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Polycystic Ovarian Syndrome in Perimenopausal Women: A Pilot Study

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Abstract

Background: Polycystic Ovarian Syndrome (PCOS), characterized by hyperandrogenism, chronic anovulation with polycystic ovaries, probably most common endocrine disorder, can occur at any age, with risks for metabolic/cardiovascular disorders in future.

Objective: Present pilot study was done to know incidence of PCOS among perimenopausal women with menstrual abnormalities and associated abnormalities.

Material methods: Study was done at a rural institute in women of 35 to 54 years with menstrual disturbances, with or without obesity, with or without hirsutism. PCOS diagnosed as per criteria of PCOS Consensus Workshop Group (2004) and correlation with socio-economic status, lifestyle, family history, Body Mass Index, co-existing disorders was studied.

Results: Twelve perimenopausal of 100 studied were diagnosed to have PCOS after clinical, sonographic, biochemical evaluation, two had hyperprolactinemia, 2 hypothyroidism. Of 12 women eight had leiomyoma uteri. They underwent hysterectomy. Endometrial, histopathology revealed cystic glandular hyperplasia without atypia in 3, atypia in one, proliferative endometrium in two. Two had atrophic endometrium. In all ovarian histopathology revealed multiple cystic ovaries with surrounding hyperthecosis typical of PCOS. Of 12 women, 8 had low fasting glucose/insulin ratio, 5 elevated LH/FSH ratio, 4 elevated free testosterone. Of 88 women with no PCOS, 3 had elevated free testosterone, 21 low fasting glucose/insulin ratio, none had deranged LH/FSH ratio. T3, T4 were elevated in two, low TSH in 2. All PCOS had metabolic disorders, 4 diabetes mellitus, 3 hypertension, 2 diabetes and hypertension, 2 hyperlipidemia with diabetes, hypertension, one (8.33%) hypothyroidism and one (8.33%) had hypertension with hypothyroidism.

Conclusion: PCOS in perimenopausal is complex. Studies are needed about de novo, PCOS and follow up of young women with PCOS through menopause.

(**Condensed Abstract:** Polycystic Ovarian Syndrome, can occur at any age with metabolic/cardiovascular risk. Present study was to know incidence of PCOS among 100 women of 35 to 54 years with menstrual disturbances, with or without, obesity, hirsutism. Twelve were diagnosed to have PCOS after clinical, sonographic, biochemical, evaluation, 8 had low fasting glucose/insulin ratio, 5 elevated LH/FSH ratio, 4 elevated free testosterone. All had metabolic disorders, 4 diabetes mellitus, 3 hypertension, 2 diabetes hypertension, 2 hyperlipidemia diabetes, hypertension, one hypothyroidism, one hypertension with hypothyroidism. Studies are needed about de novo, PCOS, follow up of young PCOS women through menopause)

Keywords: Perimenopausal women; Polycystic ovarian syndrome; Metabolic disorders

Background

Polycystic Ovarian Syndrome (PCOS), probably the most common endocrine disorder in women is characterized by hyperandrogenism, chronic anovulation with polycystic ovaries [1-5]. Diagnosis of PCOS is extremely important not only because of the problems PCOS causes, but also because it identifies risks for metabolic and cardiovascular disorders. PCOS can occur at any age between adolescence to menopause [6-13].

Diagnosis of PCOS is extremely important not only because of the problems PCOS causes, but also because it identifies risks for metabolic and cardiovascular disorders. In perimenopausal women menstrual disorders are believed to be transitional and infertility is usually not an issue, clinical manifestations, obesity, signs of androgen excess, menstrual irregularities are not taken seriously, at this age, especially in this part of the world. So, little is known about PCOS in these women.

