The effects of adding Gonadotropin-releasing Hormone antagonist on cycle characteristics and pregnancy rate in stimulated Intrauterine Insemination (IUI) cycle

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ABSTRACT

A prospective randomised (comparative) study was conducted in the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies in AL-Nahrain University, Baghdad – Iraq, from the 1st of October 2018 till 1st of September 2019 involving seventy women of infertile couples with the same inclusion and exclusion criteria. They were randomly allocated into two groups receiving minimal ovarian stimulation protocol (Clomiphene Citrate and Human Menopausal Gonadotropin) with IUI adding flexible GnRH antagonist protocol (Cetrorelix) to the study group. IUI was done 40-44 hours after ovulation trigger. There were no significant statistical variances among control and study groups in demographic characteristics concerning: age, BMI, type, duration and cause of infertility. There was no important variance in a mean day of trigger among control and study groups, 12.43 ±1.56 versus 13.11 ±1.49, at the same order (p = 0.064). The Mean number of dominant follicles was considerably greater in study groups than that of the control group, 2.40 ±1.03 versus 1.89 ±0.83, respectively (p = 0.025). Mean serum Estradiol of the study group was significantly higher than that of the control group, 478.68 ±423.61 versus 273.12 ±254.57, respectively (p = 0.016). The proportion of women with LH> 10 were significantly less frequent in the study group in comparison with the control group, 22.9% versus 68.6%, at the same order (p < 0.001). There was no important variance in mean serum Progesterone among control and study groups. There was no significant difference in the characteristic of the dominant follicle, ruptured versus not ruptured, (p = 0.124) on the day of IUI. The pregnancy rate was higher in the study group when compared with the control group; however, the difference in pregnancy rate doesn’t reach statistical import (p = 0.145)

INTRODUCTION

An important health issue that is faced by a newly married couple is the problem of infertility in which the couples failed to have a baby following 12 months of uninterrupted adequate natural intercourse (Borght and Wyns, 2018). This problem is relatively common worldwide with a prevalence rate of approximately 15 % (Agarwal et al., 2015); however, the prevalence rate shows some regional variation depending on predominant causes of infertility in a particular geographic
area (Datta et al., 2016).

The invention and practising assisted reproductive techniques have dramatically reduced the burden of such a health issue (Almasi-Hashiani et al., 2019; Huang and Rosenwaks, 2014). One of the old methods with this regard was intrauterine insemination (IUI) (Allahbadia, 2017; Ombelet and Robays, 2015). (COS) with IU. I have appeared to be accompanied by a significant improvement in clinical pregnancy outcome according to several authors, which has been attributed to higher number of ova to be present at fertilisation site by ensuring two to three dominant follicles (Allahbadia, 2017; Taerk et al., 2017; Zeng et al., 2015).

Nevertheless, the recruitment of a higher number of follicles following COS is associated with an abrupt rise in serum Estradiol level (E2) leading to a risk of premature luteinising hormone (LH) surge and subsequent premature luteinisation in several cycles (Depalo et al., 2018; Wang et al., 2016). It has been shown that premature luteinisation is accompanied by detrimental drawbacks concerning oocyte quality, fertilisation, and embryo implantation (Irani et al., 2017; Kumar and Sait, 2011; Sönmez et al., 2009). Growing evidence of research data supports the use of gonadotropin-releasing hormone antagonists (GnRH-ant) to avoid prevent premature LH surge particularly in vitro fertilisation (IVF) cycles based on immediate suppression of gonadotropin secretion by the pituitary gland. The use of such intervention is associated with significant improvement of the reproductive outcomes following COS (Depalo et al., 2018).

In the current study, the aim was to evaluate the effect of using a flexible protocol of Gonadotropin-releasing Hormone Antagonist (Cetrorelix) on follicular growth and maturation, ovulation rate and on pregnancy rate in stimulated Intrauterine insemination cycles.

