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Long Term Morbidity of Polycystic Ovary Patients with Cancer Sequelae

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Abstract: ***Polycystic ovary syndrome (PCOS) is an invigorating- androgenic disorder affiliated with persistent oligo-anovulation and polycystic ovarian structure,in concordance with psychological impairments, mainly insulin resistance and atoning hyper-insulinemia, which is perceived as leading factor responsible for altered androgen presentation and metabolism. The promising longer term morbidity of PCOS patients with cancer consequences is the focus of research in the present study. This multi- centric study was conducted both retrospectively and prospectively from July 2010 to July 2014. Patients falling under Rotterdam criteria were included in the study at Owaisi Hospital and Research Centre, Princess Esra Hospital and M.H.R.T., Hyderabad. Women diagnosed with PCOS at the age of 31-40 years has significantly shown 2.3 fold (SIR=2.3; 95% CI= 1.9-4.3) increased risk of Endometrial Hyperplasia, 41-50 years revealed significant risk (SIR=1.7; 95% CI= 1.1-2.6). of Endometrial Hyperplasia, whereas 31-40 years showed significant risk (SIR= 2.6; 95% CI= 1.9-3.1) of Endometrial cancer. In conclusion, women diagnosed with PCOS are at increased risk for endometrial hyperplasia, Endometrial and ovarian cancers. There is a need for research into several unanswered questions in PCOS and for a prototype shift to complexity driven research given the intricacy of PCOS.***

Keywords: PCOS, Endometrial Hyperplasia, Endometrial Cancer, Ovarian Cancer

1. Introduction

The polycystic ovary syndrome (PCOS) or Stein-Leventhal syndrome is a hyper- androgenic disorder associated with chronic oligo-anovulation and polycystic ovarian morphology [1,2],often correlated with psychological impairments, including depression, other mood disorders and metabolic derangements, mainly insulin resistance and atoning hyper-insulinemia, which is identified as a major factor responsible for distorted androgen production and metabolism [3].A PCOS conformanceworkshop group directedby Rotterdam ESHRE/ ASRM agreed that two of the following three criteria were required to investigate the condition after exclusion of other causes of excess androgen. The criteria included: (a)clinical and / or biochemical signs of hyper- androgenism (b) Oligo- and / or anovulation; and (c) polycystic ovary morphology on ultrasound scan, characterised as the presence of 12 or more follicles in each ovary (with one ovary being sufficient for diagnosis) measuring 2-9 mm in diameter, and / or increased ovarian volume (>10 ml).This definition was, yet, not to be related to women on the oral contraceptive pill as it changes the ovarian morphology. It was also suggested that, in the presence of a principal follicle (> 10 mm) or a corpus luteum, the scan was to be repeated in the next cycle.Some unresolved practical issues still remain with this new definition. These include the variable quality of ultrasound scans which are often operator- and machine- dependent, and the omission of measures of insulin resistance in the diagnostic criteria, which is increasingly being recognized as being central to the pathophysiology of PCOS[4].Prevalence estimates as defined by the NIH/NICHD criteria, indicate that4%–8% of women of reproductive age are affected by the most common endocrinopathy PCOS [5-9].However, 50-85% of these apparently healthy women have symptoms or signs of the syndrome such as menstrual irregularity or hirsutism. Recent studies in the literature on the prevalence of PCOS, again further heighten the need for a fundamental shift in research approach, particularly in view of reports showing that the phenotypic expression of PCOS appears to be dependent on racial origin[10].Adopting the new consensus ESHRE/ ASRM definition of PCOS as the gold standard could potentially overcome this challenge over the next few years. However, as the new ESHRE/ ASRM consensus definition does not incorporate indices of insulin resistance, this will not be easy[4].

A wide range of factors influence menstrual cycle characteristics, including body size, smoking, alcohol intake, and physical activity, as well as pathologic conditions including polycystic ovary syndrome (PCOS)[11-15].Traditional concepts of PCOS as a primarily endocrine condition secondary to aberrations in the hypothalamo-pituitary- ovarian axis manifesting as high luteinizing hormone/ follicle stimulating hormone ratios, increased androgen production and high oestrone levels from peripheral conversion in adipose tissue of androgens are increasingly being challenged[4]. Results from some family studies suggest a possible autosomal dominant phenotype. However, the largest twin study on women with PCOS found a high degree of discordance among twins with polycystic ovaries, which suggests a more complex pattern of inheritance than an autosomal dominant pattern of inheritance[16].One central paradox regarding insulin resistance in PCOS is the high responsiveness to insulin by the ovary, as opposed to the resistance of the whole body, and this model has been used to explain ovarian hyper-androgenaemia as it is thought to arise from a direct stimulatory effect of insulin on ovarian stromal cells. About 10-65% of women with PCOS are obese, and obesity in

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PCOS tends to be distributed around the abdomen. Generally a significant correlation exists between obesity and infertility and obesity and miscarriage but the mechanisms have not been completely elucidated. The complexity of the interrelationships between PCOS, androgens, ghrelin, obesity and infertility, however remains to be untangled[4].There is a need for reanalysisinto several unresolved questions in PCOS and for a paradigm shift to complexity driven research given the complexity of PCOS.

