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THE PREVALENCE AND ETIOLOGY OF POLYCYSTIC OVARIAN SYNDROME (PCOS) AS A CAUSE OF FEMALE INFERTILITY IN CENTRAL TRAVANCORE

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ABSTRACT
Recent alarming rise in the incidence of polycystic ovary syndrome (PCOS), the most common cause of female infertility is becoming a major concern among adolescent women worldwide. Altered hormonal and metabolic profiles are one of the common clinical manifestations in PCOS. The aim of the present study was to determine the prevalence and the etiology of polycystic ovary syndrome (PCOS) as a cause of female infertility in Central Travancore women, in view of their change in life style. In this cross sectional study, a consecutive series of 500 women (20-35) who were subjected to infertility treatment at specialist infertility clinics in Kottayam, Pathanamthitta and Alappuzha districts were selected. About 20 healthy volunteer females with regular menstrual cycles aged between 20 to 35 years were considered as the control. The data were collected from hospital records as well as using an investigator administered questionnaire. All data were tabulated and were subjected to statistical analysis using student's't' test, ANOVA and correlation. According to the findings of this study, PCOS is one of the most common causes of female infertility in Central Travancore women due to change in life style factors and unhealthy dietary patterns. The PCOS patients in our study also showed a wide range of hormonal and metabolic abnormalities. Insulin, FSH, LH, LH: FSH ratio, testosterone, prolactin, thyroxin (T_4), progesterone, glucose and cholesterol levels were increased in PCOS. The adoption of their unhealthy dietary habits and lack of exercise are key to improving chances of these hormonal and metabolic imbalances and increasing risks of PCOS among them.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disturbance in women of reproductive age. It occurs in approximately 5% to 10% of the female population and may be the leading cause of infertility in those of reproductive age (Knochenhauer *et al*., 1998; Azziz *et al*., 2004). The syndrome is characterized by chronic anovulation, hyperandrogenism, polycystic ovaries and decreased fertility (Ehrmann, 2005; Frank, 1995). PCOS is furthermore associated with insulin resistance, accumulation of abdominal fat and obesity (BMI >30 kg/m^2), which is present in approximately 50% of women with PCOS (Azziz *et al*., 2004). It is well known that reproductive function in women with PCOS is strongly dependent on bodyweight and the metabolic status of the patient. In the long term, PCOS is associated with an increased risk of impaired glucose tolerance, insulin resistance, hyperinsulinemia, cardiovascular disease, dyslipidemia and endometrial cancer (Ehrmann, 2005). Therefore, the syndrome is recognized as having a major impact throughout life on the gynecological and metabolic health of women.

In recent years, there is a sharp rise in the incidence of polycystic ovarian syndrome among reproductive aged women worldwide. The increasing incidence of this hormonal disorder in Central Travancore region is emerging as a major cause of concern among adolescent women here. The syndrome has been found to be one of the major causes that could lead to infertility later. In Central Travancore region 33% of total infertile women are suffering from PCOS (Roy and Malini, 2012). It is mainly due to changes in life style patterns. The influence of modernization and technological advancement reflects a lot in our present-day life. Most of the reported PCOS women are concentrated in the consumption of enriched carbohydrate diet, i.e. they are more dependent on soft drinks, fast-food, sweets, cured and smoked meats, salted nuts, canned and processed vegetables, meats, marinades and sauces and less on traditional dietary habits. The sedentary lifestyle and unhealthy dietary patterns are mostly contributed to the prevalence of PCOS. Older generations of women consume food in their most natural forms where as younger generations use processed forms. People began put their faith in the Westernized diets and lifestyle within the past two decades. Currently, no reliable information is available on the prevalence of PCOS among Central Travancore women and the etiology still remains obscure. Therefore in our study, by evaluating the medical records of the cases admitted in hospitals with complaints and symptoms suggestive of infertility, we aimed to detect the prevalence and etiology of polycystic ovary syndrome (PCOS) as a cause of female infertility in Central Travancore women.

MATERIALS AND METHODS

This was a prospective study done in specialist infertility clinics in Kottayam, Pathanamthitta and Alappuzha districts. For this, the medical records of 500 women at reproductive age (21 - 35) who admitted with complaints and symptoms suggesting various infertility cases were evaluated retrospectively. These patients presented with the clinical symptom of secondary amenorrhea (no menstruation during the previous 6 months) or oligomenorrhoea, (mean length of the menstrual cycle >41 days) dysfunctional uterine bleeding with heavy, frequent and painful menstrual cycle and infertility problems. The control group consisted of twenty healthy volunteer females with regular menstrual cycles aged between 20 to 35 years. Control subjects had regular ovulatory cycles, normal androgen levels and, no signs of polycystic ovaries on transvaginal ultrasound.

Laboratory measurement

The results of follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, thyroid stimulating hormone (TSH), thyroxin (T_4), tri iodo thyroxin (T_3), progesterone, and total testosterone of several blood tests were collected. The hormonal levels were estimated using RIA technique and assay was carried out in specially approved laboratories. The metabolic parameters such as the levels of blood glucose and serum cholesterol were estimated by standard biochemical techniques using standard kits.

Table 1: The prevalence of PCOS among 500 patients

Causes	Number of cases	% cases
Polycystic ovarian syndrome	168	33%
Other infertile cases	332	67%

RESULTS

Table 1 represents the prevalence of PCOS among 500 patients. Out of the total 500 infertile cases, 168 patients presented with polycystic ovarian syndrome (33%). Other infertile cases showed 67% incidence. Compared with corresponding controls, women with PCOS showed significantly ($p < 0.001$) increased levels of FSH (Table.2). The values were between 10 and 13 for 11 patients (6%), between 9 and 10 for 33 patients (20%), above 13 for 84 patients (50%) and between 6 - 9 for 40 patients (24 %) (Table 3).