**PATIENTS AND METHODS**

A prospective randomised (comparative) study was conducted in the great Institute for Infertility Diagnosis, Assisted Reproductive Technologies in Al-Nahrain University, Baghdad – Iraq from the 1st of October 2018 till 1st of September 2019 involving seventy women of infertile couples with the same inclusion and exclusion criteria and they were randomly allocated into two groups receiving minimal ovarian stimulation protocol (Clomiphene Citrate and Human Menopausal Gonadotropin) with IU, adding flexible GnRH antagonist protocol (Cetrorelix) to the study group. Cycle monitoring was achieved by serial Ultrasound examinations to follow follicular development and endometrial thickness. A blood sample was taken to measure Estradiol, LH and Progesterone on the day of ovulation trigger. IUI was done 40-44 hours after ovulation trigger.

The study was sanctioned via institutional ethical approval committee, and written consent was attained of every couple participating in the current study. The obtained data was then transformed into an SPSS spreadsheet (IBM, Chicago, USA, version 23) to summarise, analyse and present these data.

**RESULTS**

**Demographic Characteristics of Subfertile Women in the Study**

There was no significant difference in any of the demographic characteristics (P > 0.05) in the control and study group. Table 1.

**Serum Hormonal Levels at Cycle Day 2 in Control and Study Groups**

Comparison of mean serum hormonal levels at cycle day 2 in control and study groups showed no statistical difference. Table 2.

**Characteristics of Stimulation in Control and Study Groups**

Stimulation characteristics of control and study groups are shown in Table 3. Mean number of HMG was significantly higher in the study group than in control group, 3.97 ± 1.44 versus 2.51 ± 1.09, respectively (p < 0.001). Cetrorelix was given only to study group with a mean of 2.31 ± 0.53. There was no significant difference in the mean day of trigger between control and study groups, 12.43 ± 1.56 versus 13.11 ± 1.49, respectively (p= 0.064). Mean number of dominant follicles was significantly higher in study groups than that of the control group, 2.40 ± 1.03 versus 1.89 ± 0.83, respectively (p = 0.025), however.

Besides, there was no significant difference in mean serum LH between the control and study group, 16.74 ± 14.48 versus 11.67 ± 11.85, respectively (p = 0.114). However, when women were categorized according to LH level, < 10mIU/ml versus > 10mIU/ml, the proportion of women with LH > 10mIU/ml were significantly less frequent in study group in comparison with control group, 22.9 % versus 68.6 %, respectively (p < 0.001), Table 3. Nonetheless, there was no significant difference in mean serum progesterone between control and study groups, 0.67 ± 0.70 versus 0.47 ± 0.43, respectively (p = 0.148), even when women were categorised into those with serum progesterone ≥
Table 1: Demographic characteristics of subfertile women

| Characteristic       | Total n = 70 | Control group n = 35 | Study group n = 35 | P          |
|----------------------|--------------|-----------------------|---------------------|------------|
| **Age (years)**      |              |                       |                     |            |
| Mean ±SD             | 26.89 ± 4.82 | 25.89 ± 4.33          | 27.89 ± 5.13        | 0.082 † NS |
| <35                  | 64 (91.4)    | 33 (94.3)             | 31 (88.6)           | 0.669 ¥ NS |
| ≥ 35                 | 6 (8.6)      | 2 (5.7)               | 4 (11.4)            |            |
| **BMI (kg/m²)**      |              |                       |                     |            |
| Mean ±SD             | 25.20 ± 2.89 | 25.11 ± 3.06          | 25.29 ± 2.74        | 0.801 † NS |
| Normal               | 32 (45.7)    | 18 (51.4)             | 14 (40.0)           | 0.607 ¥ NS |
| Overweight           | 32 (45.7)    | 14 (40.0)             | 18 (51.4)           |            |
| Class I obesity      | 6 (8.6)      | 3 (8.6)               | 3 (8.6)             |            |
| **Duration (years)** |              |                       |                     |            |
| Mean ±SD             | 4.94 ± 2.73  | 5.18 ± 2.68           | 4.69 ± 2.79         | 0.455 † NS |
| <5                   | 35 (50.0)    | 15 (42.9)             | 20 (57.1)           | 0.479 ¥ NS |
| 5-10                 | 33 (47.1)    | 19 (54.3)             | 14 (40.0)           |            |
| >10                  | 2 (2.9)      | 1 (2.9)               | 1 (2.9)             |            |
| **Type of infertility** |            |                       |                     |            |
| Primary              | 53 (75.7)    | 27 (77.1)             | 26 (74.3)           | 0.780 ¥ NS |
| Secondary            | 17 (24.3)    | 8 (22.9)              | 9 (25.7)            |            |
| **Cause of infertility** |          |                       |                     |            |
| PCOS                 | 27 (38.6)    | 12 (34.3)             | 15 (42.9)           | 0.330 ¥ NS |
| Combined factor      | 15 (21.4)    | 6 (17.1)              | 9 (25.7)            |            |
| Unexplained          | 28 (40.0)    | 17 (48.6)             | 11 (31.4)           |            |

