IRAQI JOURNAL OF EMBRYOS AND INFERTILITY RESEARCHES (IJEIR)
Abdul-Hameed, et al, Vol. 9, Issue 1, Pp. 68-88, (2019) Original Research
DOI: http://doi.org/10.28969/IJEIR.v9.i1.r5 E-ISSN: 2616-6984 P-ISSN: 2218-0265

Received: 16-May-2019 Accepted: 16-Nov-2019 Published: 17-Nov-2019

Early and Short Follicular GnRH Antagonist (Sandwich) Protocol Versus Conventional GnRH Antagonist Protocol in Normal Responders

Khitam M. Abdul-Hameed[*1], Ula M.R. Al-Kawaz[1], Nadia M. Al-Hilli[2]**

*[1]High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al Nahrain University, Baghdad, Iraq. *khitam313ak@gmail.com, ** ulamhm@googlemail.com*
[2]Department of Obstetrics and Gynecology, College of Medicine, University of Babylon, Babylon, Iraq dr.nadia6@yahoo.com

Abstract

Gonadotropin-releasing hormone antagonists are one of the GnRH analogs that were used in assisted reproductive technologies to produce prompt downregulation of pituitary gonadotropin secretion. During conventional antagonist protocol (CAP), exposure to high LH and E_2 occur that have the potential to worse clinical reproductive results. So the downregulation of pituitary secretion for short period during early follicular phase will result in synchrony in follicular developments and this will improve mature oocytes and total embryos numbers. 44 women as normal responders undergoing ICSI-ET cycles were randomized into two groups. The conventional group (CG) (n 30), gonadotropin started from menstrual cycle day 2 or 3 and continue until hCG trigger day, flexible protocol in which GnRH antagonists administered with follicular size (13-14 mm). In the sandwich group (SG) (n 14), a GnRH antagonist was administered for three days in which GnRH antagonists administered with follicular size (13-14 mm). Gonadotropin started from menstrual cycle day 3 and continue until hCG trigger day. Retrieved and MII oocyte mean numbers were significantly higher in SG than in CG (P = 0.006, and 0.025), respectively. Embryos and frozen embryos mean total numbers were significantly higher in SG than in CG (P = 0.004). SG patients have a higher pregnancy rate of 9/14 (64.3 %) than CG 12/30 (40.0 %) although not significant (P =0.057). Early and short GnRH antagonists proved improvements in synchronization of follicular development, retrieved mature oocytes numbers, total embryos, frozen embryos, and pregnancy rates.

Keywords: GnRH antagonist, MII oocyte, follicles and embryo numbers.

1. Introduction

In the early years, for the in vitro fertilization (IVF), gonadotropin-releasing hormone (GnRH) agonist long protocol plays a key role for poor ovarian responders and was used for ovarian stimulation to inhibit the premature surge of luteinizing hormone. Although it had a number of side effects, this method was widely accepted and used as a long duration protocol treatment, which also increased the pregnancy rate and a number of oocytes retrieved. With the administration of the agonist, follicular stimulating hormone (FSH) and LH increases (Giri, et al 2017 [1]). Different studies have shown the ovarian hyperstimulation syndrome (OHSS) is a complication associated with controlled ovarian stimulation (Kolibianakis, et al 2006 [2]). Thus, to overcome these complications, various studies were conducted using GnRH antagonist which had an immediate mode of action, shorter duration, decrease hospital stay and beneficial to patients undergoing ovarian stimulations (Devroey, et al 2009 [3]). After the introduction of the GnRH antagonist, it has proved and appreciated as additional support to controlled ovarian stimulation in reproductive techniques on the basis of patient's benefits and the clinicians are taking advantage of these benefits (Giri, et al 2017 [1]). In the IVF cycles to improve the outcome of the GnRH antagonist protocol, flexible rather than the fixed GnRH antagonist regimen (Ludwig, et al 2002 [4]), oral contraception pretreatment (Hwang, et al 2004 [5]), initiation of GnRH antagonist from premenstrual period, with day 1 of stimulation until the day of hCG administration or earlier at the follicular phase (Kolibianakis, et al 2003 [6]; Fanchin, et al 2004 [7]; Lainas, et al 2005 [8]). The present study suggests that short pituitary

down-regulation in the early follicular phase will result in low gonadotropin levels and synchrony in the follicular developments before ovarian stimulation started and by this will be comparable in idea to the long GnRH agonist protocol while maintains the benefits of the GnRH antagonist protocol. Because the constant state of the GnRH antagonist level is reached after 2 days of treatment (Kolibianakis, et al 2004 [9]), the GnRH antagonist will be started from menstrual cycle day 1 for 3 days. The aim of this study was to investigate how such modification affects the numbers of oocytes, numbers of MII oocytes, numbers of embryos, fertilization rates, cleavage rates, embryo grading, and pregnancy rates.

2. Materials and Methods

This was a prospective comparative study in "the Higher Institute of Infertility Diagnosis and Assisted Reproductive Techniques, Al Nahrain University, Baghdad, Iraq" during the period from 2017 to 2019. 44 women as normal responders undergoing ICSI-ET cycles were randomized into two groups. The patients who normal responder were included, the patients, agree to participate in the study, age group (18-44) years, infertility due to male factors and couples with unexplained infertility were also included. While patients with endocrine disorders and anatomical and pathological abnormalities in the uterus were excluded.