Although studies do reveal linkages with genetic component and that clinical features of the disorder may change throughout life span, from adolescence to postmenopausal age, efforts to define differences in the phenotype and clinical presentation according to age are not visible [14-16]. Melissa et al. [17] reported that the rates of PCOS in mothers and sisters of patients with PCOS were 24% and 32% respectively. It has been widely recognized in the last decade that

several features of metabolic syndrome (MS), particularly insulin resistance and hyperinsulinemia, are inconsistently present in the majority of women with PCOS [18-21].

Most women with PCOS have metabolic abnormalities that include insulin resistance, hyperinsulinemia, higher levels of Cholesterol, Low-Density Lipoprotein (LDL), reduced High-Density Lipoprotein (HDL) and Hyper-triglyceridemia. So PCOS is thought to increase the cardiovascular risk [3,10,22-24], risk for hypertension and type 2 diabetes mellitus at later age [25-30]. The long term goal in such cases needs to be prevention of diabetes, heart disease and endometrial cancer [22,31-34].

Objectives

The present pilot study was done to know the incidence of PCOS among perimenopausal women with menstrual abnormalities and also to find out associated abnormalities.

Material and Methods

The present prospective pilot study was carried out in obstetrics gynaecology department of a rural institute in India with the help of department of Biochemistry. Study subjects were women of 35 to 54 years with menstrual disturbances, [hypomenorrhoea (menstruation for <2 days), oligomenorrhoea (menstrual cycle interval >35 days), abnormal uterine bleeding (cyclical/acyclical) or other menstrual abnormalities] with or without obesity and with or without hirsutism.

Women having evidence of pelvic inflammatory disease, obvious tuboovarian mass, cervical polyp, cervical/ovarian malignancy and women on hormonal replacement therapy were excluded. Study subjects with or without polycystic ovaries were further divided into 'PCO' and 'no-PCO' after pelvic ultrasonography.

PCOS was diagnosed by the presence of menstrual dysfunction, clinical signs of hyperandrogenism, hyperandrogenemia, evidence of insulin resistance, elevated LH/FSH ratio with the criteria based on PCOS Research, diagnostic criteria formed by the National Institute of Child Health and Human development [4]. The correlation with socio-economic status [35], lifestyle, family history, Body Mass Index (BMI), co-existing disorders was also studied.

Over all 9,096 women of 35-54 years of age attended the gynecological outpatient during the study period, of which 1767 women had menstrual disturbances, 715 women could have been study subjects as per inclusion criteria but only 118 women (16.5% of 715) were willing for complete work up. The serum T3, T4, TSH, prolactin, Estradiol (E2), fasting insulin glucose test were done and glucose/insulin ratio were calculated. Eighteen women (6.7% of 118) were further lost and so one hundred became the final study subjects, for finding out the incidence of PCOS at this age in relation to various variables.

Results

Of 100 women, 10% were between 35-39 years, 38% of 40-44 years, 43% between 45-49 years and 9% were of 50-54 years. Most of the subjects (81 of 100) were of 40-49 years. The mean age was 44.26 years (Table 1).

Out of 100 women 24 had less menstrual bleeding, (less duration and/or less flow) and/or interval between two phases of bleeding was more and 76 had more menstruation (bleeding duration and/or flow more) and/or interval between two phases of bleeding was less. Six women had oligomenorrhoea, 4 hypomenorrhoea, 8 oligohypomenorrhoea, 6 secondary amenorrhoea, 24 menorrhagia, 32 infrequent heavy bleeding and 20 polymenorrhagia. After complete work up, 12 were diagnosed to have PCOS and 88 were not having PCOS or thyroid disorder, [2 (2%) of oligomenorrhoea, 4 (4%) of hypomenrrhoea, 8 (8%) of oligohypomenorrhoea, 6 (6%) of amenorrhoea, 22 (22%) of menorrhagia, 29 (29%) with acyclical bleeding and 17 (17%) of polymenorrhgia].