n: number of cases; data were expressed as mean ± standard deviation; †: independent samples t-test; NS: not significant; P ≤ 0.05

Table 2: Cycle day 2 hormonal levels in control and study groups

| Hormone              | Total n = 70 | Control group n = 35 | Study group n = 35 | P          |
|----------------------|--------------|-----------------------|---------------------|------------|
| CD2 FSH (mIU/ml)     | 7.89 ± 2.09  | 7.89 ± 2.15           | 7.89 ± 2.06         | 0.999 † NS |
| CD2 LH (mIU/ml)      | 6.49 ± 5.96  | 6.80 ± 7.69           | 6.18 ± 3.56         | 0.666 † NS |
| CD2 E2 (Pg/ml)       | 30.33 ± 18.21| 27.30 ± 10.87         | 33.36 ± 23.14       | 0.165 † NS |
| Prolactin (ng/ml)    | 19.67 ± 9.06 | 19.96 ± 9.22          | 19.38 ± 9.01        | 0.790 † NS |
| Testosterone (ng/ml) | 30.65 ± 16.50| 27.65 ± 16.06         | 33.64 ± 16.63       | 0.130 † NS |
| TSH (mIU/ml)         | 2.09 ± 0.91  | 2.07 ± 0.88           | 2.10 ± 0.96         | 0.875 † NS |

n: number of cases; data were expressed as mean ± standard deviation; †: independent samples t-test; NS: not significant; P ≤ 0.05
Table 3: Characteristic of stimulation of control and study groups on day of trigger

| Characteristic                  | Total n = 70 | Control group n = 35 | Study group n = 35 | P     |
|---------------------------------|--------------|----------------------|--------------------|-------|
| Number of hMG ampoules          | 3.24 ± 1.47  | 2.51 ± 1.09          | 3.97 ± 1.44        | <0.001† |
|                                |              |                      |                    | HS    |
| Number of Cetrorelix ampoules   | ——           | ——                   | 2.31 ± 0.53        | ——    |
| Day of Trigger                  | 12.77 ± 1.55 | 12.43 ± 1.56         | 13.11 ± 1.49       | 0.064† |
|                                |              |                      |                    | NS    |
| Number of Dominant Follicles    | 2.14 ± 0.97  | 1.89 ± 0.83          | 2.40 ± 1.03        | 0.025† |
|                                |              |                      |                    | S     |
| LH at trigger mIU/ml            | 14.21 ± 13.38| 16.74 ± 14.48        | 11.67 ± 11.85      | 0.114† |
|                                |              |                      |                    | NS    |
| ≥ 10 mIU/ml                    | 32 (45.7 %)  | 24 (68.6 %)          | 8 (22.9 %)         | < 0.001 ¥ |
| <10 mIU/ml                     | 38 (54.3 %)  | 11 (31.4 %)          | 27 (77.1 %)        |       |
| Progesterone (ng/ml)            | 0.57 ± 0.58  | 0.67 ± 0.70          | 0.47 ± 0.43        | 0.148† |
|                                |              |                      |                    | NS    |
| ≥ 1 ng/ml                      | 12 (17.1 %)  | 8 (22.9 %)           | 4 (11.4 %)         | 0.205 ¥ |
| <1 ng/ml                       | 58 (82.9 %)  | 27 (77.1 %)          | 31 (80.6 %)        |       |
| Estradiol (Pg/ml)              | 375.90 ± 362.04| 273.12 ± 254.57     | 478.68 ± 423.61    | 0.016† |
|                                |              |                      |                    | S     |

