basal E2, slightly higher level of E2 in the antagonist group at the beginning of stimulation days and lower levels at the day of trigerring for the same group of patients, this consitanat with findings **of {Albano et al., 2000 - The European and Middle East Orgalutran Study Group, 2001 - European Orgalutran study Group, 2000 and North American Ganirelex study group 2001)** this explained by the fact that there is no initial pituitary suppression in the antagonist group. On the other hand on the day of HCG administration we have found that in the antagonist group there were significantly fewer follicles, and lower E2 levels. This corresponds to the findings of Other clinical trials **(Badrawi 2005, The North American Ganireibc Study Group, 2001 - The European and Middle East Orgalutran Study Group, 2001 and Al-Anany and Abouighar, 2002).** This may be partly explained by the shorter mean duration of treatment and lower total dose of HMG administration in subjects treated with cetrotide (antagonist).

The number of oocytes retrieved was significantly lower in the antagonist group, this correspond to the finding of clinical trials of **(orvieto et al., 2008, Badrawi. 2005 and Al-Anany and Abouighar, 2002).** how ever Stimpfel et al., 2015, Bodri et al., 2011, Vlaisavljevic et al., 2003) have found that there is similar number of retrieved oocytes in both group.

In our current study their were no statistical difference between both groups regarding the quality of oocytes represented by (number of M2), fertilization rate and implantation rate. This were in accordance to the findings of other clinical trials **Bodri et al., 2011, orvieto et al., 2008, Vlaisavljevic et al., 2003 and Albano et al., 2000)** in contrast to **(Badrawi, 2005 and Al-Anany and Abouighar, 2002)** They found signicant lower number of good quality oocytes in the antagonist group.

Regarding pregnancy out come we found that the pregnancy rate in the antagonist group was insignificantly lower than agonistic group this finding is in agreement with **(Mekaru et al., 2011, Bodri et al., 2011, badrawi 2005, Vlaisavljevic2003 Al-Anany and Abouighar, 2002 and Albano et al., 2000).**

The possible explanation to this findings is that may be there is a direct adverse effect of the GnRH antagonist on the embryo. Ludwing et al., 2002 however did not agree on this explanation, their point of view was that In IVF treatment the risk of embryo

exposure to the antagonist is minimal. As the antagonist was not detectable in the serum and foilicular fluid during oocyte retrieval and embryo transfer when small doses (0.25 mg) were used. Their finding was supported by the findings of Seeling et al., 2002 who found that the implantation and pregnancy rates after the transfer of frozen pronuclear oocytes did not differ between the agonist and antagonist group, in the present work we favored that point of view where we found that the quality of embryos did not differ in both groups.

Another possible explanation for the lower pregnancy rate in the antagonist group could be an adverse effect of GnRh antagonists on the endometrium quality. **Kolibianakis et al., 2002** found that endometrial advancment is present in all cycles stimulated with GnRh antagonists this might result in a slightly lower ongoing pregnancy rate as the chance of an ongoing pregnancy in substantially reduced when endometrial advancement at oocyte pick-up is >3-5 days as compared to the expected chronological date.

Rackow et al., 2008 investigate the effect of GnRH antagonist on endometrial receptivity by evaluating HOXA10 protein expression in endometrial glands and stroma. Endometrial stromal cell HOXA10 protein expression was significantly decreased in cycles using GnRH antagonist compared with cycles using GnRH agonist or natural cycle controls. No difference was noted in glandular cell HOXA10 protein. How ever this –ve impact is known to be dose dependant with high doses of antagonist (1-3 mg).

Stimpfel et al., 2015 even found that pregnancy rate was significantly higher in GnRH antagonist mild protocol in comparison with both GnRH antagonist and agonist protocol who show no statistical difference in both. In our study there were no statistical difference regarding incidence of clinical pregnancy, multiple pregnancy and miscarriage, in contrast to Orvieto et al., 2008 who states a significantly lower clinical pregnancy rate and ongoing pregnancy/live birth rate in the antagonist group compared with the agonist group.

How ever our study was in accordance to Other Studies **Badrawi, 2005, Albano et al., 2000 -Al-Anany and Aboulghar, 2002 and The European and Middle East Orgali Oran Study Group, 2001)**. Who found the same results.

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic serious potentially life-threatening complication of ovarian stimulation. It is now becoming increasingly more recognized due to the higher number of women undergoing assisted reproductive techniques. several studies have been conducted to evaluate the optimum regimen for COH with less effective dose in order to decrease the risk of OHSS.