Age	Parity	PCOS +ve	PCOS -ve	Total
35-44	Nullipara	1	10	11
	Multipara	8	29	37
45-54	Nullipara	0	1	1
	Multipara	3	48	51
Grand Total		12	88	100

Table 1: Age, parity and pelvic sonography

Of 12 women with PCOS, 6 (50%) women were of 35-39 years, 4 (33.3%) between 40-44 years, 2 (16.6%) between 45-49 years. Of 24 women with menorrhagia, 2 (8.33%), of 32 women with infrequent heavy bleeding, 3 (9.37%), of 20 women with polymenorrhagia, 3 (15%) and of 6 women with oligomenorrhoea, 4 (66.6%) were diagnosed to be having PCOS. None of the women with hypomenorrhoea and amenorrhoea were diagnosed to have PCOS. So of 12 with PCOS 4 (33.3%) had oligomenorrhoea, 2 (16.67%) menorrhagia, 3 (25%) had infrequent heavy uterine bleeding and 3 (25%) had polymenorrhagia. Of 100 women, 6 had oligomenorrhoea, of which 4 (66.66%) were diagnosed to have PCOS.

Seven (58.33%) of 12 women with PCOS were from upper economic class, 2 (16.66%) each from upper middle and middle class respectively and only one (8.33%) from lower class [35]. Of the 88 women with no PCOS, 29 (32.95%) were from upper class, 6 (6.8%) each from upper middle and lower middle class respectively, 30 (34.09%) from middle class and 17 (19.31%) from lower class. Of 12 women with PCOS, 3 (25%) had sedentary life and 9 (75%) active life. Of 88 women with no PCOS, 14 (16%) had sedentary life and rest 74 (84%) had active life (Table 2).

Age	Parity	Life Style				Total
(in years)		Sedentary		Active		
		PCOS +	PCOS-	PCOS +	PCOS-	
35-44	Nullipara	0	0	2	9	11
	Multipara	2	6	4	29	41
45-54	Nullipara	0	0	0	1	0
	Multipara	1	8	3	35	47
Grand Total		3	14	9	74	100
PCOS: Polycystic ovarian syndrome						

Table 2: Age, parity, life style and diagnosis.

Of 12 women diagnosed to be having PCOS after clinical, sonographic and biochemical, evaluation, two had hyperprolactinemia and 2 had hypothyroidism also. Of seven of those diagnosed with PCOS as per diagnostic criteria, 4 had elevated fasting insulin and 3 had low fasting glucose insulin ratio, 2 women had elevated LH/FSH ratio and low fasting glucose insulin ratio and one woman had elevated FT, LH/FSH ratio and low fasting glucose insulin ratio.

Of 12 women with PCOS, 8 (66.66%) were found to have leiomyoma uteri, All these 8 women underwent hysterectomy and histopathology revealed cystic glandular hyperplasia without atypia in

3 (37.5%), with atypia in one (12.5%), endometrium was proliferative in 2 (25%) and 2 (25%) had atrophic endometrium. In all the cases ovarian histopathology revealed multiple cystic ovaries with surrounding hyperthecosis, typical of PCOS.

Of the 12 women with PCOS, 8 (66.6%) were obese (BMI>35) and of 88 women without PCOS 45.4% were obese, significant difference (p value <0.05). It was observed that 6 (75%) of the 8 obese women with PCOS had waist:hip ratio >0.8 and 16 (40%) of the 40 women with neither PCOS nor hyperthyroidism or hypothyroidism had WHR >0.8 (p value <0.05, significant) (Table 3).

Age (in years)	Parity	Body Mass Index								
		<25				>25				
		WHR				WHR				
		<0.8		>0.8		Total	<0.8		>0.8		Total
		PCOS +	PCOS -	PCOS -	PCOS +		PCOS +	PCOS -	PCOS +	PCOS -	
35-44	Nullipara	1	2	1	0	4	0	4	0	3	7
	Multipara	3	10	2	0	15	1	12	3	6	22
45-54	Nullipara	0	1	0	0	1	0	0	0	0	0
	Multipara	1	26	5	0	32	0	9	3	7	19
Grand Total		5	39	8	0	52	1	25	6	16	48
PCOS: Polycystic ovarian syndrome										

Table 3: Age, parity, body mass index, waist to hip ratio and diagnosis.

