ORIGINAL ARTICLE:

Ageing Ovaries and Endometrium in PCO

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ABSTRACT:

Objective: to measure the outcome of age on ovarian and uterine morphology in women with primary infertility due to polycystic ovarian syndrome (PCOS)

Materials and Methods: It was an observational cross sectional study. Two hundred primary infertile women with PCOs were subdivided into age groups (years) 20-30 (group I) and 31- 40 (group II). The ovarian volume (OV), follicles count (FC) and size (FS), uterine area (UA) and endometrial thickness (Endo) were determined by transabdominal (TAS) and trans -vaginal scan (TVS) using the ultrasound machine. Unpaired t-test was applied to evaluate the result

Results: Comparison between group I and group II was made to evaluate the outcome. A significant raise was noted in the uterine morphology of group II. The UA was $89.99\pm5.83cm^2$ v/s $119.0\pm23.33cm^2$ (0.001) and endometrial thickness was $0.48\pm0.11mm$ v/s $0.59\pm0.13mm$ (0.001). A significant decline was noted in the ovarian morphology of group II; the OV (TAS) was $15.36\pm2.56cm^2$ v/s $10.57\pm12cm^2$ (0.001) and TVS showed $15.74\pm2.23mm$ v/s $10.37\pm1.08mm$ (0.001). The FC was 14.05 ± 1.56 v/s 12.47 ± 0.89 (0.022) and FS was 9.45 ± 7.98 v/s 4.33 ± 5.88 (0.00).

Conclusion: The OV, FC and FS (ovarian morphology) variables decreases in the elder infertile group with PCOs but the uterine morphology variables showed an increase in area with thickening of endometrium in the elder group.

Keywords: Polycystic ovaries, Hyperandrogenism, Infertility, Ovarian volume, Follicle count, Follicle size, Uterine area, Endometrial thickness.

INTRODUCTION:

The presence of 12 or more follicles measuring 2-9mm in diameter or increased ovarian volume (>10cm3) is known as polycystic ovarian syndrome (PCOS). It is associated with oligo-/anovulation and raised serum levels of androgens, or evidence of hyperandrogenism after all known potential causes have been excluded. The ultrasound examination can play an important role in early diagnosis, and evaluating PCOS patients for endometrial hyperplasia.[1,2] Polycystic ovary syndrome (PCOS) is the most commonly encountered endocrine disorder in women of reproductive age; recent studies have shown that 5- 10% females of reproductive age group are affected. It has marked reproductive and non-reproductive consequences. Raised serum levels of luteinizing hormone (LH), testosterone and androstenedione, along with decreased or normal levels of follicle stimulating hormone (FSH) are believed to be present[1,2]. Many different definitions for PCO have thus been proposed. Twelve or sometimes more follicles measuring 9mm in diameter along the periphery like a string of pearls with an increased ovarian volume (>10cm3) is known as PCO[2]. There are also deranged androgen levels and women tend to show increase levels of testosterone in the young age group which may be attributed to physical abnormalities like menstrual disturbances and hair growth in abnormal places[3].

The ratio of follicular androstenedione to estradiol is high in patients with PCO, suggesting defect in the enzyme causing aromatization of ovarian androgens produced by LH, estrogens by FSH in the ovary. A P450 aromatase gene mutation has been found to cause a form of this syndrome. The anovulatory cycles when last for a considerable period of time, the "polycystic ovary" results. As a consequence, affected women develop single or bilaterally enlarged ovaries, resulting in PCOs.[4] Infertility is defined as failure to conceive after one year of unprotected intercourse[5]. PCO is considered as one of the most common disease resulting in infertility. Lack of the ability to conceive due to PCO affects around 5-10% of women who are in their young reproductive age. The majority of these cases are associated with menstrual irregularities and is also linked to an increase in luteinizing hormone.[6,7,8] Such women have frequent failure during assisted reproductive techniques (ART) and show miscarriages after this technique.[9] Several studies have also linked PCO with other diseases one of which is cardiovascular diseases. Correlation of PCO with insulin resistance and obesity has also been reported since long. The symptoms resulting from infertility is a result of long term anovulation and menstrual irregularities, obesity, presence of adipose tissue in upper parts of the body, and skin changes such as hirsutism, acne, seborrhea etc [*] The presenting complaints in such women of reproductive age afflicted with this disease are

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chiefly hyperandrogenism and menstrual irregularities, examples of which are, oligomenorrhea or amenorrhea, where as infertility is the chief presentation in adult women with PCOS during the reproductive age.