The potential longer term morbidity of PCOS patients with cancer sequelaeis the focus of research in the present study and is aimed to assess the incidence and association between PCOS and endometrial pathology, endometrial cancer, endometrial hyperplasia and ovarian cancer; and also to know the predisposing risk factors in PCOS.

2. Materials and Methods

It is a multi- centric retrospective study for 5 years and prospective study of 10 years.

- **Retrospectively:** The patient case sheets were used to identify patients who underwent laparoscopy and who were identified to have polycystic ovaries from July 2010 to July 2014 at Owaisi Hospital and Research Centre, Princess Esra Hospital and M.H.R.T Hospital and Research Centre, Hyderabad.
- **Prospectively:** All the patients who followed following inclusion criteria were included in the study:
- Patients followingRotterdam'scriteria havingoligo/anovulation, hyperandrogenism, clinical (hirsutism or less commonly male pattern alopecia) orbiochemical (raised FAI or free testosterone), polycystic ovaries on ultrasound were included in the study.
- Infertile women and; married for more than 5 years, age greater than 30 years, BMI greater than 25, infertile even after six cycles of clomiphene citrate and who underwent laparoscopy and were identified to have polycystic ovarian morphology.

3. Results

Table 1 gives an implication of the total number of infertile patients and number of patients who underwent laparoscopy, Laparoscopic findings (risk factors) in patients who underwent laparoscopy, and the demographic characteristics and hormone profile distribution in PCOS patients from 2011-2017.

Characteristics, Years	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
Total number of infertile patients and number of patients who underwent laparoscopy								
No. of infertile patients	4807	5183	5873	6241	5167	7058	1531	35860
No. of patients who underwent laparoscopy	2089	2597	2217	2463	2219	3145	743	15473
Laparoscopic findings in patients who underwent laparoscopy								
Tubal block	872	1090	930	1022	922	1328	307	6471
Ovarian cyst	198	235	276	234	210	305	73	1531
Adhesion	424	513	446	485	427	645	142	3082
PID	786	978	926	1007	914	1287	294	6192
Endometriosis	97	155	102	124	146	158	34	816
PCO	512	735	541	657	508	752	210	3915
Demographic characteristics and hormone profile distribution in PCOS patients								
BMI> 25	295	371	356	278	281	215	264	2060
Irregular menstrual cycles	473	514	567	689	520	582	268	3613
Testosterone> 150 ng/dl	432	512	507	515	457	502	243	3168
Hyperinsulinemia>25mcIU/ml	342	344	336	286	298	471	320	2111

- Post laparoscopy, patients were observed with tubal block, ovarian cyst, adhesion, PID, endometriosis and PCO. Women with BMI> 25, irregular menstrual cycles, testosterone levels >150 ng/dl and hyper-insulinemia>25mcIU/ ml were the demographic characteristics and hormone profile distribution in PCOS patients.

Table 2: Observed (Obs) and expected (Exp) numbers and standardized incidence ratios (SIRs) for endometrialhyperplasia in patients with polycystic ovary syndrome (PCOS)

Age (years)	Observed (Obs)	Expected (Exp)	SIR (95% CI)
20-30	7	8.1	0.9 (0.7-1.6)
31-40	23	24.6	**2.3 (1.9-4.3)**
41-50	9	5.0	**1.7 (1.1-2.6)**

- Women in whom PCOS was diagnosed at the age of 31-40 years has shown 2.3 fold increased risk of EndometrialHyperplasia, we found significantly increased SIRs (SIR=2.3; 95% CI= 1.9-4.3)
- Age 41-50 years also has revealed significant risk of Endometrial Hyperplasia (SIR=1.7; 95% CI= 1.1-2.6)

Table 3: Observed (Obs) and expected (Exp) numbers and standardized incidence ratios (SIRs) for endometrial cancer patients with polycystic ovary syndrome (PCOS) according to age at cancer diagnosis.