2.1 Ovarian Stimulation

Recombinant FSH (rFSH) (Gonal f, Merck Serono Company, Geneva, Switzerland), Menogon injections (Ferring, GmbH Company; Germany) 75 IU of both urinary FSH and LH and the GnRH antagonist (Cetrorelix 0.25 mg) were used for controlled ovarian stimulation. The gonadotropin dose was assessed for each woman

according to age, body mass index (BMI), antral follicle count, and/or previous responsiveness to ovarian stimulation. Further dose adjustments were performed on the basis of ovarian response, as evaluated using serum E_2 measurement and follicular diameter by transvaginal ultrasound. The conventional GnRH antagonist group (n 30), gonadotropin started from menstrual cycle day 2 or day 3 and continue until the day of hCG trigger, flexible GnRH antagonists (Cetrorelix 0.25 mg/d) administered according to the follicular size (13-14 mm). In the sandwich protocol group (n 14), a GnRH antagonist (Cetrorelix 0.25 mg/d) was administered for three days started from day one of the menstrual cycles and continue as flexible GnRH antagonists administered according to the follicular size (13-14 mm). Gonadotropin started from menstrual cycle day 3 and continue until the day of the hCG trigger. According to the ovarian response when transvaginal ultrasound shows 2 or more follicles with diameters ≥18 mm (Copperman and Benadiva, 2013 [10]). Ovum picks up by transvaginal ultrasound was performed 35 hours hCG trigger. Human chorionic gonadotropin (10,000 IU Pregnyl; NV Organon) or Oviterlle injections 6500IU/vial (250 mg) of Human chorionic gonadotropin (hCG) (Merck -Serono Company, Geneva: Switzerland). Luteal phase was supported since day of oocytes retrieval or the day after of oocytes retrieval by vaginal progesterone (Cyclogest®400mg twice: Cox Pharmaceuticals, Barnstaple, UK), or (Crinone,® 8% progesterone gel, MERK), and serum ß-hCG assay was done on day 14 after the embryo transfer indicative of biochemical pregnancy. A woman with a positive result was indicated by an ultrasound examination later in

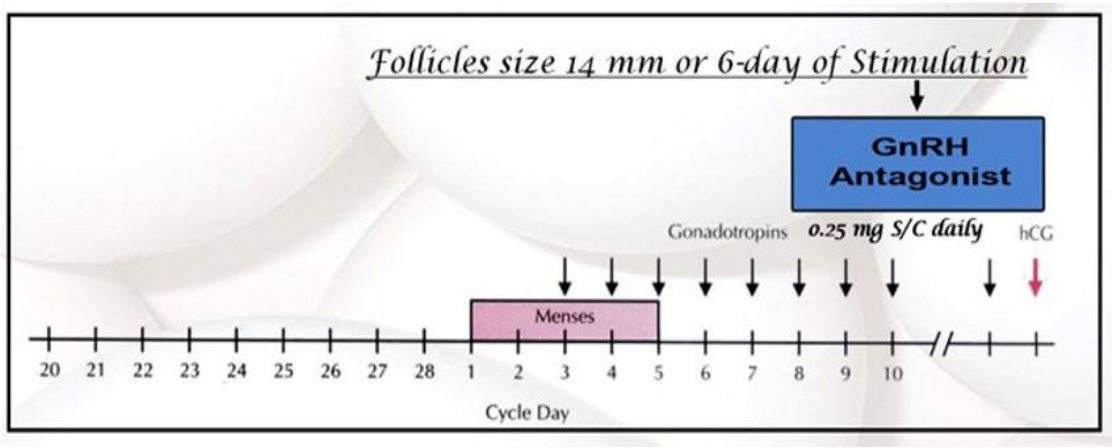

Figure (1): *Conventional antagonist protocol*

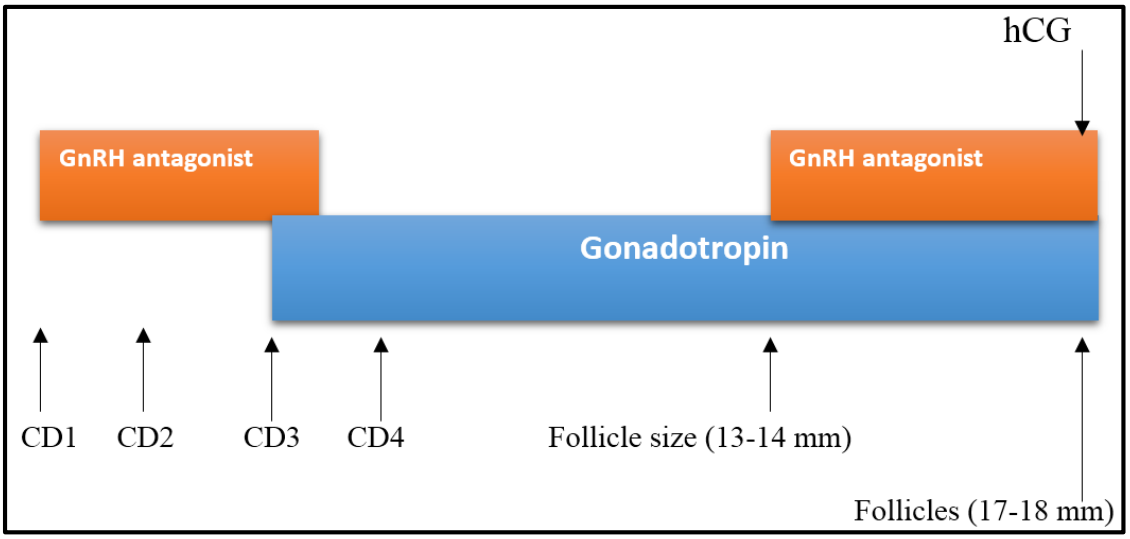

Figure (2): *Early follicular antagonist (sandwich) protocol, CD= cycle day*

order to objectify the existence of cardiac fetal activity that indicates clinical pregnancy.