Of 17 obese women with WHR <0.8, PCOS was diagnosed in one (5.88%). Of 6 women who had menstrual abnormalities, hirsutism, obesity, PCOS was diagnosed in 4 (66.66%), all 6 had PCO on USG of which 2 had elevated free testosterone, LH/FSH ratio, and low glucose/fasting insulin ratio, and one had only low glucose/fasting insulin level. Of 4 women with menstrual abnormalities, hirsutism but no obesity, no woman had PCOS. Of 42 with menstrual abnormalities and obesity but no hirsuitism, PCOS was diagnosed in 4 (9.5%) women and all had PCO on USG, 2 had low fasting glucose to fasting insulin ratio and elevated LH/FSH ratio and the other 2 women had elevated T3 and T4 and low TSH levels and elevated insulin levels.

Of 48 women with menstrual abnormalities but no obesity, PCOS was diagnosed in 4 (8.3%), of which only one had PCO on USG, had elevated FT, and low fasting glucose to fasting insulin ratio. Rest 3 women with PCOS, did not have PCO, 2 had low fasting glucose to insulin ratio and one had raised FT level.

Of 12 women with PCOS, 8 had low fasting glucose/insulin ratio, 5 had elevated LH/FSH ratio and 4 women had elevated free testosterone. Of 88 women with no PCOS, 3 had elevated free testosterone, 21 had low fasting glucose/insulin ratio, none had deranged LH/FSH ratio, T3, T4 were elevated in two and low TSH in 2.

Of 100 women, 27 had PCO on USG, of which 9 (33.33%) were diagnosed to have PCOS and of 73 women who had no PCO on USG, 3 (4.10%) had PCOS (significant difference p<0.05) but neither all women with PCO had PCOS, nor all PCOS cases had PCO on USG.

Forty six of 100 women had significant family history, diabetes mellitus in 4, PCOS was diagnosed in one of them, hypertension in 13, PCOS was diagnosed in 4 (30.76%), diabetes as well as hypertension in 6, PCOS was diagnosed in 3 (50%) of them. History of ischaemic heart disease was present in 4 (8.69%), PCOS was diagnosed in 2 of them. So of 12 women with PCOS, 10 (83.33%) had significant positive family history of diabetes, hypertension, ischemic heart disease and menstrual irregularities in mother. Of 88 women who did not have PCOS, 36 (40.90%) had significant family history of diabetes, hypertension, ischemic heart disease and menstrual irregularities in mother (significant difference p<0.05).

All perimenousal women with PCOS had metabolic disorders, 4 (33.33%) diabetes mellitus, 3 (25%) hypertension, 2 (16.66%) had diabetes as well as hypertension, 2 (16.66%) had hyperlipidemia with diabetes and hypertension, one (8.33%) had hypothyroidism. Of 88 women who neither had PCOS nor hyperthyroidism or hypothyroidism, 4 (4.5%) had only diabetes, 3 (3.4%) had hypertension, 3 (3.4%) had diabetes and hypertension, 5 (5.6%) had hyperlipidemia, 3 (3.4%) had hyperlipidemia with diabetes and hypertension with a significant difference (p<0.05).

Discussion

PCOS is one of the most common endocrine disorders which continue into and after menopause. In recent years, it has become apparent that PCOS is not only the most frequent cause of anovulation and hirsuitism, but is also associated with characteristic metabolic

disturbances that have important implications for long term health [23,36-39]. There are little studies of PCOS in perimenopausal women.

