

Research Article

Influence of Elevated LH: FSH Ratio on IVF Outcome, Comparing the Impacts of Different Triggering Medicines

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Abstract

Objective: To study how elevated LH: FSH ratio influence IVF outcome in High response patients with different triggering medicines.

Design: This study was observational study performed in Medcare Fertility Centre, Dubai, UAE, between April 2016 to July 2017.

Patients: 81 high ovarian response women (AMH ≥ 4 ng/ml and LH/FSH ≥ 1).

Main outcome: Measures the impact of high LH/FSH ratio on IVF outcome in according to the triggering used.

Results: The LH/FSH ratio (when less than 1.5) has significant effect ($p < 0.05$) on the total number of M2 oocytes and subsequently on the fertilization rates (IVF outcome) but no significant ($p > 0.05$) effect on the number of total retrieved oocytes. But as LH/FSH ratio increases further (> 1.5), all parameters significantly decreased. Furthermore, patients using uhcg (Pregnyl®) recorded higher number of matured oocytes retrieved (81%) and improves fertility rate (66%) while GnRHa (Gonapeptyl.01®) has better effectiveness (114%) only on the total number of oocytes retrieved and it has less rate of oocytes maturation comparable to uhcg (74% vs. 81%).

Conclusion: This study observed that for high response patients, with LH/FSH ratio less than 1.5 has significant effect on total matured oocytes retrieved and subsequently the fertilization when we use of uhcg (Pregnyl®) as ovulation triggering medicine improves IVF outcome. Also, noted that when LH/FSH ratio more than 1.5, baseline characteristics parameters began to significantly decrease to find the triggering with GnRHa (Gonapeptyl.01®) proved to be better in the number of Oocytes retrieved and maturation rate of oocytes.

Keywords: High LH:FSH ratio; Human chorionic gonadotropin (HCG); Luteinising hormone(LH); Follicle stimulating hormone (FSH); *In vitro* fertilization (IVF); Ovulation triggering medicine; High ovarian response; Fertilization rate

Introduction

The accurate measurement of FSH and LH levels on Cycle day 3, in patients with diagnosis and monitoring and in therapeutic preparations for clinical use, is essential for safe and successful treatment [1] and also crucial for the success of an IVF cycle. Women with LH and FSH concentrations within the normal limits and those with an elevated LH/FSH ratio are typically defined as 'normal' and 'high' responders respectively [2]. Lenton et al. demonstrated that an increase in (FSH) occurs several years before (LH) [3] and elevated day 3 serum FSH/LH ratio may identify patients less likely to respond adequately to ovulation induction during IVF treatments. Patients with LH:FSH ratios were more likely to have highly responded to ovarian stimulation programme. The relative importance of LH/FSH ratio on fertilization rate is still debatable in the clinical settings [4]. Liu et al. demonstrated that day 3 LH/FSH ≥ 2 is associated with higher rates of cancellation of IVF cycles since there was less expecting the number of Oocytes retrieved together with very poor maturation [5]. The hypothesis in conducting the present study was to observe whether elevated day 3 LH/FSH ratio ≥ 1 and above in high response women are really impacting IVF outcome (total number of oocytes retrieved and Total matured oocytes) while using different triggering medicine for ovulation stimulation [6] (Figures 1 and 2).

Materials and Methods

Study design

This observational study was conducted using data accumulated in a single IVF centre (Medcare Fertility Clinic, Dubai). 81 high responder

patients undergoing IVF program from April 2016 to July 2017 were available for review, and Institutional review board of Medcare Fertility Clinic approval was collected because this was an observational study which was not routinely done. The patients were stimulated and treated in the same clinic and by same physicians and Embryology team.

Patient selection

High responder women undergoing ovarian stimulation for IVF/ICSI cycle regardless the infertility factor. Patients (n=81) underwent ovarian stimulation by either GnRH Agonist Long Protocol (Gonapeptyl0.1, Ferring Pharmaceuticals, Germany) or GnRH antagonist protocol (Cetrorelix Acetate Injection; Cetrotide, Serono, Italy). Ovarian stimulation was administered as recombinant FSH (rFSH; Gonal-F, Serono) alone or in combination with human menopausal Gonadotrophins (Menopure, Ferring Pharmaceuticals, Kiel, Germany). However, the majority of the patients (n=59) ovulation stimulation protocol was the antagonist which was randomly prescribed to trigger the ovulation as part of an assisted reproductive cycle by using rHCG, uHCG or GnRHa. A total of 81 patients were eligible using the inclusion criteria for high responder undergoing ovarian stimulation

