INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a principal endocrine system disorder affecting women of reproductive age [1]. It is a chronic disease and represents a major health and economic burden [2]. It has important and various implications, including reproductive, metabolic, and psychological features [3]. Diagnosis of PCOS largely depends on Rotterdam criteria which require two of three cardinal features: Oligo- or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound [4].

Although clomiphene citrate (CC) is still the first-line ovulation induction (OI) treatment, Aromatase inhibitors (letrozole) score over CC for the OI in anovulatory infertile polycystic ovary women in terms of avoiding adverse effects and lower risk of multiple pregnancies [5]. In a meta-analysis of 26 randomized controlled trials (RCTs), letrozole was found to enhance live birth and pregnancy rates in subfertile women with anovulatory PCOS, compared to CC [6]. Therefore, letrozole with its oral route of administration, safety profile, and effectiveness in OI and ovarian stimulation is an attractive option and can be considered the first-line option for induction of ovulation in PCOS women [7]. Gonadotropin therapy considered second-line therapy in anovulatory PCOS women who fail to conceive on OI [8].

The luteal phase is defined as the period between the ovulation and pregnancy occurrence or the start of the new menstruation [9].

Luteal phase deficiency (LPD) is a clinical expression of Corpus Luteal deficiency results from different pathophysiological mechanisms, comprise abnormal follicular development, and secretory dysfunction and both interne lead to the inadequate transformation of the endometrium to secretory, resulting in defective implantation of the blastocyst and deficient embryonic development [10].

LPD and PCOS are independent disorders, but they share common pathophysiological profiles. Many factors associated with PCOS, such as hyperinsulinemia, elevated antiminaler hormone levels, and impaired angiogenesis are also involved in the pathophysiology of LPD. Given the importance of CL function for the achievement and maintenance of pregnancy, LPD could be another possible factor involved in infertility observed in women with PCOS [11]. On the other hand, OI with the change in endocrine metabolism has negative effect on the luteal phase function [9].

The objective of the current study was to assess the effect of progesterone as luteal phase support (LPS) on pregnancy rates in infertile PCOS patients who used letrozole alone or letrozole gonadotropin combination regime as a method of OI.

METHODS

A prospective randomized clinical study conducted in the infertility clinic - Al-Yarmouk Teaching Hospital in Baghdad/Iraq from June 2016 to January 2018 after approval of the ethical and scientific committee of the obstetrics and gynecology department.

Unovulatory infertile women with PCOS between 20 and 35 years of age had been enrolled in the study after taking informed written consent from them. Modified Rotterdam criteria had been used to diagnose the PCOS. Thyroid dysfunction, hyperprolactinemia, and other causes of hyperandrogenism had been excluded. All participants had normal hysterosalpingography, and their partner had a normal seminal fluid analysis.

A total of 149 infertile polycystic ovary women who achieved ovulation using letrozole alone or letrozole with gonadotropin as OI protocol enrolled, a woman who failed to show a response to both regimes were...
excluded from the study. Accordingly, the study group divided into two: Group A (letrozole group, no=99) and Group B (letrozole gonadotropin group, no=50).

All the participant start treatment on 2nd or 3rd day cycle once baseline transvaginal ultrasound is done and no ovarian cyst was seen.

Group A women (no=99) received 5mg letrozole from day 2 or 3 of the cycle and followed up by ultrasound till the time of ovulation when the leading follicle ≥17, then ovulation triggered by hCG (oviril). At that time, the 100 women were re-randomized into two subgroups, Group A - one (no=49) who continue without LPS till 14 days after triggering when PT with or without ultrasound was done to confirm biochemical and or clinical pregnancy. The second subgroup A - two (no=50) they continue on LPS by oral progesterone (dydrogesterone 10 mg twice daily) starting on the day after hCG triggering and continue for 14 days when pregnancy test with or without ultrasound done to confirm biochemical and or clinical pregnancy.

Group B women (no=50) received letrozole 5mg from day 2 or 3 of the cycle for 5 days and reassessed by ultrasound, if no response (no B: cycle ≥10 mm) and recombinant gonadotropin FSH (Gonal F) were added for 3–5 days (3–5 ampoules 75 IU) with meticulous ultrasound monitoring until one follicle at least, and not more than two, ≥17 mm achieved then triggering by hCG (oviril). The women then were re-randomized again into two subgroups; Group B - one (no=25) who continue without LPS until 14 days after triggering when PT with or without ultrasound was done to confirm biochemical and or clinical pregnancy. The second subgroup B - two (no=25) they continue on LPS by oral progesterone (dydrogesterone 10 mg twice daily) the day after hCG triggering and continue for 14 days when pregnancy test with or without ultrasound done to confirm biochemical and or clinical pregnancy.

The protocol used for participating women in each group was repeated for 3 cycles unless biochemical or clinical pregnancy happened which it was the primary outcome measure.

Statistical analysis

SPSS 20.0.0, GraphPad Prism 7.0 software package used to make the statistical analysis, p-value considered when appropriate to be significant if <0.05.