2.2 Procedures of ICSI Laboratory

The ICSI procedures will be performed similarly in all women. Cumulus oocytes complex incubated for 2 hours, the stage of oocytes will be assessed after denudation

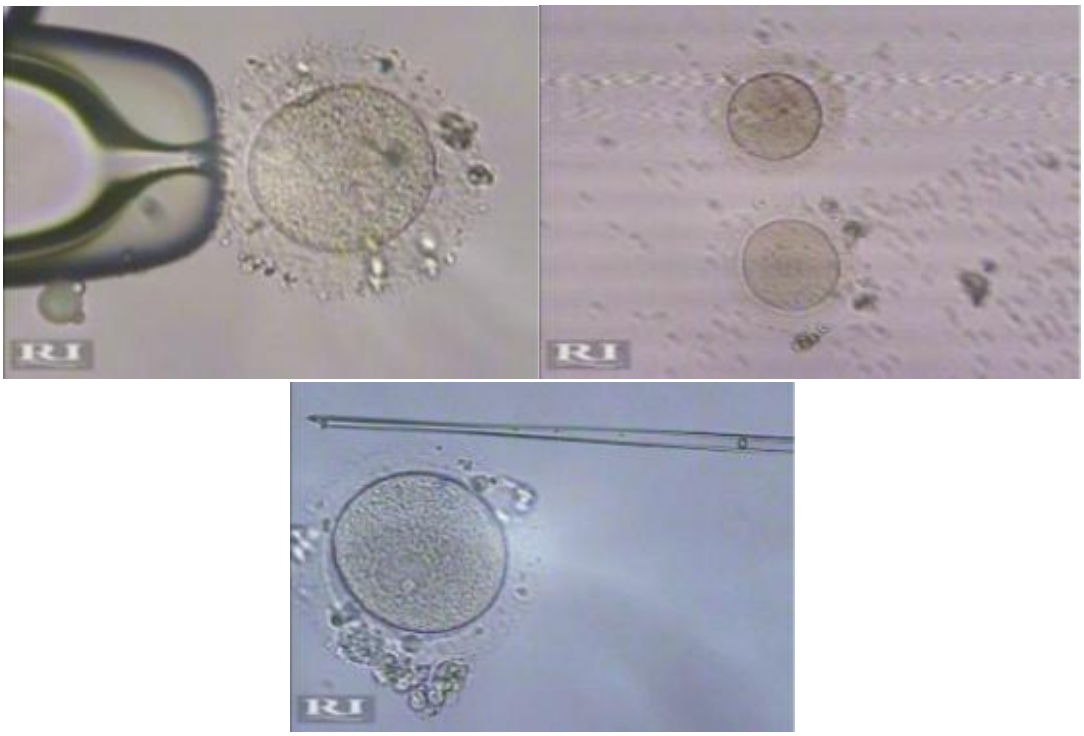

Figure (3): *Oocyte maturation A: MII, B: MI, C: GV*

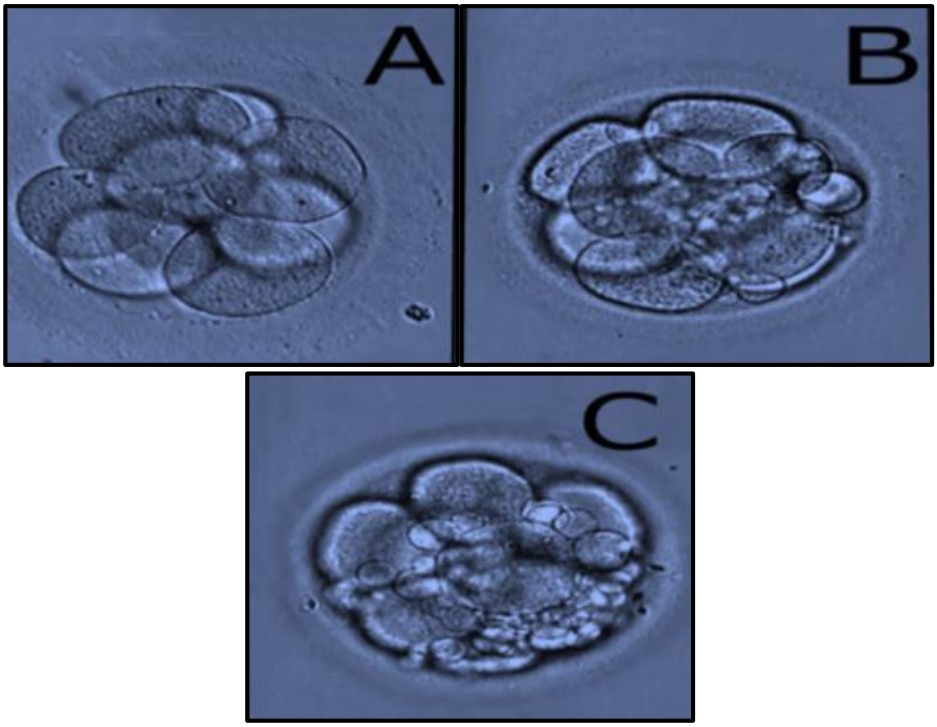

Figure (4): *Embryo grading A: G1, B: G2 and C: G3*

(enzymatic and mechanical) as in (Figure 1). The oocytes classified as MII with the presence of the first polar body in the previtallin space. The ICSI procedure was carried out as described by (Pereira, et al 2015 [11]). By Integra 3™ and Nikon ICSI Micromanipulators, freshly ejaculated or frozen spermatozoa will be injected into the mature oocytes. Assessment of fertilization was performed 16–18 hours after ICSI. Embryo transfer was performed day 2 or day 3 after oocyte retrieval. Embryos were scored according to the Istanbul consensus workshop (Alpha Scientist in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011 [12]) and classified into grades 1, 2, 3. According to (blastomere homogeneity, fragmentation and the degree of anucleated fragments) criteria.

3. Results

Normal responders underwent either conventional antagonist or early and short follicular antagonist (sandwich protocol). These women have exhibited an insignificant difference in mean age, body mass index, infertility duration, cause of infertility and type of infertility when categorized according to the type of protocol, sandwich versus conventional ($p > 0.05$), (Table 1). Hormonal status with respect to the type of protocol is shown in Table 2. There was no significant difference in mean serum FSH, LH as well as FSH / LH ratio between normal responders undergoing sandwich protocol and those undergoing conventional protocol ($p > 0.05$). Mean serum E_2, prolactin and TSH also have exhibited an insignificant difference between the sandwich and conventional groups in normal responders ($p > 0.05$), as shown in (Table 2).