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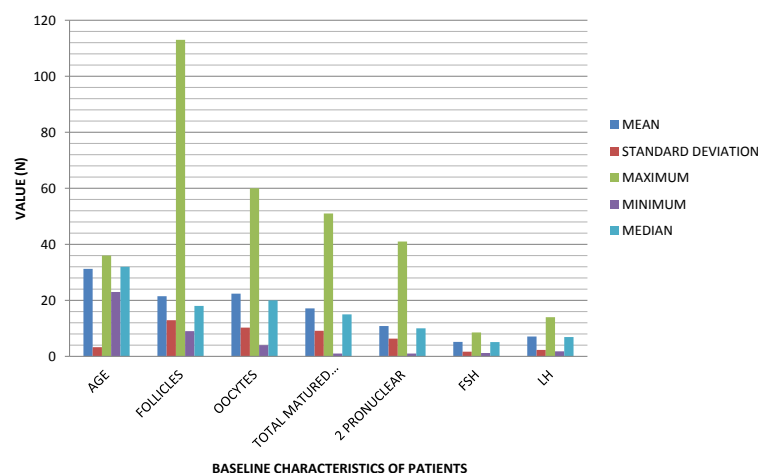


Figure 1: Baseline characteristics of patients.

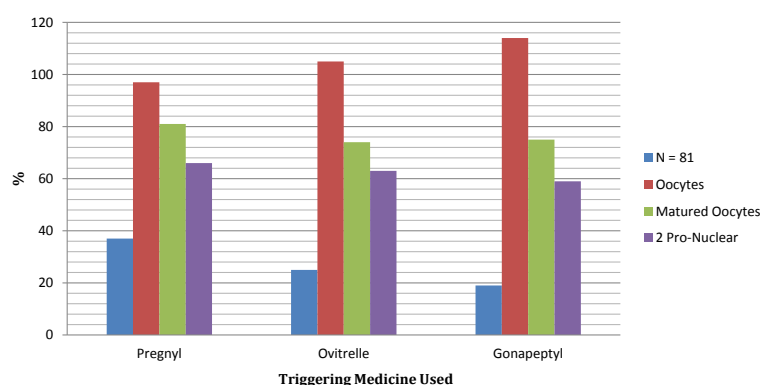


Figure 2: Relationship between triggering medicine and baseline characteristics.

cycles were recruited into this study. These criteria are:

- Age > 36 years old.
- Hyper response when AMH < 4 ng/ml (as per Medcare Laboratory references)
- LH/FSH ratio equal or more than 1 (basic on Cycle day 3)

Women with High Ovarian response (AMH < 4 ng/mL) who underwent IVF treatment were divided into those with LH/FSH ratio (>1 to <1.5), (>1.5 to <2), (>2 to <2.5), (>2.5 to <3) and (LH/FSH > 3).

The three groups of patients observed were:

- Group A (n=37) consisted of women triggered by Urinary HCG, Pregnyl[®] (Dose: 10,000 IU)
- Group B (n=25) comprised women triggered with recombinant HCG, Ovitrelle[®]
- Group C (n=19) consisted of women triggered by Agonist GnRH, Gonapeptyl[®] (Dose: 0.2 mg/ml)

Serial vaginal ultrasonography for response monitoring and measurement of serum Estradiol level, stimulation sheets were well completed with considering the policies in the protocol used, when reaching the right time for triggering; the patients were randomly divided into three groups according to the triggering Medicine used.

Oocyte retrieval

In all groups, 35 h after triggering medicine injection; transvaginal ultrasound-guided oocyte retrieval by using a 17 gauge needle was performed. The numbers of retrieved oocytes were recorded. Standard laboratory protocols were followed and approximately two hours after retrieval the cumulus cells were removed and an assessment of oocytes maturity under an inverted microscope was made.

Oocyte fertilization

After triggering of ovulation and oocytes retrieval, for Fertilizing rate, we consider the number of 2PN (2 pro-nuclei) oocytes seen after 18 h from injecting by ICSI the whole number of matured oocytes retrieved. The patient with freeze all oocytes to avoid hyper stimulation syndrome, were consider and study after thawing. We did not calculate the 2PN oocytes which occurred after late maturation of oocytes at meiosis stage 1(M1).

