

The Endometrial Thickness in Infertile Women with Polycystic Ovarian Syndrome

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Abstract

Background: The polycystic ovarian syndrome is a common cause of infertility and responsible for many changes in endocrine and metabolic activities with a possible role in changing the endometrial thickness.

Objective: To evaluate the effect of endometrial thickness in infertile polycystic ovarian syndrome women on ovulation outcome.

Patients and Methods: A case control study was carried out in Gynecology Consultancy Clinic of Al-Zahraa Maternity and Pediatric Hospital in Diyala province through the period from 1st of December 2016 to 30th of November 2017. The study sample was 40 infertile women with polycystic ovarian syndrome on program of ovulation induction and 40 healthy control women. Endometrial thickness was assessed by transvaginal ultrasonography. The ovulation was assessed regularly for each cycle and each woman was followed up for 6 month.

Results: The means of endometrial thickness for infertile women with polycystic ovarian syndrome at different periods of menstrual cycle were significantly increased in comparison to controls ($p < 0.001$). There was a highly significant difference in means of endometrial thickness between ovulated and not ovulated infertile polycystic ovarian syndrome women at different menstrual cycle periods ($p < 0.001$).

Conclusion: The endometrial thickness of infertile polycystic ovarian syndrome women is clearly higher than healthy controls with a prominent role of endometrial thickness in ovulation among infertile women with polycystic ovarian syndrome.

Key words: Infertility, Polycystic ovarian syndrome, Endometrial thickness, Ovulation.

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Introduction

The endometrial thickness is changeable for premenopausal women during the menstrual cycle in range of 3-15 mm.¹ The polycystic ovarian syndrome (PCOS) is an endocrinal disease affecting 5-10% of women at reproductive age characterized by hyperandrogenism and ovarian dysfunction^[2]. The insulin resistance is

thought to be as the main etiological factor for PCOS in combination with multiplicity of risk factors. In addition to infertility, the PCOS lead to many clinical hazards such as non-insulin dependent diabetes mellitus, hypertension, abnormal lipid profile, heart disease and cerebrovascular disease^[3].

The endometrial thickness (EMT) is the results of abnormal proliferation of endometrium contents and ranges from atypia to neoplasia that is detected by biopsy.⁴ The polycystic ovarian syndrome endocrinal and metabolic changes are related to the endometrial changes and endometrial diseases.⁵ The endometrial thickness could be assessed by transvaginal ultrasonography (TVU). Long duration exposure to the estrogen hormone associated with chronic anovulation among PCOS women accompanied by prolonged endometrial androgen receptor expression that is stimulated by estrogen and inhibited by progesterone are commonly responsible for endometrial thickness.⁶ Many authors regarded the endometrial parameters like endometrial status, endometrial blood supply and endometrial thickness as predictors for primary infertility.^{7, 8} Increased endometrial thickness is correlated with lower in vitro fertilization (IVF) success rates^[9].

The endometrial receptivity is the cornerstone in planning for successful fertilization programs for infertile women.¹⁰ Ovulation induction strategies depending on drugs alone are not enough to acquire better gestational rates in primary infertility.¹¹ Low success rates of IVF among women with PCOS are reported although high quality of transferred embryos, however, the poor endometrial receptivity attributed to EMT may be the common acceptable reason. This suggests that anovulation is not the only cause of infertility^[4, 7, 12]. In Iraq, there is a sustainable increase in prevalence of PCOS

among younger age women 13 and about one third of premenopausal women attending in vitro fertilization centers are diagnosed with PCOS¹⁴ with scarcity of national literatures discussion the endometrial thickness in PCOS infertile women. This study aimed to evaluate the effect of endometrial thickness in infertile PCOS women on ovulation outcome.

Patients and Methods

A case control study that was carried out in Gynecology Consultancy Clinic of Al-Zahraa Maternity and Pediatric Hospital in Al-Muqdadia District (which is a district of Diyala Health Directorate) through the period from 1st of December 2016 to 30th of November 2017. All infertile women attending the Gynecology Consultancy Clinic were the study population. Inclusion criteria were premenopausal age women (20-40 years) with confirmed diagnosis of primary infertility and polycystic ovarian syndrome. The exclusion criteria were secondary infertility, endometrial polyps, uterine anomalies and previous tubal or ovarian surgery. A sample of 40 infertile women with PCOS were selected from infertile women attending to Consultancy clinic and recruited in program of ovulation induction by clomephin citrate 50-150 on day two then after conformation of ovulation by ultrasound given ovotril or pregnel. The forty healthy controls were selected from women attending Gynecology Consultancy Clinic with regular cycles and no ultrasonographic findings of PCOS. An informed oral consent was taken from each woman before enrolling in the

study and an ethical agreement was taken from administration of the hospital in addition to treatment maintenance and consultation for selected women by the researcher.