Table (1): Demographic characteristics of normal responders

Characteristic	Statistics	Total *n* = 44	Sandwich *n* = 14	Conventional *n* = 30	*P*
Age (years)	Mean ±SD	28.77 ± 4.90	28.71 ± 3.95	28.80 ± 5.35	0.958* NS
BMI (kg/MII)	Mean ±SD	28.53 ± 4.41	29.09 ± 4.66	28.27 ± 4.34	0.569* NS
Infertility duration (years)	Median (IQR)	6.50 (6.50)	5.00 (8.00)	7.00 (5.25)	0.276† NS
Number of IVF cycles	Median (IQR)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.599† NS
	Range	0.00 - 2.00	0.00 - 1.00	0.00 - 2.00	
Infertility cause	Female, *n* (%)	3 (6.8)	1 (7.1)	2 (6.7)	0.307 ¥ NS
	Male, *n* (%)	28 (63.6)	10 (71.4)	18 (60.0)	
	Combined, *n* (%)	1 (2.3)	1 (7.1)	0 (0.0)	
	Unexplained, *n* (%)	12 (27.3)	2 (14.3)	10 (33.3)	
Type of infertility	Primary,	27 (61.4)	9 (64.3)	18 (60.0)	0.786 ¥ NS
	Secondary,	17 (38.6)	5 (35.7)	12 (40.0)	

n: number of cases; SD: standard deviation; IQR: interquartile range; BMI: body mass index; IVF: in vitro fertilization; *: Independent samples t-test; †: Mann Whitney U test; ¥: Chi-square test; S: significant at $p \leq 0.05$ NS: not significant at $p > 0.05$.

Table (2): Hormonal status of normal responders

Hormone	Statistic	Total *n* = 44	Sandwich *n* = 14	Conventional *n* = 30	*P* *
FSH (IU/L)	Mean ±SD	6.52 ± 3.07	5.90 ± 2.88	6.81 ± 3.16	0.368 NS
LH (IU/L)	Mean ±SD	3.79 ± 1.65	4.06 ± 1.77	3.66 ± 1.61	0.456 NS
FSH/LH	Mean ±SD	1.92 ± 1.00	1.54 ± 0.63	2.09 ± 1.09	0.088 NS
E_2 (pg/ml)	Mean ±SD	29.41 ± 14.79	24.64 ± 6.72	31.64 ± 16.96	0.145 NS
Prolactin (ng/ml)	Mean ±SD	16.81 ± 11.70	16.68 ± 14.89	16.87 ± 10.19	0.960 NS
TSH (mIU/L)	Mean ±SD	1.72 ± 0.53	1.77 ± 0.61	1.70 ± 0.50	0.658 NS

n: number of cases; SD: standard deviation; FSH: follicle-stimulating hormone; LHL luteinizing hormone; E_2: estradiol; TSH: thyroid-stimulating hormone; *: Independent samples t-test; S: significant at $p \leq 0.05$; NS: not significant at $p > 0.05$.

Table (3): Ovarian stimulation characteristics in normal responders

Parameter	Total *n* = 44	Sandwich *n* = 14	Conventional *n* = 30	*P*
Stimulation days	8.98±1.50	8.29±1.44	9.30±1.44	0.035 S
total r FSH (ampule75IU)	20.36±7.66	19.79±6.94	20.63±8.07	0.737 NS
total HMG (ampule75IU)	3.16±3.86	4.36±3.77	2.60±3.83	0.162 NS
Day antagonist start	8.36±1.30	8.71±1.20	8.20±1.32	0.224 NS
Number of antagonists (not including first 3 days)	3.73±1.30	3.71±1.27	3.73±1.34	0.965 NS
Number of follicles	16.18±5.58	17.93±6.50	15.37±5.01	0.159 NS
E_2 at trigger (pg/ml)	1431.90±753.42	1498.90±631.56	1400.60±812.21	0.692 NS
Progesterone at trigger day (ng/ml)	0.73±0.58	0.76±0.80	0.71±0.41	0.857 NS
Progesterone / Estrogen ratio (pg/ml)	0.58±0.52	0.57±0.66	0.60±0.43	0.909 NS
The endometrial thickness on the day of oocyte pickup	9.08±1.56	9.11±1.78	9.07±1.47	0.947 NS

Data were expressed as mean ±standard deviation; n: number of cases; SD: standard deviation; FSH: follicle-stimulating hormone; E_2: estradiol; *: Independent samples t-test; S: significant at $p \leq 0.05$; NS: not signif0icant at $p > 0.05$

Table (4): Oocyte characteristics in normal responders according to the protocol

Parameter	Total *n* = 44	Sandwich *n* = 14	Conventional *n* = 30	*P*
Retrieved oocyte	10.02 ± 5.01	13.00 ± 5.79	8.63 ± 3.99	0.006 HS
MII oocyte	6.41 ± 3.98	8.36 ± 4.60	5.50 ± 3.36	0.025 S
Maturation rate	63.24 ±18.58	64.63 ±22.21	62.59 ±17.01	0.739 NS
MI oocyte	1.82 ± 1.50	1.64 ± 2.02	1.90 ± 1.21	0.602 NS
GV oocyte	0.89 ± 1.82	1.71 ± 2.84	0.50 ± 0.90	0.038 S
Abnormal oocyte	0.50 ± 0.88	0.71 ± 1.14	0.40 ± 0.72	0.273 NS
Ruptured oocyte	0.27 ± 0.50	0.43 ± 0.65	0.20 ± 0.41	0.160 NS

Data were expressed as mean ± standard deviation; n: number of cases; FSH: follicle-stimulating hormone; E_2: estradiol; *: independent samples t-test; NS: not significant at $p > 0.05$; S: significant at $p \leq 0.05$.