Outcome assessment

Primary outcomes: It was to study the impact of the triggering Medicine on: (i) the total number of oocytes retrieved per number of aspirated follicles (more than 14 mm); and (ii) the total number of mature oocytes obtained; (maturation rates of oocytes was defined as the numbers of mature oocytes per numbers of total retrieved oocytes).

Secondary outcomes: It was to compare the impacts of the triggering medicine on fertilization rates regarding the LH:FSH ratio.

Statistical analysis

Statistical analysis was carried out using the statistical package for the social science (IBM SPSS version 20.0 for Windows). Chi-square test was used to detect significant differences ($p < 0.05$) of the all variables.

Results

In our study, 81 patients participated, and were divided, as mentioned above, into 3 groups, Group A ($n=37$) consisted of women triggered by Urinary HCG, Pregnyl, Group B ($n=25$) comprised women triggered with recombinant HCG, Ovitrelle and Group C ($n=19$) consisted of women triggered by GnRHa (Gonapeptyl^{0.1}) respectively. Baseline marks of patients observed include age, a total number of follicles < 14 mm; total oocytes and mature oocytes retrieved were expressed in mean, standard error, median, standard deviation, minimum and maximum values, shown in Table 1.

The LH/FSH ratio (> 1 and < 1.5) has significant ($p < 0.05$) effect on total number of matured oocytes retrieved and subsequently on the fertilization rates (IVF outcome) (Tables 2 and 3) but no significant ($p > 0.05$) effect on number of retrieved oocytes (Tables 4 and 5) and as LH/FSH ratio increases further (> 1.5), all baseline characteristics parameters significantly decreased.

Furthermore, patients using uHCG (Pregnyl) recorded a higher

number of matured oocytes retrieved (81%), while GnRHa (Gonapeptyl^{0.1}) has better effectiveness (114%) on the total number of oocytes retrieved, a similar effect on oocytes maturation with rHCG (Ovitrelle) (74%-75%), respectively; but with uHCG showed higher effectiveness in maturation rate in comparison to the others 81% (Table 6).

For fertilizing rate (in checking 2PN) there was significance rate in using uHCG (66%) to decrease with the other Medicines; HCG (63%) and GnRHa (59%) when we consider the fertilizing after thawing in most of our patients since we do not do fresh embryo transfer and fertilizing when trigger by Gonapeptyl^{0.1} [7,8].

Discussion

In this study, it was observed that the LH/FSH ratio (> 1 and < 1.5) has significant ($p < 0.05$) effect Baseline featured of patients (total number of oocytes retrieved and matured oocytes) and subsequently on the fertilization rates (IVF outcome) and as LH/FSH ratio increases further (> 1.5), all parameters significantly decreased which is similar to the finding by Prasad et al. [9], where he found that women with an elevated LH/FSH ratio ≥ 2 required higher doses of gonadotrophins and the outcome of IVF was poor in these patients and they had poor maturation rate, fewer retrieved oocytes and fewer pregnancy rates which we had not study it in this article. Also, this study finds an increase in LH/FSH ratio effect on IVF outcome is similar to that by

N=81	Age (years)	Number of follicles ≤ 14 mm	Oocytes retrieved	Matured oocytes	2 PN	FSH	LH
Mean	31.24	21.48	22.39	17.13	10.83	5.16	7.09
Std. Error of mean	0.36	1.43	1.13	1.01	0.70	0.18	0.25
Median	32.00	18.00	20.00	15.00	10.00	5.10	6.90
Std. Deviation	3.26	12.89	10.25	9.11	6.34	1.66	2.28
Minimum	23.00	9.00	4.00	1.00	1.00	1.20	1.80
Maximum	36.00	113.00	60.00	51.00	41.00	8.54	13.99

Relationship of LH/FSH ratio to baseline characteristics

Table 1: Baseline characteristics of patients.

Range		<10	>10 ≤ 20	>20 ≤ 30	>30 ≤ 40	>50 ≤ 60	Total (n=81)
LH/FSH Ratio X²=28.253 df=16 p-value=0.029	>1 ≤ 1.5	11	35	11	5	0	62
	>1.5 ≤ 2	4	5	3	0	1	13
	>2 ≤ 2.5	2	0	1	0	0	3
	>2.5 ≤ 3	1	0	1	0	0	2
	>3	0	0	0	1	0	1

LH/FSH ratio versus matured retrieved ($p\text{-value}$ =significant)

Table 2: Total number of matured oocytes.