Diagnosis of primary infertility with PCOS was done by the researcher in the Consultancy clinic. All participants received full history and examination. The PCOS group was diagnosed according to Rotterdam criteria. A venous blood sample of 5 ml was obtained from study participants at room temperature and then centrifuged. Serum was collected and stored at $-20\text{ }^{\circ}\text{C}$. Oligomenorrhea was defined as eight cycles or more in one year menstrual interval 35 days. The body mass index was classified according to world health organization classification; Normal BMI is $<25(\text{Kg}/\text{m}^2)$, overweight $25\text{-}29.9(\text{Kg}/\text{m}^2)$ and obese $\geq 30(\text{Kg}/\text{m}^2)$. The endometrial thickness was measured by transvaginal ultrasonography (TVU) at three steps (2-3, 13-14 and 21-22 days) to check the difference and then all women were given leutinizing hormone kit (5 strips) and checking ovulation and midluteal phase in cooperation with Gynecologist in the Infertility center. TVU was done by Specialist in Radiology in Al-Zahraa Maternity and Pediatric Hospital using a 6.5 MHZ transducer, Siemens SL1 and SD 250

system (Munich, Germany). The procedure wholly explained to the patient in waiting room for at least 15 minutes before scanned completely with empty bladder. Serum progesterone test (mid luteal) for study participants was done in laboratory of Al-Muqdadia General Hospital. The ovulation is defined as progesterone level $>30\text{ ng/ml}$ and no ovulation as $\leq 30\text{ ng/ml}$. The ovulation was assessed regularly for each cycle and each woman was followed up for 6 month.

Statistical Analysis

Statistical analysis was carried out with SPSS software version 22. On analysis, the independent t-test and Fischer's exact test were used for statistical analysis as appropriate. P value less than 0.05 was considered statistically significant.

Results

Studying baseline characteristics of both study groups are shown in Table 1. No significant differences were observed between the two study groups for age categories ($p=0.3$). Body mass index was significantly different between study groups; infertile PCOS women were significantly associated with obesity ($p=0.02$). There was a highly significant association between oligomenorrhea and infertile PCOS women ($p<0.001$).

Table (1): Baseline characteristics of infertile PCOS cases and healthy controls (n=40, for each group).

| Variable | Infertile PCOS No. (%) | Control No. (%) | P value |
|-----------------|---------------------------|--------------------|----------|
| Age | | | 0.3* |
| 20-29 years | 16 (40.0) | 20 (50.0) | OR=0.6 |
| 30-40 years | 24 (60.0) | 20 (50.0) | |
| BMI | | | {CI=0.2- |
| Normal | 11 (27.5) | 10 (25.0) | 0.02** |
| Overweight | 12 (30.0) | 23 (57.5) | |
| Obese | 17 (42.5) | 7 (17.5) | |
| Menstrual cycle | | | <0.001** |
| Normal | 7 (17.5) | 40 (100.0) | |
| Oligomemorrhea | 33 (82.5) | 0 (-) | |

*Not significant, ** Significant

The mean of EMT at 2-3 days of menstrual cycle for infertile PCOS women was (2.6 mm) which was significantly higher than mean EMT of (1.07 mm) for controls (p<0.001). At 13-14 cycle days, the mean EMT of infertile PCOS women (13.1 mm) was significantly higher than mean EMT of

controls (11.2 mm) (p<0.001). The mean of EMT at 21-22 days of menstrual cycle for infertile PCOS women was (16.6 mm) which was significantly higher than mean EMT of (13.9 mm) for controls (p<0.001), as shown in table (2).

Table (2): The endometrial thickness for infertile cases and healthy controls at different menstrual cycle periods (n=40, for each group).

| Variable | Infertile PCOS Mean ± SD | Control Mean ± SD | P value |
|--|-----------------------------|----------------------|---------|
| Endometrial thickness at 2-3 days (mm) | 2.6±1.3 | 1.07±0.3 | <0.001* |
| Endometrial thickness at 13-14 days (mm) | 13.1±1.9 | 11.2±1.1 | <0.001* |
| Endometrial thickness at 21-22 days (mm) | 16.6±1.9 | 13.9±1.3 | <0.001* |

The ovulation was demonstrated among 33 (82.5%) infertile PCOS women while 97.5% of controls had ovulation with significant

difference between two study groups (p=0.02) table (3).