Ovarian stimulation characteristics include Stimulation days, total rFSH, total HMG, day of starting antagonist, number of antagonists, number of follicles, E_2 level at the trigger, progesterone level at the trigger, progesterone to estrogen ratio and endometrial thickness on the day of oocyte pickup. The mean stimulation duration was significantly higher in the conventional group than sandwich group ($p = 0.035$). However, there was no significant difference in mean total rFSH, total HMG, day of starting antagonist, number of antagonists, number of follicles, E_2 level at trigger, progesterone level at trigger, progesterone to estrogen ratio and endometrial thickness at day of oocyte pickup between conventional antagonist and sandwich groups in normal responders, (Table 3). Oocyte characteristics include a number of the retrieved oocyte, number of MII oocyte, maturation rate, MI oocyte, GV oocyte, abnormal oocyte, and ruptured oocyte. the mean number of retrieved oocyte was significantly higher in sandwich than in conventional antagonist protocol ($p = 0.006$), in addition, the mean number of MII oocyte was significantly higher in sandwich than in conventional antagonist protocol ($p = 0.025$); however, there was no significant difference in maturation rate between sandwich and conventional antagonist protocol and mean number of MI oocyte was insignificantly different between sandwich and conventional protocol ($p = 0.603$) while the mean number of germinal vesicle (GV) oocyte was significantly higher in sandwich than in conventional antagonist protocol ($p = 0.038$). Nevertheless, there was insignificant difference in mean abnormal and ruptured oocytes between sandwich and conventional antagonist protocol ($p > 0.05$), as shown in Table (4).

Table (5): Fertilization and cleavage characteristics in normal responders according to protocol

Parameter	Total n = 44	Sandwich n = 14	Conventional n = 30	*P*
2PN %	49.37 ± 19.94	54.66 ± 15.72	46.90 ± 21.42	0.234 NS
Cleavage rate	88.06 ± 26.89	85.94 ± 21.35	89.06 ± 29.41	0.725 NS
G1 %	42.68 ± 27.86	48.51 ± 24.88	39.97 ± 29.15	0.350 NS
G2 %	49.64 ± 27.96	44.69 ± 18.56	51.96 ± 31.43	0.428 NS
G3 %	5.40 ± 14.41	6.81 ± 14.08	4.74 ± 14.76	0.662 NS
Total embryos	4.59 ± 2.76	6.29 ± 3.36	3.80 ± 2.04	0.004 HS
ET %	72.26 ± 33.32	61.39 ± 36.60	77.33 ± 31.01	0.141 NS
Number of frozen embryos	1.02 ± 2.05	2.29 ± 3.07	0.43 ± 0.94	0.004 HS
Fertilization rate	67.38 ± 23.48	72.36 ± 9.29	65.06 ± 27.59	0.343 NS
Abortion (n %)	6/9 (66.7 %)	3/5 (60.0 %)	0/4 (0.0 %)	0.167 F NS
OHSS (n %)	5 (11.4 %)	1 (7.1 %)	4 (13.3 %)	1.000 F NS

Data were expressed as mean ± standard deviation; n: number of cases; FSH: follicle-stimulating hormone; E_2: estradiol; *: independent samples t-test; S: significant at $P \leq 0.05$; NS: significant at $p > 0.05$.

Table (6): Pregnancy rate according to the protocol

Group	Protocol	Rate of biochemical pregnancy %
Normal	**Sandwich**	9/14 (64.3 %)
	Conventional	12/30 (40.0 %)

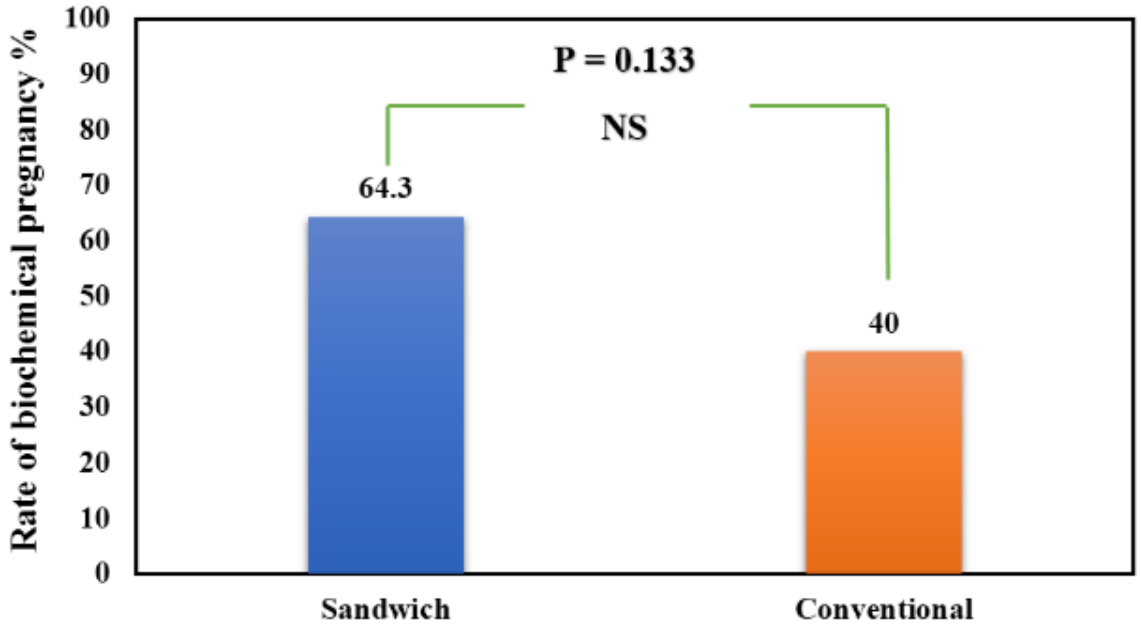

Figure (5): *Pregnancy rate according to protocol in normal responders*

Fertilization and cleavage characteristics are shown in Table 5. There was no significant difference in mean 2PN percentage as well as in cleavage rate in normal responders between the sandwich and conventional antagonist protocol (p> 0.05). The mean total number of embryos was significantly higher in sandwich than in conventional antagonist protocol (p = 0.004); however, there was insignificant difference in mean grade I, grade 2 and grade 3 embryo percentage in normal responders between sandwich and conventional antagonist protocol (p > 0.05). There was also insignificant difference in mean transferred embryo numbers (p = 0.141); however, there mean number of frozen embryos was significantly higher in sandwich than in conventional antagonist protocol (p = 0.004). In addition, there was insignificant difference in mean fertilization rate, abortion rate and rate of ovarian hyperstimulation (OHSS) between sandwich and conventional

antagonist protocol in normal responders ($p > 0.05$), as shown in (Table 5). Regarding normal responders, the pregnancy rates, biochemical and clinical, were higher in the sandwich (64.3 %) than conventional antagonist protocols (40.0 %), although not significant ($p = 0.133$). As in Table 6 and Figure 3.