There is enhanced evidence that the endocrine and metabolic abnormalities in PCOS have intricate effects on the endometrium, contributing to infertility and endometrial disorders [8,9] The hazards include unimpeded estrogen stimulation of the endometrium in anovulatory PCOS women, obesity, insulin resistance, insulin like growth factors, diabetes, nulliparity and progesterone resistance [2,10] association of BMI with PCOs and infertility has been very well- known and is documented in several studies [11,12] By relating BMI with the morphology of pelvic reproductive organs the underlying mechanism for sub fertility can be better understood especially in PCOs females who often suffer from obesity. The effect of BMI on endometrial thickness and uterine size can also help in predicting the risk factor for endometrial carcinoma and fibroids. A study [11] showed that PCOS is related to consumption of food. The authors have shown that certain type of food items like fried potatoes and white bread were taken in large amounts by the recruited subjects suffering from PCOS. Further investigation is needed with larger sample size on morphology of ovaries and uterus like organs to establish a strong relation with BMI so that preventive measures can be taken to control many associated diseases.[7] The ultrasound examination can play a role in evaluating PCOS patients for endometrial hyperplasia, in accordance with menstrual history. Anthony et al found positive correlation between endometrial thickness and endometrial hyperplasia.[11] The long term effects of consistently high estrogen levels results in increased risk of endometrial hyperplasia and endometrial cancer. The risk is three times higher in women with polycystic ovaries as compared to normal women.[4]

MATERIALS AND METHODS:

After obtaining ethical approval from the ethical review committee of Ziauddin University, this observational cross sectional study was conducted from January 2009 to March 2010, the subjects were sought from Ziauddin Hospital, Nazimabad Karachi. The sampling technique used was non probability simple random type. In this study women diagnosed with PCOs after ultrasound were included. Those included were diagnosed clinically and then ultrasound was performed to induct them in the study. The subjects were educated and belonged to the middle class who were determined by their monthly income according the set criteria by World Health Organization for developing countries. They were informed about the study and agreement was sought via a written informed consent and before the procedure signature of the subject along with two witnesses was sought.

The subjects were included in the study if they fulfilled the following criteria a) primary infertility b) females of ages between 20-40 years c) existence of 12 or more cystic follicles in one or both ovaries However the subject were excluded due to any one or more of the following reasons a) using ART for conception b) any pathology of pelvic reproductive organs other than PCOs c) a lab report showing that husband is infertile d) hypertension, diabetes, cancer etc or any other chronic illness e) secondary infertility f) The subject not using contraceptives for at least 2 months preceding the study Between 2nd to 7th day of the menstrual cycle scanning of the ovaries and uterus was performed [12] using Toshiba ultrasound machine. Transabdominal and transvaginal probes were used which were respectively of 3.75 MHz and 7.5 MHz frequency. Transabdominal scan (TAS) was performed on a full urinary bladder. This was carried out in order to eliminate abnormalities other then PCOs e.g. adhesions, tubal ligation, absence of ovaries (one or both), endometriosis, fibroids, cancers etc. Transvaginal scan (TVS) was performed only in those patients who were diagnosed with PCO during TAS.

Following variables were measured and noted a) ovarian volume b) follicle count and size (2- 9mm) c) uterine area d) endometrial thickness. "Scanning of the two ovaries was done in the longitudinal (D1), anteroposterior (D2) and transverse diameter (D3); the total volume was analysed by applying the ellipsoid equation which is $D1 \times D2 \times D3 \times 0.523 cm^3$ and the sum of the two ovaries was considered". [12]

Uterine length X anteroposterior diameter in the the uterine area was calculated and applied

further analysis. From the top of the fundus to the cervix was the uterine length and by TVS the anteroposterior diameter was measured. [10, 11, 12] By TAS the endometrial thickness was measured in mm. [12]

For validation of the results all variables were measured twice and the mean of the two readings was taken as the final value. Clinically diagnosed 254 women with signs and symptoms of PCO during this period visited the ultrasound clinic. Out of the total women on scanning 14 had normal anatomy of the ovaries in spite of have clinical signs of hirsutism, 10 subjects out of 254 had adhesion bands and endometriosis, 11 were not suffering from primary infertility, 8 had undergone some assisted procedure, 4 were suffering from other associated problems and 7 did not give their consent. Therefore 54 women were excluded. The subjects were recruited till our desired number was achieved which was 200. These two hundred women were finally selected to be a part of the study group of which 100 belonged to the age group of 20-30 years and 100 of 31-40 years. The women finally selected were divided into two study groups; age range 20-30, Group I and with age range 31-40 were a part of Group II.

STATISTICAL ANALYSIS:

"SPSS version 12 for windows was used to enter and analyze the measurements"; unpaired t-test was applied. The results were demonstrated as mean± standard deviation (SD). "P-value of 0.05 or less was considered statistically significant. Comparison of ovarian morphology with PCOs was assessed by ovarian volume (OV), follicle count and follicle size. Effect of age on uterine area and endometrial thickness was also evaluated.