Table (3): Ovulation assessment of for infertile cases and healthy controls (n=40, for each group).

| Variable | Infertile PCOS No. (%) | Control No. (%) | P value |
|--------------------|---------------------------|--------------------|---------------------|
| Progesterone level | | | 0.02** |
| >30 ng/ml | 33 (82.5%) | 39 (97.5) | OR=0.12 {CI=0.1- |
| ≤30 ng/ml | 7 (17.5) | 1 (2.5) | |

*Not significant, ** Significant

Regarding the ovulation of infertile PCOS women, the EMT of ovulated women at three menstrual cycle periods (at 2-3 days, 13-14 days and 21-22 days) were 2.3 mm, 12.6 mm and 16.1 mm, respectively, while the EMT of non-ovulated women at three

menstrual cycle periods (at 2-3 days, 13-14 days and 21-22 days) were 4 mm, 15.5 mm and 18.7 mm, respectively, there was a highly significant association between increased EMT and no ovulation of infertile PCOS women at different menstrual cycle periods (p<0.001) (Table 4).

Table (4): The endometrial thickness for infertile PCOS cases according to ovulation success (ovulation no=33, no ovulation no=7).

| Endometrial thickness | Ovulation Mean ±SD | No ovulation Mean±SD | P value |
|--|-----------------------|-------------------------|---------|
| Endometrial thickness at 2-3 days (mm) | 2.3±1.2 | 4±0.8 | <0.001* |
| Endometrial thickness at 13-14 days (mm) | 12.6±1.7 | 15.5±0.9 | <0.001* |
| Endometrial thickness at 21-22 days (mm) | 16.1±1.7 | 18.7±0.9 | <0.001* |

* Significant

Discussion

Ovulation induction and in vitro fertilization success rates are dependable commonly on receptivity of uterus and quality of embryo. Nowadays, the assisted reproductive technology (ART) concentrated on availability of endometrial receptivity[15]. In present study, a significant increase in endometrial thickness of infertile PCOS women at three times of menstrual cycles by TVU examinations was observed in comparison to controls (p<0.001). This finding is consistent with results of Park et al 16 study in South Korea

which reported that endometrial thickening among PCOS women is predominated. Another study in Pakistan by Usmani et al 17 found a significant increase in endometrial thickness among older infertile women with PCOS. Among PCOS women with prolonged unopposed estrogen, hyperinsulinemia, elevated free insulin growth factor-1 and androgens may further augment the mitogenic activity of endometrial cells, leading to acceleration of hyperplasia and perhaps transformation to cancer.18 In Iraq, previous study carried out

by Eleawi et al 19 revealed that PCOS represented more than one forth of infertility causes and was associated with many endocrine and metabolic changes that affect the ovulation and uterine receptivity.

Current study showed a significant difference in endometrial thickness between ovulated and non-ovulated infertile PCOS women ($p < 0.001$). This is similar to results of Liu et al 20 study in China which found that endometrial thickness of less than 7mm is needed for appropriate ovulation among infertile women. Current study showed that endometrial thickness in PCOS women need to be reduced for appropriate ovulation. Our study findings are inconsistent with results of Sharma et al 21 study in India that found higher pregnancy rates among women with higher endometrial thickness. This inconsistency is due to fact that our study included PCOS women and not normal healthy women like Indian study. The excessive increase in endometrial thickness among PCOS women is proved to be an obstacle for appropriate ovulation.¹⁷ Zhao et al 15 study in China reported that in women with no PCOS, the pregnancy rate was increased among women with moderate endometrial thickness (≥ 14 mm) while Boys et al 22 study in Australia in their systematic review stated that extreme endometrial thickness may have a negative effect on success rates of in vitro fertilization. Despite the findings of many studies regarding the predictive effect of endometrial thickness and successful outcomes of in ovulation induction, there is still suspicion on accuracy

of endometrial ultrasound. Many authors had shown a direct relationship between endometrial thickness or a certain type of echogenic pattern and uterine receptivity²³⁻²⁵.

Obesity among infertile PCOS women in current study was significantly higher than controls ($p = 0.004$). This is similar to results of Mahmoud et al 26 study in Saudi Arabia which documented that obese PCOS women had significantly signs of hyperandrogenism and acanthosis nigricans more than non-obese PCOS women. In our study, oligomenorrhea was significantly prevalent among infertile PCOS women than controls ($p < 0.001$). This is consistent with results of Hussein and Alalaf study in Iraq 14 which found the oligomenorrhea as common symptom among infertile women with PCOS. The comparison with healthy controls and adaption of specific Rotterdam criteria for PCOS with single cause of infertility increased the power of current study. However, our study had many limitations like absence of temporal relationship because of its design and debate regarding endometrial thickness effect on ovulation with absence of standard cutoff values for EMT measurements affecting our study.

Conclusion

In conclusion, endometrial thickness of infertile polycystic ovarian syndrome women is clearly higher than healthy controls with a prominent role of endometrial thickness in ovulation among infertile women with polycystic ovarian syndrome. Encouraging use of transvaginal ultrasonography routinely

for women with primary infertility should be recommended to assess the endometrial thickness.

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