4. Discussion

The current study clearly demonstrates that early and short follicular GnRH antagonist supplementation (sandwich) significantly improved the number of the retrieved oocytes and the numbers of MII oocytes with Mean ±SD (13.00 ± 5.79) (8.36 ± 4.60), respectively in (sandwich) and Mean±SD (8.63 ± 3.99) (5.50 ± 3.36) respectively in conventional antagonist protocol. Total embryos number and number of frozen embryos highly significant with a sandwich than in conventional antagonist protocol. In addition, the fertilization rate and cleavage rate achieved were higher in the sandwich but not significant. This agrees with (Younis, et al 2010 [13]) study that showed that this modification(sandwich) has resulted in a significant improvement of the follicular recruitment, numbers of oocytes retrieved, the numbers of MII oocytes and increasing fertilization rate. Also with this modification, good follicular recruitment was achieved, although it was not significantly different. (Huirne, et al 2007 [14]) showed that follicular development improved by suppression of endogenous FSH and LH at the beginning of the follicular phase. The explanation of these results attributed to the presence of two factors in the sandwich protocol that shares in its efficacy, the first one the endogenous FSH and LH will get low before starting with gonadotropin and this will lead to synchrony in the follicular

development. The second one constant level of LH and progesterone levels during the follicular phase and this will improve the endometrial receptivity and implantation rates (Younis, et al 2010 [13]). All these are achieved using the long GnRH agonist protocol, and because of these achievements, the clinical results with the long agonist protocol are better than the results from the GnRH antagonist protocol (Xing, et al 2015 [15]). High serum FSH and LH levels in addition to high E_2 levels at the beginning of the stimulation are present in a GnRH antagonist protocol, early and short GnRH antagonist administration results in constant hormonal environment during the follicular phase (Hamdine, et al 2013 [16]). Follicular synchronization that achieved by early GnRH antagonist protocol may improve the mature oocyte yield (Park, et al 2014 [17]). In this study, the stimulation period in sandwich protocol was significantly shorter than conventional antagonist. This agrees with (Elham, et al 2017 [18]) that show the treatment duration was shorter in the group that received antagonist on days 1, 2, and 3 of menstruation. In contrast to (Younis, et al 2010 [13]) that show the stimulation period was increasing in sandwich protocol. In addition, (Blockeel, et al 2011 [19]) study showed that duration of hormonal stimulation was similar in the two groups, this may be due to differences in sample size between these studies. (Blockeel, et al 2011 [19]) noted that the antagonist administered in the follicular phase induces higher estradiol levels on the day hCG trigger, due to the simultaneous growth in the oocyte. While (Elham, et al 2017 [18]) showed that the serum level of estradiol was not significantly different between early follicular antagonist and

conventional antagonist. In the present study, there was no significant difference in progesterone and progesterone to estrogen ratio at the hCG trigger between sandwich and conventional antagonist protocols. Increasing the normal amount of progesterone by increasing the numbers of the follicles rather than excessive amounts of progesterone during early luteinization that produced by granulosa cells (Bosch, et al 2010 [20]). Progesterone elevation will be detrimental to endometrial receptivity and lower clinical pregnancy rates and this adverse effect occurs mainly in subgroup with an elevated P_4/E_2 ratio >1 (Mascarenhas, et al 2015 [21]; Labarta, et al 2011 [22]; Younis, et al 1998 [23]) describe the progesterone elevation as a P_4/E_2 ratio of > 1 by this could distinguish between the progesterone secretion from dysmature follicles and physiologic progesterone secretion from multiple normal mature follicles. Moreover, other studies showed that for prediction of clinical pregnancy, P_4/E_2 ratio was more dependable than serum progesterone alone (Cetinkaya, et al 2013 [24]; Mascarenhas, et al 2015 [21]). Likewise, (Younis, et al 2010 [13]) study in the current study there was no significant difference in the number of antagonists (not including first 3 days) and day of antagonists start between the two groups. The patients in sandwich group has higher pregnancy rate (9/14 (64.3 %) than conventional antagonist group 12/30 (40.0 %) although not significant (p = 0.057) as shown in Figure (4-1) and this is agreed by (Younis, et al 2010 [13]) study that showed, GnRH antagonist administration in early follicular phase can improve clinical results in IVF GnRH antagonist cycles. According to the results of (Elham, et al 2017 [18]) study, the pregnancy rate was higher in early and short follicular

antagonists than conventional antagonists although it is not significant while the variables associated with oocyte and embryo were not significantly different. The pregnancy rate may reduce due to high FSH, LH, and E_2 in the early follicular phase (Kolibianakis, et al 2003 [25]; Blockeel, et al 2011 [19]) study showed that early and short follicular phase GnRH antagonist administration for 3 days resulted in improvement in the numbers of oocytes but failed to improve pregnancy rates.

Acknowledgment

We would like to acknowledge the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al Nahrain University.

Funding

This work received no funding.

Author Contribution

This research was done by Dr. Khitam M. Abdul-Hameed as a part of her Ph.D. thesis under the supervision of Prof. Dr. Ula M.R. Al-Kawaz, and Dr. Nadia M. AlHilli.

Conflict of Interest

The authors declare no conflict of interest.

Ethical Clearance

The study was approved by the Ethical Approval Committee.