Of 100 women of 35-54 years who had presented with menstrual abnormalities with or without hirsutism and obesity, 12% had PCOS as per inclusion criteria (two of them had hypothyroidism also). Incidence is lower than reported, 37.3% in Kashmiri women presenting with hirsutism by Zargar et al [40] but they had included women of 15-75 years. PCOS has been well studied in young women. It is reported that PCOS is diagnosed in at least 5% to 10% of women between adolescence and menopause, making it one of the most prevalent hormonal disorders in this population [41]. Koivuner et al. [42] reported that PCOS varies with age but continues to be more common among women aged less than 35 years than in those above 35 years. Incidence of PCOS in perimenopausal women is not well known. Present pilot study is of women beyond 35 years of age without any record or history suggestive of PCOS so as to say it could have been continuation of PCOS at young age. Studies are needed about de novo PCOS in perimenopausal women as well as follow up of young women with PCOS through menopause which as of now does not seem to be easy in India unless women keep records and population based studies are done. Present study is of perimenopausal women where studies are scarce.

In the present pilot study with few cases it was found that more women with PCOS were from upper class but difference was insignificant (p value >0.05,). This needs further studies in a large population. Of 100 women, 6% women presented with oligomenorrhoea, 4% hypomenorrhoea, 8% oligohypomenorrhoea, 6% secondary amenorrheoa, 24% had menorrhagia, 32% had infrequent heavy uterine bleeding and 20% had polymenorrhagia. More women with oligomenorrhoea had PCOS (33%), 4 out of 12, similar to the study done by David et al. [4] who reported that 70% of women of PCOS have oligomenorrhoea however their study subjects were of 15-45 years. In the present pilot study most of the women with PCOS were obese, having hirsutism with menstrual abnormalities (p value <0.05, significant difference). Association of obesity was significantly high, 9 (75%) of 12 had WHR >0.8 with PCOS compared to those with no PCOS, WHR >0.8 in 40%, (16 out of 40). (p<0.05). Of 12 women with PCOS, 7 were obese similar to the study reported by Robert et al. [34], 35-50%. Hyperandrogenism is the prominent biochemical abnormality in women with PCOS. 6 (50%) of 12 had clinical features of hyperandrogenism. However Winter et al. [43] reported that hyperandrogenism partly resolves before menopause in women who have PCOS in young age. The reduction in hyperandrogenism explains the tendency of some women with PCOS to menstruate regularly as they grow older [44]. Etling et al. [45] also suggested that menstrual cycle abnormalities tend to normalize with age. This could be due to diminishing follicle cohort following ovarian aging [46]. It is possible that younger women with PCOS become better over the years, so follow up of women towards menopause and beyond is needed. Welt et al. [47] reported that inhibin known to stimulate ovarian androgen production decreases in normal women during middle age and contributes to decrease in testosterone production. It may also result from an age-related decrease in one of the testosterone biosynthesis enzymes, P450c17, implicated, in the development of PCOS [48]. However it could be that in those in whom such change does not occur will have menstrual abnormalities. Testosterone remains elevated in older women with PCOS, and may contribute to their increased risk for cardiovascular disease, endometrial cancer, and other diseases.

Of 12 women with PCOS after clinicosonographic biochemical findings, 8 had fibroid uterus, all underwent hysterectomy. Polsen et al. [49], Teleman and Mahailovici [50] also reported that hysterectomy, because of fibroids and menorrhagia had to be done more frequently among PCOS subjects.

In the present study PCO was significantly more in women with PCOS (75%, 9 out 0f 12) compared to women with no PCOS (20.45%, 18 of 88). Welt et al [51] compared USG appearance of ovaries in normal women with PCOS and reported that 14% of women with PCOS did not have PCO on USG. Hence absence of PCO does not rule out PCOS and presence does not diagnose PCOS.