RESULTS

Mean age of all patients was 26.7±2.4 years, with mean body mass index (BMI) 26.2±1.4, 65.1% was null parity with a mean duration of infertility 21.8±7.1 months, as illustrated in Table 1.

BMI, parity, and duration of infertility were not statistically significant among the different groups, while there was a statistical difference in the mean age between patients receiving letrozole with letrozole support compared to letrozole with gonadotropin without LPS, as illustrated in Table 2.

There was no significant difference in the size of the dominant follicle between patients receiving letrozole only and the patient receiving letrozole with LPS. There was also no significant difference between patients on letrozole gonadotropin alone and patients receiving letrozole gonadotropin with LPS. On the contrary, patients receiving gonadotropin with or without LPS had significantly higher follicle size compared to their respective group that on letrozole only. The number of dominant follicles was significantly higher in patients receiving gonadotropin. There was no significant difference in the endometrial thickness and number of cycles among the different groups, there was no significant difference in the rate of positive pregnancy and US findings (GS with or without fetal pole and positive fetal heart) between the groups (although the rate of positive PT is higher for those on LPS) as illustrated in Table 3.

Patients receiving LPS achieve nonsignificantly higher rate of positive pregnancy test compared to letrozole alone or letrozole gonadotropin without LPS, as illustrated in Table 4.

After adjustment of possible confounders; patients receiving letrozole with gonadotropin with LPS had significantly correlated with a successful pregnancy test, while patients receiving letrozole with LPS had non-significantly correlated with positive PT, all these in comparison to patients receiving letrozole only without LPS, parity significantly correlated with positive PT, as illustrated in Table 5.

DISCUSSION

The benefit of progesterone for LPS in in vitro fertilization (IVF) cycles has been proved beyond doubt, but there is little agreement about the use of LPS following OI [14].

Since most of the patients with anovulatory infertility are treated with either CC or letrozole as a first line, it is vital to recognize women who may preferentially benefit from LPS before moving to more invasive assisted reproductive technologies. Patients with PCOS are one group that may benefit from progesterone supplementation [15].

Few studies were done to evaluate LPS in OI cycles using aromatase inhibitors.

In our study, two group had been taken; Group A includes 99 women who study the role of progesterone for LPS in OI cycles using aromatase inhibitors. Our study results go with Foroozanfard et al. results which showed LPS cycle was associated with a 10% higher pregnancy rate than cycles without, although this difference did not reach statistically significant, and they ended up with conclusion that administration of vaginal progesterone for LPS may improve the pregnancy rate in women with PCOS using letrozole or CC in combination with HMG for OI [17].

Our study results go with Yazici et al. who study the role of LPS on gonadotropin OI cycles in patients with PCOS and end up in conclusion that there might be a clinical benefit of luteal progesterone supplementation on OI/intrauterine insemination (IUI) cycles for

| Table 1: Basic characteristics of the patients |
|---------------------------------------------|
| Variables | Value |
| Number | 149 |
| Age (years), mean±SD (range) | 26.7±2.4 (21.0–33.0) |
| BMI [kg/m²], mean±SD (range) | 26.2±1.4 (18.0–29.0) |
| Parity, no. (%) | |
| Null parity | 97 (65.1) |
| Prime parity | 44 (29.5) |
| Second parity | 8 (5.4) |
| Duration of infertility (months), mean±SD (range) | 21.8±7.1 (12.0–48.0) |
| SD: Standard deviation, BMI: Body mass index |
women with PCOS, although the results again did not reach a statistically significant [18].

Hill et al. did a systematic review and meta-analysis on Progesterone as a luteal support after OI but with IUI and ended up in a conclusion that LPS may be of benefit to women undergoing OI with PCOS women using letrozole alone or with gonadotropins may improve pregnancy rate and its value is more pronounce in gonadotropin OI regimes. Our study shows that administration of progesterone as LPS in infertile PCOS women undergoing OI [20].

In terms of route of administration, progesterone used as LPS in our study was oral Dydrogesterone (10 mg twice daily). This route of use in the study was supported by systematic review and meta-analysis of RCT done by Barbosa et al. who ended up in a conclusion that the use of oral dydrogesterone seems to be as effective as vaginal progesterone for LPS in ART cycles and appears to be better tolerated [21]; furthermore, oral route efficacy confirmed in IVF by Phase III-RCT that compares the efficacy, safety, and tolerability of oral dydrogesterone versus micronized vaginal progesterone for LPS [22]. Similar reports on equivalent efficacy were documented from RCTs in Iran and India [23,24].