References

[1] Giri R, Ji Y, Yang F, Tong X. A Comparison between GnRH Agonist Long and GnRH Antagonist Protocol for In-vitro Fertilization: A Review. Biomedical Letters. 2017,3(1): 27-33. [Biomed_Lett]

[2] Kolibianakis E, Collins J, Tarlatzis B, Devroey P, Diedrich K, Griesinger G. Among patients treated for IVF with gonadotrophins and GnRH analogues, is the probability of live birth dependent on the type of analogue used? A systematic review and meta-analysis. Human Reproduction Update. 2006,12(6):651–671. Doi: http://dx.doi.org/10.1093/humupd/dml038 [PubMed] [OxFord]

[3] Devroey P, Aboulghar M, Garcia-Velasco J, Griesinger G, Humaidan P, Kolibianakis E, Ledger W,

Tomás C, Fauser B. Improving the patient's experience of IVF/ICSI: a proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment. Human Reproduction Update. 2009,24(4):764–774. Doi: http://dx.doi.org/10.1093/humrep/den468 [PubMed] [OxFord]

[4] Ludwig M, Katalinic A, Banz C, Schroder A, Loning M, Weiss J, Diedrich K. Tailoring the GnRH antagonist cetrorelix acetate to individual patients' needs in ovarian stimulation for IVF: results of a prospective, randomized study. Human Reproduction. 2002,17:2842–5. Doi: https://doi.org/10.1093/humrep/17.11.2842 [PubMed] [Oxford]

[5] Hwang J, Seow K, Lin Y, Huang L, Hsieh B,Tsai Y, Wu G, Huang S, Chen C, Chen P, Tzeng C. Ovarian stimulation by concomitant administration of cetrorelix acetate and HMG following Diane-35 pre-treatment for patients with polycystic ovary syndrome: a prospective randomized study.Human Reproduction. 2004,19(9):1993-2000. Doi: https://doi.org/10.1093/humrep/deh375 [PubMed] [Oxford]

[6] Kolibianakis E, Albano C, Kahn J, Camus M, Tournaye H, Van Steirteghem A, Devroey P. Exposure to high levels of luteinizing hormone and estradiol in the early follicular phase of gonadotropin-releasing hormone antagonist cycles is associated with a reduced chance of pregnancy. Fertility and Sterility. 2003,79(4):873-880. Doi: https://doi.org/10.1016/S0015-0282(02)04920-8 [PubMed] [Elsevier]

[7] Fanchin R, Castelo Branco A, Kadoch I, Hosny G, Bagirova M, Frydman R. Premenstrual administration of gonadotropin-releasing hormone antagonist coordinates early antral follicle sizes and sets up the basis for an innovative concept of controlled ovarian hyperstimulation. Fertility and Sterility. 2004,81(6):1554–1559. Doi: https://doi.org/10.1016/j.fertnstert.2003.11.037 [PubMed] [Elsevier]

[8] Lainas T, Zorzovilis J, Petsas G, Stavropoulou G, Cazlaris H, Daskalaki V, Lainas G, Alexopoulou E. In a flexible antagonist protocol, earlier, criteria-based initiation of GnRH antagonist is associated with increased pregnancy rates in IVF. Human Reproduction. 2005,20(9):2426–2433. Doi:

https://doi.org/10.1093/humrep/dei106 [PubMed] [OxFord]

[9] Kolibianakis E, Zikopoulos K, Schiettecatte J, Smitz J, Tournaye H, Camus M, Steirteghem A, Devroey P. Profound LH suppression after GnRH antagonist administration is associated with a significantly higher ongoing pregnancy rate in IVF Human Reproduction. 2004,19(11):2490-2496. Doi: https://doi.org/10.1093/humrep/deh471 [PubMed] [OxFord]

[10] Copperman A, Benadiva C. Optimal usage of the GnRH antagonists: a review of the literature. Reproductive Biology and Endocrinology. 2013,11(1):20. Doi: https://doi.org/10.1186/1477-7827-11-20 [ResearchGate] [PMC]

[11] Pereira N, Neri Q, Lekovich J, Spandorfer S, Palermo G, Rosenwaks Z. Outcomes of intracytoplasmic sperm injection cycles for complete teratozoospermia: A case–control study using paired sibling oocytes. Biomed Research International. 2015,470819. Doi: http://dx.doi.org/10.1155/2015/470819 [PubMed] [PMC] [ResearchGate] [Hindawi]

[12] Alpha Scientist in Reproductive Medicine and ESHRE Special Interest Group of Embryology. The Istanbul consensus workshop on embryo assessment: proceeding of an expert meeting, Human Reproduction. 2011,26(6):1270–1283. Doi: https://doi.org/10.1093/humrep/der037 [PubMed] [OxFord]

[13] Younis J, Soltsman S, Izhaki I, Radin O, Bar-Ami S, Ben-Ami M. Early and short follicular gonadotropin-releasing hormone antagonist supplementation improves the meiotic status and competence of retrieved oocytes in in vitro fertilization–embryo transfer cycles. Fertility and Sterility. 2010,94(4):1350–1355. Doi: https://doi.org/10.1016/j.fertnstert.2009.08.033 [PubMed] [Elsevier]

[14] Huirne J, Homburg R, Lambalk C. Are GnRH antagonists comparable to agonists for use in IVF? Human Reproduction. 2007,22(11):2805-2813. Doi: https://doi.org/10.1093/humrep/dem270 [PubMed] [OxFord]

[15] Xing W, Lin H, Li Y, Yang D, Wang W, Zhang Q. Is the GnRH Antagonist Protocol Effective at Preventing OHSS for Potentially High Responders Undergoing IVF/ICSI? Public Library of

Science One. 2015,10(10):140286. Doi: https://doi.org/10.1371/journal.pone.0140286 [PLosOne] [PMC] [ResearchGate]

[16] Hamdine O, Broekmans F, Eijkemans M, Lambalk C, Fauser B, Laven J, Macklon N. Early initiation of gonadotropin-releasing hormone antagonist treatment results in a more stable endocrine milieu during the mid- and late-follicular phases: a randomized controlled trial comparing gonadotropin-releasing hormone antagonist initiation on cycle day 2 or 6. Fertility and Sterility. 2013,100(3):867-874. Doi: https://doi.org/10.1016/j.fertnstert.2013.05.031 [PubMed] [Elsevier]