Range		<10	>10 ≤ 20	>20 ≤ 30	> 40 ≤ 50	Total (n=81)
LH/FSH Ratio X²=26.681 df=12 p-value=0.009	>1 ≤ 1.5	37	22	3	0	62
	>1.5 ≤ 2	8	4	0	1	13
	>2 ≤ 2.5	2	1	0	0	3
	>2.5 ≤ 3	2	0	0	0	2
	>3	0	0	1	0	1

LH/FSH ratio versus fertilized oocytes ($p\text{-value}$ =significant)

Table 3: Number of fertilized oocytes.

Range		<10	>10 ≤ 20	>20 ≤ 30	>30 ≤ 40	>50 ≤ 60	Total (n=81)
LH/FSH Ratio X²=16.349 df=20 p-value=0.695	>1 ≤ 1.5	5	31	21	4	1	62
	>1.5 ≤ 2	0	7	5	0	1	13
	>2 ≤ 2.5	0	2	0	1	0	3
	>2.5 ≤ 3	0	2	0	0	0	2
	>3	0	0	1	0	0	1

LH/FSH ratio versus follicle retrieved ($p\text{-value}$ =not significant)

Table 4: Total number of follicles ≤ 14 mm.

Range		<10	>10 ≤ 20	>20 ≤ 30	>30 ≤ 40	>40 ≤ 50	>50 ≤ 60	Total (n=81)
LH/FSH Ratio X ² =30.004 df=20 p-value=0.070	>1<1.5	4	29	18	8	3	0	62
	>1.5<2	2	4	5	1	0	1	13
	>2<2.5	2	0	1	0	0	0	3
	>2.5<3	1	0	1	0	0	0	2
	>3	0	0	0	1	0	0	1

Comment: LH/FSH ratio versus oocytes retrieved (p-value=not significant)

Table 5: Total number of oocytes retrieved.

Triggering medicine	N=81	Follicle	Oocytes	Matured oocytes	2 PN
Pregnyl	37	783	761 (97%)	615 (81%)	404 (66%)
Ovitrelle	25	413	432 (105%)	319 (74%)	201 (63%)
Gonapeptyl	19	545	621 (114%)	466 (75%)	273 (59%)

Table 6: Effect of triggering medicine

Barroso et al. [7] and Shrim et al. [10], which reported similar results in patients with elevated LH/FSH ratio >3. Also from this study, GnRHa (Gonapeptyl.01') has better effectiveness (114%) on total number of oocytes retrieved than other triggering medicine as well as similar effectiveness in stimulating oocytes maturation as uHCG (75% to 81%) which is in agreement with the concept by Shahar and Peter, 2013 which suggested that a 0.2 mg of gonadotrophin-releasing hormone agonist (GnRHa) can replace human chorionic gonadotrophin (HCG) as a trigger of final oocyte maturation and that GnRHa trigger offers important advantages, including significant prevention of ovarian hyperstimulation syndrome (OHSS), safety and comfort of patients. The benefit of GnRHa was also emphasized by Humaidan et al. [8], that GnRHa triggering is more physiological, resembling the natural midcycle surge of gonadotropins, without the extended action of HCG, resulting in luteal phase steroid levels closer to those of the natural cycle and the reported retrieval of more mature oocytes when compared with HCG triggering. GnRHa triggering significantly reduces or eliminates the OHSS risk after ovarian stimulation for IVF/ICSI in comparison with hCG triggering.

Moreover, Humaidan et al. [8] showed in a randomized controlled trial that more metaphase II oocytes were obtained after GnRHa trigger compared with after HCG trigger, which came similarly in our study.

Conclusion

This study observed that LH/FSH ratio between the range of >1 to <1.5 has significant effect on total matured oocytes retrieved and subsequently the fertilization (IVF outcome) in high response patients and also noted that at LH/FSH ratio increases (>1.5), baseline characteristics parameters began to significantly decrease; i.e., at higher LH/FSH (>1.5) ratio fertilization rate (IVF outcome) decreases [11]. Also, all triggering medicines had an effect on ovulation induction but GnRHa (Gonapeptyl.01') proved to be better in collecting the higher number of oocytes from the total number of follicles; and has a similar effect for maturation of oocytes. The use of uHCG (Pregnyl') as ovulation triggering medicine improves IVF outcome.

Implications for Research

More research and wide analysis is needed to assess the influence of

elevated LH/FSH ratio on IVF pregnancy rate comparing with patient with normal hormones profile.

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