n: number of cases; data were expressed as either mean ± standard deviation or number (%); †: independent samples t-test; ¥: Chi-square test; HS: Highly significant at P ≤ 0.01; NS: not significant at P ≤ 0.05; S: significant at P ≤ 0.05

Table 4: Dominant Follicle on day of IUI

| Dominant follicle | Total n = 70 | Control group n = 35 | Study group n = 35 | P  |
|-------------------|--------------|----------------------|--------------------|----|
| Rupture           | 57 (81.4 %)  | 26 (74.3 %)          | 31 (88.6 %)        | 0.124 ¥ |
| Not ruptured      | 13 (18.6 %)  | 9 (25.7 %)           | 4 (11.4 %)         |    |

n: number of cases; (%) ¥: Chi-square test; NS: not significant at P ≤ 0.05

Table 5: Pregnancy outcome of infertile women enrolled in the study

| Pregnancy | Total n = 70 | Control group n = 35 | Study group n = 35 | χ² | P    |
|-----------|--------------|----------------------|--------------------|----|------|
| Positive  | 15 21.4 %    | 5 14.3 %             | 10 28.6 %          | 2.121 | 0.145 |
| Negative  | 55 78.6 %    | 30 85.7 %            | 25 71.4 %          |     | ¥ NS |

n: number of cases; ¥: Chi-square test; NS: not significant at P ≤ 0.05

1ng/ml versus those with serum progesterone < 1ng/ml, the difference was statistically insignificant (p = 0.205), as shown in Table 3. Besides, mean serum Estradiol of the study group was significantly higher than that of the control group, 478.68 ± 423.61 versus 273.12 ± 254.57, respectively (p = 0.016), Table 3.

There was no significant difference in the characteristic of the dominant follicle, ruptured versus not ruptured, (p= 0.124) examined on the day of IUI by transvaginal Ultrasound Table 4.

Pregnancy Outcome

Overall the positive pregnancy outcome of the entire sample subjected to IUI was 15 out of 70, accounting for 21.4 %. The positive pregnancy rate of the study group was 28.6 % (10 out of 35), and that of the control group was 14.3 % (5 out of 35).

Thus, the pregnancy rate was higher in the study group when compared to that of the control group;
Table 6: Stimulation characteristics of infertile women according to pregnancy outcome

| Characteristic          | Negative pregnancy n = 15 | Positive pregnancy n = 55 | P     |
|-------------------------|---------------------------|---------------------------|-------|
| Number of hMG ampouls   | 3.07 ± 1.37               | 3.87 ± 1.68               | 0.063† |
| Day of Trigger          | 12.65 ± 1.62              | 13.20 ± 1.21              | 0.230† |
| Number of dominant Follicles | 2.05 ± 0.95              | 2.47 ± 0.99               | 0.145† |
| LH (mIU/ml)             | 14.82 ± 14.58             | 11.96 ± 7.50              | 0.467† |
| Progesterone (ng/ml)    | 0.61 ± 0.64               | 0.42 ± 0.26               | 0.265† |
| Estradiol Pg/ml         | 316.21 ± 307.19           | 594.77 ± 465.51           | 0.007† HS |

n: number of cases; data were expressed as mean ± standard deviation; †: independent samples t-test; NS: not significant at P ≤ 0.05; HS: Highly significant at P ≤ 0.01

however, the difference in pregnancy rate did not reach statistical significance (P = 0.145), as shown in Table 5.