RESULTS:

Mean age in group I (n=100) was 26.46±3.55 and in group II (n=100) was 36.73±3.19 (Mean ± SD). (Figure 1) Trans abdominal and Trans vaginal scan showed a significant decrease in OV with the progression of age (p=0.001, p=0.001 at 95% CI. A decline in follicle count as well as follicle size in group II was noted; p=0.001 and p=0.001 at 95% CI respectively (Table 1).The association of age with uterine area between group I and group II was 89.99± 5.83 vs 119±23.33 The endometrial lining of PCO showed significant ascend in group II; 0.48±0.11 vs 0.59±0.13 (p=0.001 in both variables at 95%CI).

Figure 1
Relation of age with ovarian morphology in primary infertile women with PCOs
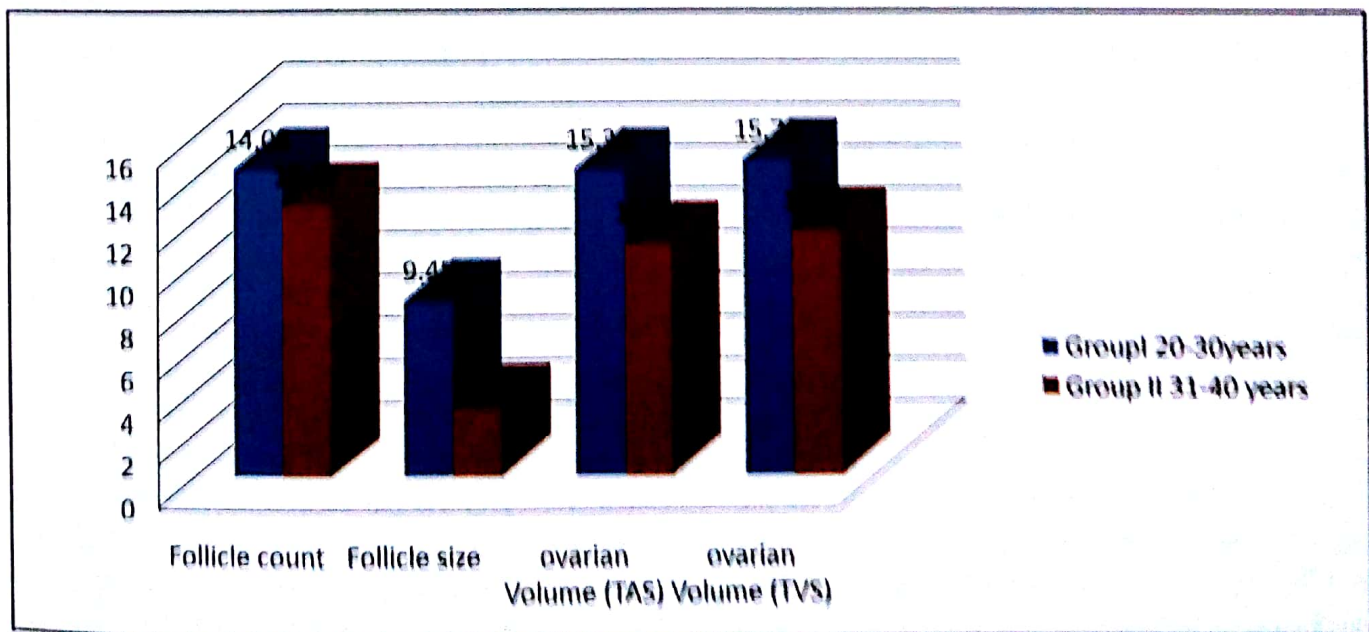
Note: OV (TAS) = ovarian volume in cm³ (TAS: Trans abdominal scan; TVS: transvaginal scan), follicle count in numbers, follicle size in mm. All Values expressed are mean ± SD; p-value is < 0.05 at 95% CI

Table 1
Relation of age with uterine morphology in primary infertile patients with PCO

Variable	Group I: (n=100) Age: 20-30(mean: 26.46±3.55)	Group II: (n=100) Age: 31-40(mean: 36.73±3.19)	P-value
UA	89.99 ± 5.83	119.0 ± 23.33	0.001
Endo	0.48 ± 0.11	0.59 ± 0.13	0.001

UA=uterine area in cm^2, ENDO= endometrial thickness in mm. Values expressed are mean ± SD; p-value< 0.05 are considered to be significant

DISCUSSION:

This study is an attempt to show a comparison between younger and elder primary infertile women affected with PCOs. An enormous increase in the incidence of PCO has been observed which can be credited to the technological development of ultrasonography. Polycystic ovary syndrome (PCOS) is the most common endocrine-metabolic disorder in women of reproductive age with 5-10% of prevalence [12,13]