Table 2: Clinical characteristics according to the therapy

| Variables                  | Letrozole alone | Letrozole with LPS | Letrozole gonadotropin alone | Letrozole gonadotropin LPS | p value |
|----------------------------|----------------|-------------------|------------------------------|----------------------------|---------|
| Number                     | 49             | 50                | 25                           | 25                         | -       |
| Age                        | 26.6±2.3       | 25.9±2.5          | 28.0±2.3                     | 27.1±2.1                   | 0.005   |
| BMI                        | 26.1±1.6       | 25.9±1.3          | 26.6±1.2                     | 26.4±1.2                   | 0.138   |
| Parity (%)                 |                |                   |                              |                            | 0.812   |
| Null parity                | 28 (57.1)      | 36 (72.0)         | 16 (64.0)                    | 17 (68.0)                  |         |
| Prime parity               | 17 (34.7)      | 12 (24.0)         | 8 (32.0)                     | 7 (28.0)                   |         |
| Second parity              | 4 (8.2)        | 2 (4.0)           | 1 (4.0)                      | 1 (4.0)                    |         |
| Duration of infertility    | 22.0±8.4       | 22.7±7.7          | 22.6±8.0                     | 21.8±7.1                   | 0.561   |

One-way ANOVA was done. LPS: Luteal phase support

Table 3: Maternal pregnancy outcome according to the treatments

| Variables                  | Letrozole alone | Letrozole with LPS | Letrozole and GnRH alone | Letrozole and GnRH with LPS | p value |
|----------------------------|----------------|-------------------|--------------------------|-----------------------------|---------|
| Number                     | 49             | 50                | 25                       | 25                          | -       |
| Size of dominant follicle  | 18.5±0.70      | 18.4±0.71         | 19.32±1.02               | 19.17±1.21                  | <0.001* |
| Dominant follicles number (%) |                |                   |                          |                             | 0.009c  |
| One                        | 48 (98.0)      | 49 (98.0)         | 20 (80.0)                 | 22 (88.0)                   |         |
| Two                        | 1 (2.0)        | 1 (2.0)           | 5 (20.0)                  | 3 (12.0)                    |         |
| Number of cycles (%)       |                |                   |                          |                             | 0.900c  |
| I                          | 2 (4.1)        | 1 (2.0)           | 0 (0.0)                   | 0 (0.0)                     |         |
| II                         | 7 (14.3)       | 10 (20.0)         | 3 (12.0)                  | 3 (12.0)                    |         |
| III                        | 40 (81.6)      | 39 (78.0)         | 22 (88.0)                 | 22 (88.0)                   |         |
| Endometrial thickness      | 7.68±0.45      | 7.71±1.17         | 8.03±0.40                 | 7.92±0.21                   | 0.181b  |
| Positive pregnancy test (%)| 15 (30.6)      | 22 (44.0)         | 7 (28.0)                  | 11 (44.0)                   | 0.347b  |
| Positive US findings (%)   | 15 (30.6)      | 22 (44.0)         | 7 (28.0)                  | 11 (44.0)                   | 0.347b  |

ANOVA test used, Chi-square test used, Fisher-Freeman-Halton exact test. LPS: Luteal phase support

Table 4: Pregnancy outcome according to therapy

| Therapy                        | OR   | 95% CI of OR | p value |
|--------------------------------|------|--------------|---------|
| Letrozole alone                | 1.781| 0.789–4.065  | 0.170   |
| Letrozole and GnRH alone       | 0.881| 0.304–2.553  | 0.816   |
| Letrozole and GnRH with LPS    | 1.781| 0.658–4.823  | 0.256   |
| Letrozole only                 | 1.0  | -            | -       |

Binary logistic regression. LPS: Luteal phase support, CI: Confidence interval, OR: Odds ratio

Table 5: Multivariate analysis of the predictors of positive PT

| Variable                  | OR   | 95% CI of OR | p     |
|---------------------------|------|--------------|-------|
| Age                       | 0.85 | 0.669–1.068  | 0.160 |
| Parity                    | 2.99 | 1.108–8.081  | 0.031 |
| BMI                       | 1.00 | 0.794–1.407  | 0.980 |
| Duration of infertility   | 0.96 | 0.985–1.039  | 0.308 |
| Size DF                   | 1.08 | 0.667–1.745  | 0.756 |
| ET                        | 0.77 | 0.481–1.246  | 0.291 |
| Cycle no                  | 0.01 | 0.001–0.090  | <0.001|
| Therapy                   |      |              |       |
| Letrozole with LPS        | 2.89 | 0.901–9.259  | 0.074 |
| Letrozole and GnRH alone  | 2.06 | 0.458–9.272  | 0.346 |
| Letrozole and GnRH with LPS| 5.26| 1.323–20.884| 0.018 |
| Letrozole only            | 1.0  | -            | -     |

Multiple binary logistic regression analysis. LPS: Luteal phase support, CI: Confidence interval, OR: Odds ratio, BMI: Body mass index

CONCLUSION

Our study shows that administration of progesterone as LPS in infertile PCOS women using letrozole alone or with gonadotropins may improve pregnancy rate and its value is more pronounce in gonadotropin OI regimes.

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AUTHORS’ CONTRIBUTIONS

Concept and collection of data, writing the article and critical review of the article - Fadia J Alizzi.

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