Of 12 women who had PCOS, 8 (66.66%) had insulin resistance. Shayya et al. [52] reported that the impairment of insulin metabolism is central to the pathophysiologic cascade of PCOS. A positive but weak correlation between age and fasting glucose to insulin ratio has been reported, suggesting that a slight amelioration of insulin resistance occurs in PCOS with age [39,53,54]. Earlier Poretsky [55] reported that coexistence of insulin resistance and ovarian hyperandrogenism is a well-known phenomenon although the precise mechanism has not been clearly defined, the hypothesis that hyperandrogenism of insulin-resistant state is due to ovarian stimulation by high levels of circulating insulin. Rosenbaum et al. [56] reported a defect in glucose transport as a result of diminished production of GLUT-4 glucose transporter protein, a cause of insulin resistance in women with PCOS. In the present study all, perimenopausal women with PCOS had metabolic disorders (4 had Diabetes mellitus, 3 had hypertension, 2 had diabetes and hypertension, 2 had hyperlipidemia with diabetes and hypertension, one had hypothyroidism, significantly higher compared to women with no PCOS or hypothyroidism or hyperthyroidism. Researchers reported that PCOS is associated with characteristic metabolic disturbances that have important implications for long term health [23,30,37-39]. Most affected women are hyperinsulinemic and have altered lipid profiles, hypertension, increased risk of cardiovascular diseases. In perimenopausal women with PCOS, dyslipidemia is variable, significantly higher triglycerides, low density lipids, cholesterol and high density lipids [57] and is related to elevations in circulating androgen levels [31,58]. The incidence of heart disease with menopause is 6-7 times greater in women with PCOS, than in normal population [22,59]. Dursun et al. [24] did a study on patients with PCOS and reported increased risk for the development of hypertension and atherosclerotic heart disease (AHD). Kidson [10] have reported that 42% of women before the age of 60 years undergoing coronary angiography for ischaemic heart disease had PCO on ultrasound and out of these 10% were diagnosed to have PCOS. Kandarakis et al [29], and Wild et al [60] report that clinical presentation of PCOS is highly variable, so is missed unless investigated. These women are prone to developing complications obesity, impaired glucose tolerance and type-2 diabetes, dyslipidemia, metabolic syndrome and cardiovascular disease and endometrial cancer. Those with metabolic syndrome and/or type 2 diabetes mellitus are at high risk for cardiovascular disease (CVD). BMI, waist circumference, serum lipid/glucose, and blood pressure determinations are recommended for all women with PCOS, oral glucose tolerance testing in those with obesity, advanced age, personal history of gestational diabetes, or family history of type 2 diabetes mellitus.

The PCOS is a familial disorder, though genetic basis of the syndrome remains to be studied in depth. Familial clustering of PCOS and its symptoms reflect a strong genetic pathogenesis contributing to

the development of PCOS [61]. In the present pilot study overall 10 (83.33%) of the 12 women with PCOS had significant positive family history of diabetes, hypertension, ischemic heart disease and menstrual irregularities in mother, 36 (40.90%) of 88 women without PCOS had significant family history (p<0.05). Exact mechanism of inheritance has not been uncovered by researchers despite rigorous efforts. Ovalle et al. [62] after review of literature, have reported that it remains to be determined whether PCOS and type 2 diabetes mellitus represent no more than different clinical manifestations of the same insulin resistance syndrome, with their phenotypic differences due to the presence or absence of a coincidental genetic defect at the level of the ovary or pancreas, respectively, or representing the result of etiologically different subtypes of IR syndromes. Sheehan [14] reported that the significance of epigenetic role play in PCOS is evident from the fact that active amendments in lifestyle or dietary ingredients attenuate some of the detrimental effects and so adherence to regular physical activity for weight loss with intake of food bearing low glycaemic index and fat content have perpetually been the first line of management of PCOS. Also, existing evidence on epigenetic modifications in development of PCOS associated co-morbidities like CVD and type–2 diabetes mellitus (T2DM) are a definite prelude towards imminent epigenetic studies in PCOS [15,16].

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