Age at first PCOS (years)	Observed (Obs)	Expected (Exp)	SIR (95% CI)
20-30	0		
31-40	2	1.9	**2.6 (1.9-3.1)**
41-50	1	1.2	0.9 (0.8-1.3)
Age at cancer (years)			
< 50	1	1.0	0.8 (0.6-1.8)
≥ 50	2	1.5	**2.1 (1.3-2.7)**

- With regard to endometrial cancer, we found significantly increased SIRs among women in whom PCOS was diagnosed at the age of 31-40 years (SIR= 2.6; 95% CI= 1.9-3.1)

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- Age 41-50 years did not show any significant risk of cancer (SIR= 0.9; 95% CI= 0.8-1.3)

Table 4: Observed (Obs) and expected (Exp) numbers and standardized incidence ratios (SIRs) for ovarian cancer in patients with polycystic ovary syndrome (PCOS) according to age at cancer diagnosis.

Age (years)	Observed (Obs)	Expected (Exp)	SIR (95% CI)
20-30	0		-
31-40	1	0.8	1.0 (0.5- 1.3)
41-50	0		-
Age at cancer (years)			
< 50	0		-
≥ 50	1	0.8	1.2(0.8-2.3)

- With regard to ovarian cancer, we did not find any significantly increased SIRs among women in whom PCOS was diagnosed at the age of 20-50 years.

4. Discussion

Recent activity in the long- term risks of PCOS have also concentrated on its possible correlations with endometrial, ovarian and breast cancer.

- A correlation between PCOS and endometrial carcinoma (EC) was first recommended in 1949[17].The process which is generally predicted to be responsible for greater risk of endometrial carcinoma in women with PCOS relates to chronic anovulation with consequent continued secretion of estrogen unopposed by progesterone[18].With regard to endometrial cancer, we found significantly increased SIRs among women in whom PCOS was diagnosed at the age of 31-40 years (SIR= 2.6; 95% CI= 1.9-3.1). Thus demonstrating an unambiguous link between PCOS and EC. Ourfinding is similar with a meta-analysis study (1966-2011) by Haoula *et al*., which evaluated the association between EC and polycystic syndrome women with PCOS had an Odds ratioof developing EC of 2.89 with a 95% CI of 1.52–5.48. Nearlythree-fold risk of endometrial carcinoma in women with PCOS explains a lifetime risk of 9% given the background lifetime risk of EC in the general population of 3%. Even though most women with PCOS (91%) donot develop EC, their study has shown that such women are more likely at chronic risk and hence builds up evidence base in support of link between Polycystic Ovary Syndrome and Endometrial Cancer. It has relevant conclusion for clinical practice as it calls for the imposition of risk-reducing measures including the prospective of introducing a screening scheme for detecting early cancer as treatment of Endometrial Cancer at an early stage [19].
- With regard to ovarian cancer, we did not find any significantly increased SIRs among women in whom PCOS was diagnosed at the age of 20-50 years which may be due to differences in associations when stratified by BMI and oral contraceptive use. Few lines of evidence also suggest that women with PCOS may be at lower risk of ovarian cancer as shown by Wild and colleagues[20]on mortality in PCOS when the standardized mortality ratio in women with PCOS was 0.34. In another similar study, there was no correlation between menstrual cycle characteristics or self-reported PCOS and ovarian cancer risk as shown by Harris et al. However, they observed significant differences for the association between menstrual cycle irregularity and ovarian cancer risk by histologic subtype[19].
- However, conflicting this link between PCOS and ovarian cancer is the study by Whittemore et al[21]and Rossing et al[22]for greater risk of ovarian cancer observed among women with PCOS is that women with PCOS are more likely to be exposed to ovulatory- stimulating medications, thus conferring an increased risk for ovarian cancer. Two large Danish studies also suggest that infertility on its own boosts the risk of borderline and invasive ovarian tumors[23, 24].
- In the present study, women diagnosed with PCOS at the age of 31-40 years has shown 2.3 fold increased risk of EndometrialHyperplasia (EH), with significantly increased SIRs (SIR=2.3; 95% CI= 1.9-4.3). Age 41-50 years also has revealed significant risk of Endometrial Hyperplasia (SIR=1.7; 95% CI= 1.1-2.6). This finding however complies with Greentop guidelines, which confirms that Oligo- or amenorrhea in women with PCOS may predispose to endometrial hyperplasia and later carcinoma. Another study by Lidor *et al*., 1986,says that majority of women with EH will present clinically with abnormal uterine bleeding (AUB) and EHs have previously been estimated to account for 15% of all cases of post-menopausal bleeding[25]and pre-menopausal patients with polycystic ovarian syndrome (PCOS), due to hyper androgenic anovulation are in particular at higher risk as shown by Bobrowska *et al*., 2006[26].

5. Conclusion

In conclusion, women with PCOS are at increased risk for endometrial hyperplasia, Endometrial and ovarian cancers. There is a need for research into several unanswered questions in PCOS and for a paradigm shift to complexity driven research given the complexity of PCOS. This strategy acknowledges that in complex conditions such as PCOS, a complex interplay of genetic, epigenetic and environmental factors may influence its expression.

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