In our study we can conclude that antagonist protocol carry less risk of OHSS than agonist protocol. as the incidence of OHSS was statsicaly signicant lower in group 2 antagonistic group. this consistent to **(Barritt et al.2009**Where they find statisticaly lower incidence in OHSS with the use of antagonist. This finding may be explained by the smaller cohort of growing follicles and the lower serum oestradiol concentrations in the GnRh antagonist-treated subjects during the late follicuiar phase, which are predictors of the syndrome **(Navot et al., 1992; Brinsder et al., 1995)**. However **Badrawi, 2005 and Al-Anany and Aboulghar, 2002** found after pooling the results that there was no significant difference in the incidence of OHSS in the two groups, also **The European Middle East Qrgalurran Study Group, 2001** found the incidence of OHSS to be similar in both groups.

To further evaluate these subtle differences between the agonist and antagonist protocols, several meta-analyses have been performed so far.

In conclusion, GnRH antagonists offer a number of clinical advantages, but are apparently often not employed as a first line treatment. The pregnancy rates achieved are reduced as compared to GnRH agonist long protocol cycles in both controlled studies and observational registry data. However, in registry reports the effect of an unfavourable patient selection for GnRH antagonists has to be taken into consideration. We advocate that GnRH antagonist protocols deserve optimization rather than second place **(Engel et al., 2006).**

Several recently published papers concluded that, GnRHagonist and antagonist provide comparable results in terms of implantation and pregnancy rates in young healthy infertile women with normal ovarian reserve testing, while antagonist allows a greater flexibility in their treatment and reduced risk of OHSS.

Moraloglu et al. (2008), compared the results of GnRH Agonists (long protocol) and flexible daily dose oftrorelix acetate 0.25 mg Antagonists in Normoresponder patients after IVF/ICSI cycle. They found that, in the GnRHa group, more antral follicles, a longer induction duration and higher peak E2 levels were observed. No differences were observed in the number of oocytes retrieved, embryos achieved and transferred, or fertilisation rates between the two groups. There was no statistically significant difference between groups in clinical pregnancy rates, cycle cancellation and ovarian hyperstimulation. They Concluded that GnRHant and GnRHa provide comparable results in normoresponder patients, while

GnRHant allows a greater flexibility in their treatment.

Depalo et al.2009, evaluated the response to treatment in a group of patients undergoing IVF and randomised to receive GnRH-antagonist or the GnRH-agonist and found that better follicular growth and oocyte maturation are achieved with GnRH agonist treatment. However, both regimens seem to have similar efficacy in terms of implantation and pregnancy rates.

Barritt et al.2009, included 1277 infertile patients <35 years of age, with normal ovarian reserve testing (baseline FSH <10 IU/L) who underwent their first IVF cycle with a GnRH antagonist or down regulation protocol. The results of patients included, 21% (268) were stimulated with a GnRH antagonist protocol, while 79% (1009) with a gnRH agonist down regulation protocol. Of cases in the antagonist group, 45.1% had a day 3 ET and 51.9% a day 5 ET, while 45% in the down regulation regimen completed a day 3 ET, and 55% a blastocyst ET. The mean number of embryos transferred and the implantation rates for blastocyst ETs were similar between both groups. However, the implantation rate was noted to be higher in the down regulation group who underwent a day 3 ET. Overall, the clinical pregnancy and multiple pregnancy were not different. They concluded that, In a group of young healthy infertile women with normal ovarian reserve testing, GnRH antagonists include rapid effective suppression of LH, fewer injections, and the lack of hypoestrogenic side-effects such as those often accompanying luteal suppression with GnRH agonists. pregnancy rates were comparable in the antagonist group to the down regulation group without increasing the incidence of multiple pregnancy.

Murber et al.2009, compared the efficacy of a multiple-dose GnRH antagonist protocol with that of the GnRH agonist long protocol on oocyte/embryo quality and embryo development. They observed that there is less cytoplasmic abnormality in the mature oocytes, there are more oocytes with normal fertilization and there are more zygotes with normal pronuclear morphology after stimulation with GnRH agonist analogues. In contrast, there are more blastomeres in the embryos on day 2 when GnRH antagonists were administered. While there was no significant difference between clinical pregnancy rates of the two groups, the advantageous and the disadvantageous effects of the GnRH analogues on the quality of the oocytes and the embryos may be equalized.

Also, for any drug the optimum position of an experimental treatment would has to be both save costs and have greater effectiveness relative to a comparator. In the published guidelines for the management of infertilityb (The British National Formulary, 2004), the cost of antagonists for a five-day treatment schedule is around £120 and the cost of agonists for a much longer schedule (24 to 31 days) is £111. The cost of gonadotrophins is the same for both treatments since it typically involves around ten days of treatment the total cost of gonadotrophins (using The British National Formulary prices) is around £544. The cost of agonists is between £623 per cycle of treatment and £666 for antagonist.

In our study the cost effectiveness was higher in the antagonist group than the agonistic group, this should be put into consideration because this could prevent some patients from undergoing ICSI especially in countries donot have medical insurance and couples had to do ICSI on their cost.

As a conclusion: we belive that ovarian controled hyperstimulation using GnRH antagonist treatment is effective and safe with shorter duration of treatment and more friendly with patient and most important less incidence of OHSS.

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