Correlations of Pregnancy Outcome to Stimulation Characteristics

Results of parameters assessed in the day of ovulation trigger are shown in Table 6. Positive pregnancy outcome was not significantly correlated to a number of hMG (p = 0.063). In addition, it was not significantly correlated today of trigger (p = 0.230) and pregnancy was not significantly correlated to number of dominant follicles (p = 0.145). Pregnancy was not significantly correlated to mean serum LH (mIU/ml) (p = 0.467) Furthermore, it was not significantly correlated to serum Progesterone (ng/ml) (p = 0.265).

However, mean serum Estradiol (Pg/ml) was significantly higher in women with successful pregnancy in comparison with those with negative pregnancy outcome, 594.77 ± 465.51 versus 316.21 ± 307.19, respectively (p = 0.007), Table 6.

DISCUSSION

Premature ovulation is linked to early LH surge (Cantineau and Cohlen, 2007). It has been stated that premature LH surge can be identified when the level of LH is > 1010mIU/ml (Cantineau and Cohlen, 2007). In the current study, we observed that the level of LH at trigger was lower in the study group than in the group control, but the variance was insignificant in terms of statistics. Nevertheless, we observed that women in the study group with premature LH surge (LH level of more than 10mIU/ml) were significantly less frequent than those in the control group, 8 out of 35 (22.9 %) versus 24 out of 35 (68.6 %) and the difference was highly significant from a statistical perspective (P < 0.001). This observation indicates that the use of GnRH antagonist (Cetrorelix) has significantly reduced the phenomenon of premature LH surge associated with minimal ovarian stimulation protocol. This finding is similar to other authors (Wadhwa et al., 2016). However, in the current study, there was no significant difference in mean progesterone level at the day of trigger between study and control group, indicating that the use of GnRH antagonist (Cetrorelix) does not affect serum progesterone level. It has been suggested that serum progesterone level of ≥ 1 ng/ml at the day of a trigger is also indicative of premature LH surge (Sönmezer et al., 2009); however, in the current study, there was no significant difference when women were categorised into those with serum progesterone ≥ 1 ng/ml versus those with serum progesterone < 1ng/ml, therefore we suggest that the role of progesterone in identifying premature ovulation remains controversial and needs more research work to reach a consensus.

It is worth to mention that serum Estradiol level at trigger day was significantly higher in the study group than in the control group in the current study. This observation indicates that low serum estrogen level at the day of a trigger is associated with premature ovulation; whereas, high Estradiol at the day of a trigger is associated with less early LH surge and ovulation. This observation is similar to that of other authors (Lu et al., 2018). Another striking observation in the current study is that the mean number of dominant follicles obtained in the study...
group was meaningfully greater than that obtained in the group control. This is in line with the observation made by Tiwary et al. (2015) similarly reported a considerably greater follicle number in association with the addition of GnRH antagonist to conventional minimal stimulation protocol. The current study finding was similar to that of (Gómez-Palomares et al., 2005) and to (Espejo-Catena et al., 2016). Despite the fact that the important rise in the number of follicles > 16 mm in hCG day, (Dansuk et al., 2015) revealed no significant increase in pregnancy rate when GnRH antagonist was utilised in ovulation induction with gonadotropin and IUI cycles (8.9% versus 7.9%). In contradiction to this study, the mean number of dominant follicles was no significantly different between study and control according to Wadiwa et al. (2016).

Despite the delay in LH surge and prevention of premature ovulation as well as the obtaining of a higher number of dominant follicles in association with Cetrorelix use, the clinical pregnancy rate at the end of the study was insignificantly different between study and control group. Still, at least it was higher in the study group than in control group, 28.6 % (10 out of 35) and 14.3 % (5 out of 35), respectively.