With rising age the ovarian reserve (collection of primordial follicles) declines and ultimately results in menopause. [14,15,16] This depletion of the primordial follicles at the age of 45± 5 years results in the female being unable to conceive. PCOs and other pelvic disorders can however develop during regular ovarian functioning. Association of PCOs with endocrinopathies and certain genetic mutations is now evident and has been proved by several laboratories. [17,18]

In this study morphological changes has been observed in pelvic reproductive organs in two groups of patients (group- I: 20-30 years & group II: 31-40 years) through ultrasound scanning. It was observed that the endometrial thickness was significantly increased in older age group (group II). Other studies also proved that the endocrine-metabolic abnormalities in PCOS may have complex effects on the endometrium due to the prolonged stimulatory effects of unopposed estrogen by chronic anovulation. [14,15] Park JC et al proposed that the endometrial thickness and age were positively correlated with the presence of endometrial disease in women with PCOS. 12 Another study showed no such correlation and abnormal endometrial thickness has been associated with obesity, and diabetes mellitus along with PCO. [16,17]

In our study we observed that women with PCOs and primary infertility the ovarian volume, follicle count and follicular size was significantly raised in the younger group. Another study was proven to have similar results [18], reason being due to hormonal imbalance in PCO patients, the luteinizing hormone causes the follicle reserve to increase in size and becomes cystic, the result of which is increase in the ovarian volume, and becomes >10ml. [19,20,21] The reason for observed results is the fact that exhaustion of the primordial pool which is available at the time of birth is a physiological course which is present from menarche till menopause. The development continues in PCO, as an effect the follicle count decreases yet uterine size persists to be increased. [22,23]

Endometrial thickness undergoes changes according to different phases of menstrual cycle. At the time of menstruation the endometrium is about 1- 4 mm thick, becomes about 5- 7 mm during proliferative phase and reaches maximum thickness of 7-14 mm at the peak of secretary phase [21]. Significant agreement is present with regard to the relationship between BMI and endometrial thickness in multiple studies. Studies showed that the frequencies of thicker endometrium increased in relation to body mass index. [22,23,24,25]

Owing to the expansion in the field of ultrasonography and researches, PCOs are now being recognized at a much earlier stage. It has also been found that the changes in ovarian and uterine anatomy between fertile and infertile women show that the ovarian volume, follicular count and size decrease considerably in the infertile group of women. The authors have shown a decrease in

endometrial thickness in women afflicted with infertility resulting in a decrease in uterine size[8]. The PCOs women are often coupled with obesity, Type 2 diabetes, elevated cholesterol levels and insulin resistance. The relation of insulin resistance when develops the ovaries create oocyte with anomalous morphology. Due to the uncertain worth of the oocyte there is a shortage of fertilization potential of the ovum resulting in infertility.[7] The accurate cause of PCO is still under exploration but researchers have shown genetic connection to this condition. H Þ and LHR gene mutation have been reported to be associated to anovulatory PCOs. Amongst these, obesity and PCOs show cause-effect bond which is highly contentious since obesity has been acknowledged in 40-80% of PCOs women[9]. It has lately been reported that in PCOs patients the effect of the obesity-linked gene [24,25] is mediated all the way through the overload fat deposited due to unevenness in sex hormone. Insulin resistance, one of the imperative dysmetabolic factors of PCOs, is closely related to body weight.[24] At the identical time, obesity does aggravate many aspects of the phenotype, particularly cardiovascular threat factors such as glucose intolerance and dyslipidemia. The damaging synergic effects in PCOs with obesity thus [9] reduces chances of conception at the level of the ovary as well as on endometrial lining more than lean patients with PCOs. Due to the improvement in the field of ultrasonography, PCOs are now being diagnosed at an early age which is significant since early diagnosis leads to timely treatment which can avoid infertility due to this state and associated problems including genetic mutations.[24,25]

Further study is required to be carried out to evaluate the relationship between the endometrial diseases and endometrial thickness in patients with PCO.

CONCLUSION:

Primary infertility may be an outcome of PCOS; this study measures the ovarian and uterine morphology in such women by using ultrasonography. In this study the ovarian volume, follicle count and follicle size are found to be significantly increased in the younger primary infertile women however the uterine area and endometrial thickness are found to be raised in the older primary infertile women with PCOs. A larger number of PCOs is being timely diagnosed by this simple radiographic technique. Due to this, diagnosis at an early age is possible. By using this diagnostic tool researchers have identified that the incidence of this disease is increasing in younger women of reproductive age. Therefore ultrasound can serve as an important tool in preventing primary infertility as evident by this study. There is limited research of the association of uterine morphology with PCOs and none in this region. In order to fulfill this gap, it is pertinent to understand this relationship to avoid misdiagnosis of endometrial cancer especially in the older age group.

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