[17] Park C, Hwang Y, Koo H, Kang I, Yang K, Song I. Early gonadotropin-releasing hormone antagonist start improves follicular synchronization and pregnancy outcome as compared to the conventional antagonist protocol. Clinical and Experimental Reproductive Medicine. 2014,41(4):158-164. Doi: https://doi.org/10.5653/cerm.2014.41.4.158 [PubMed] [CERM] [PMC] [ResearchGate]

[18] Elham R., Shahnaz A, Niloofar M, Afsaneh G, Zohreh Z. Comparison between the efficacy of short-term and fixed protocols of GnRH antagonist in IVF cycles. Acta Medica Mediterranea. 2017,33,785. [actamed]

[19] Blockeel C, Riva A, De Vos M, Haentjens P, Devroey P. Administration of a gonadotropin-releasing hormone antagonist during the 3 days before the initiation of the in vitro fertilization/intracytoplasmic sperm injection treatment cycle: impact on ovarian stimulation. A pilot study. Fertility and Sterility. 2011,95(5):1714–1719. Doi: https://doi.org/10.1016/j.fertnstert.2011.01.028 [PubMed] [Elsevier]

[20] Bosch E, Labarta E, Crespo J, Simón C, Remohí J, Jenkins J, Pellicer A. Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for in vitro fertilization: analysis of over 4000 cycles. Human Reproduction. 2010,25(8):2092–2100. Doi: https://doi.org/10.1093/humrep/deq125 [PubMed] [OxFord]

[21] Mascarenhas M, Kamath M, Chandy A, Kunjummen A. Progesterone/Estradiol Ratio as a Predictor in the ART Cycles with Premature Progesterone Elevation on the Day of hCG Trigger. The

Journal of Reproduction & Infertility. 2015,16(3): 155–161. [PubMed] [ResearchGate] [PMC]

[22] Labarta E, Martínez-Conejero JA, Alamá P, Horcajadas JA, Pellicer A, Simón C, Bosch E. Endometrial receptivity is affected in women with high circulating progesterone levels at the end of the follicular phase: a functional genomics analysis. Human Reprodroduction. 2011,26(7):1813-1825. Doi: https://doi.org/10.1093/humrep/der126 [PubMed] [OxFord]

[23] Younis J, Haddad S, Matilsky M, Ben-Ami M. Premature luteinization: could it be an early manifestation of low ovarian reserve? Fertility and Sterility. 1998,69(3):461–465. Doi: https://doi.org/10.1016/S0015-0282(97)00561-X [Elsevier]

[24] Cetinkaya E, Berker B, Aytac R, Atabekoglu C, Sonmezer M, Ozmen B. The value of the progesterone-to-estradiol ratio on the day of hCG administration in predicting ongoing pregnancy and live birth rates in normoresponders undergoing GnRH antagonist cycles. The European Journal of Obstetrics & Gynecology and Reproductive Biology. 2013,170(2):452-457. Doi: https://doi.org/10.1016/j.ejogrb.2013.07.033 [PubMed] [Elsevier]

[25] Kolibianakis E, Albano C, Camus M, Tournaye H, Van Steirteghem A, Devoroey P. Initiation of gonadotropin releasing hormone antagonist on day 1 as compared to day 6 of stimulation: effect on hormonal levels and follicular development in in vitro fertilization cycles. Journal of Clinical and Endocrinological Metabolism. 2003,88:5632-5637. Doi: https://doi.org/10.1210/jc.2003-030805 [PubMed][OxFord]

Biography

Dr. Khitam Malik Abdul-Hameed

She was born in Karbala in 1976. She received M.B.CH.B. from Al-Mustansiriya University, College of Medicine in 2001, the High Diploma in ART from Al-Nahrain University, the High Institute for Infertility Diagnosis and ART's in 2010, the Ph.D. in Infertility and Clinical Reproduction from Al Nahrain University, the High Institute for Infertility Diagnosis and ART's in 2019.

Dr. Ula M. R. Al-Kawaz

He is a Professor of Urology at Al-Nahrain University. Currently he is the dean of the high institute of infertility diagnosis and ARTs, Al Nahrain

University. He is a fellow of the Iraqi Board for Medical Specialization, Council of Urology since 2006, and a fellow of the European Board of Urology, since 2009. He published more than 27 articles both local and international. He supervised many M.Sc. and Ph.D. students.

Dr. Nadia Mudher Sulaiman Al-Hilli

She was born in Babylon, Iraq in 1976. She received the M.B.Ch.B. from College of Medicine, University of Babylon in 1999, the Diploma in Obstetrics & Gynecology in 2005, Iraqi Board in Obstetrics & Gynecology (FIBMS) in 2006, the Part I MRCOG in 2006, and the Certificate of minimal access surgery from the Iraqi Ministry of Health in 2017. Currently she is an Assistant Professor, and the Head of department in Obstetrics & Gynecology department, College of Medicine, University of Babylon. She is also a lecturer and supervisor of PhD students in the High Institute of Infertility and Assisted Reproductive Technologies since 2016. She is a member in the medical education committee in University of Babylon, College of Medicine, and a member of scientific committee of Obs. & Gyne. department in the University of Babylon, College of Medicine. She participated in more than, 25 Symposiums, 3 International Symposiums, 18 National Conferences, 15 International Conferences, 16 Workshops, and 9 Training Courses. She published more than 21 articles both local and international. She has more than 200 diagnostic & operative hysteroscopy operations & More than 200 diagnostic and operative laparoscopies performed for infertility patients.

How to cite:
Abdul-Hameed KM, Al-Kawaz UMR, Al-Hilli NM. Early and Short Follicular GnRH Antagonist (Sandwich) Protocol Versus Conventional GnRH Antagonist Protocol in Normal Responders; Iraqi Journal of Embryos and Infertility Researches (IJEIR), (2019);9(1):68-88.
Doi: http://doi.org/10.28969/IJEIR.v9.i1.r5