Allowing the study led via Kamath et al. (2013), the occurrence of premature LH surge and premature luteinisation was lesser in the antagonist group as related to the group control not. GnRH antagonist (5 vs. 10.3 %, p = 0.45 and 5 % vs. 13.8, p = 0.31) but no statistically important. The clinical pregnancy rates were lesser in the group antagonist (2.8 vs 10 %, p = 0.12)

A meta-analysis conducted by Luo et al. (2014) suggested that “GnRH-ant can reduce the incidence of PL and increase the CPR when used in COS/IUI cycles, and it was especially useful for non-PCOS patients. However, evidence to support its use in PCOS patients is still insufficient”. (Ozelci et al., 2019) include only women with PCOS managed by COH and IUI and found that the mean Estradiol, LH and progesterone in hCG day were significantly lower in the group receiving GnRH antagonist and a slight improvement in pregnancy rate which don’t reach a level of import (25% vs 14.9%, p = 0.96). A study via Cantineau and Cohen (2007) has reported no rise in live birth rates vi addition a Gn. RH antagonist in cycles of COS in a program IUI. The study conducted in 2006, Lambalk et al. (2006) evaluated the role of the GnRH antagonist (ganirelix) in the handling of subfertile couples. Though the effect of a premature increase of progesterone in IV F cycled was explained, its part in IUI is not pure. Ghasemzadeh et al. (2020) conduct a survey of relative among midscale Progesterone level for IUI. Cycle success rate and appeared that the level improved of progesterone in the h.C.G injection day is accompanied by less rate pregnancy; the result is inconsistent with the current study result.

Singh et al. (2015) supported a concept that increasing P4 levels is a reflection of the number of follicles and not due to premature luteinisation and concluded a negative association of increasing P4 and pregnancy in ICSI cycles, this is dissimilar to this study result adopting the minimal ovarian stimulation protocol with the lesser number of dominant on the trigger day.

The mechanism perfect that causes enhancement of the progesterone is subject controversial between researchers. It could be connected with the rising activity of the steroidogenic of ovary due to excitation of various oocytes of exogenous FSH. (Bosch et al., 2010; Elnashar, 2010).

In the current study, mean serum Estradiol on the day of ovulation trigger was significantly higher in women with successful pregnancy in comparison with those with negative pregnancy outcome. Present results are in convention to (Jawed et al., 2016) who argued that high E2 measured on the day of hCG administration reflects response and pregnancy outcome relating to higher oocyte number and improve implantation.

rises rates success of high levels of the peak; some studies appear more mediocre outcomes due to the detrimental effect of increasing Estrogen on endometrial susceptibility (Kutlu et al., 2016). Concentrations of the Estradiol is no very rise in cycles IUI that they should be detrimental to endometrial susceptibility, it might be utilised as a reflection of oocyte quality, and this is the case in the current study. (Kutlu et al., 2016).

This study findings reflect that pregnancy outcome in every IUI cycle is a function of a multitude of variables including the age of women, the number of mature oocytes, total motile sperm count, successful fertilisation, good quality embryo and successful implantation and, not merely a single factor of these.

In (Vitagliano et al., 2019) meta-analysis, no difference was observed in total gonadotrophin dose (MD = -26.51; 95% CI -22.85 to 75.86, I2 = 84%) among groups, this is in contrary to this study result in which the mean number of hMG was considerably higher in the study group than in the group control, 3.97 ± 1.44 versus 2.51 ± 1.09, respectively (p < 0.001).
CONCLUSION

Despite that Gonadotropic Releasing Hormone antagonist (Cetrorelix) is useful in the prevention of premature LH surge, the increase in pregnancy rate was statistically insignificant after addition of Cetrorelix in stimulated IUI cycles. Adding Gonadotropic Releasing Hormone antagonist flexible protocol in ovarian stimulation – IUI cycles increased the number of dominant follicles and Estradiol level on the day of ovulation trigger. Since Intrauterine Insemination success is multifactorial, maturing multiple follicles could not solely predict cycle success. However, Estradiol level at the day of trigger affected pregnancy rate.

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Ethical clearance

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Conflict of interest

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