The levels of luteinizing hormone were significantly ($p < 0.001$) increased in PCOS women when compared to control (Table. 2). The values were between 5 and 9 for 22 patients (14%), between 9 and 13 for 18 patients (10%), above 13 for 88 patients (52%) and between 13 - 17 for 40 patients (24%) (Table 3). The levels of insulin were significantly ($p < 0.001$) increased in PCOS women when compared to control (Table. 2). The values were between 5 and 15 for 18 patients (10%), between 15 and 25 for 28 patients (17%), between 25-35 for 40 patients (24 %) and above 35 for 82 patients (49%) (Table 3).

A comparable level of thyroid stimulating hormone (TSH) and tri iodo thyroxine (T_3) were observed in PCOS subjects and control (Table 2). However, the level of thyroxine (T_4) was

Table 2: The hormonal and the metabolic profile in control and PCOS subjects

Parameter	Control			PCOS			P values
	Mean	S.D.	Variance	Mean	S.D.	Variance	
FSH (µ/L)	4.98	0.83	0.70	11.4*	2.80	7.82	P< 0.001
LH (µ/L)	5.00	0.79	0.63	13.60*	9.58	91.70	P< 0.001
Insulin (µIU/ml)	10.27	1.88	0.83	39.61*	20.08	20.08	P< 0.001
TSH (µu/mL)	1.89	0.50	0.25	1.72	0.42	0.18	NS
T3 (p mu/L)	107.05	17.16	244.58	97.62	37.82	1430.41	NS
T4 (n mol/L)	9.28	1.68	2.82	18.90*	40.44	1635.48	P< 0.05
Prolactin(ng/mL)	21.95	2.43	5.84	*26.67	4.53	20.54	P< 0.05
Progesterone (ng/ml)	13.00	2.10	4.42	7.11*	2.10	4.42	P< 0.05
Testosterone (ng/dL)	46.70	12.67	160.43	77.18*	12.67	160.63	P< 0.05
Cholesterol (ng/dL)	201.250	3.9320	15.46	251.26*	60.711	3686.25	P< 0.05
Glucose (mg/100ml)	122.00	12.92	166.84	138.17*	31.86	1015.09	P< 0.05

*S - Significant, NS - Not significant

Table 3: Range, frequency and percentage of (FSH, LH and insulin) in PCOS and control subjects

Control			PCOS Group		
Range	Frequency	Percentage	Range	Frequency	Percentage
FSH					
3-4	6	30%	6-9	40	24%
4-5	8	40%	9-10	33	20%
5-6	6	30%	10-13	11	6%
			Above 13	84	50%
LH					
3 - 4	8	40%	5 - 9	22	14%
4 - 5	5	25%	9 - 13	18	10%
5 – 6	7	35%	13 -17	40	24%
			Above 13	88	52%
Insulin					
4 -7	5	25%	5 - 15	18	10%
7- 10	6	30%	15 - 25	28	17%
10 - 13	9	45%	25 - 35	40	24%
			Above 35	82	49%

Table 4: Range, frequency and percentage of (TSH, $T_3$and T_4) in PCOS and control subjects

Control Range	Frequency	Percentage	PCOS Range	Frequency	Percentage
TSH					
Less than 0.5	12	60%	0.5 - 1	65	39%
Above 0.5	8	40%	1 – 1.5	36	22%
			Above 1.5	67	39%
T_3					
40 -90	11	55%	20 - 45	40	24%
Above 90	9	45%	45 -70	37	22%
			70-95	27	16%
			Above 95	64	38%
T_4					
2-6	6	30%	2 -6	12	7%
6-10	9	45%	6 -10	17	12%
10 -14	5	25%	10 -14	67	39%

Table 5: Range, frequency and percentage of (prolactin, progesterone and testosterone) in PCOS and control subjects

Control Range	Frequency	Percentage	PCOS Range	Frequency	Percentage
Prolactin					
18-20	5	25%	Less than 24	51	30%
20-22	6	30%	24.28	55	33%
22-24	7	35%	28.32	22	13%
24-26	2	10%	32.36	40	24%
Progesterone					
10-12	9	45%	Less than 5	62	37 %
12-14	4	20%	5-10	97	57%
14-16	7	35%	10-15	6	4 %
			Above15	3	2%
Testosterone					
30-40	3	15%	36-50	4	2%
40-50	17	85%	50-86	134	80%
			Above 86	30	18%

Table 6: Range, frequency and percentage of (cholesterol and glucose) in PCOS and control subjects

Control Range	PCOS Frequency	Percentage	Range	Frequency	Percentage
Cholesterol					
190-200	15	75%	Below 250	88	52%
200-201	5	25%	Above 250	34	20%
			Above 300	46	28%
Glucose					
105 - 110	3	15%	100 - 115	24	14%
110 -115	8	40%	115 - 130	38	23%
115 - 120	9	45%	130 - 145	70	42%
			Above 145	36	21%

found to be significantly ($p < 0.05$) higher in the PCOS group when compared to control (Table 2). The values were between 2 and 6 in 12 patients (7%), between 6 and 10 in 17 patients (12%), between 10 and 14 in 67 patients (39%) and above 14 in 72 patients (42%) (Table 4). There was a significant ($p < 0.05$) difference observed in the mean prolactin level of both control and PCOS groups (Table 2). However, 51 cases (30%) in the PCOS groups showed normal prolactin levels where as 40 cases (24%) showed higher levels (32-36 ng/mL of prolactin (Table5) .The progesterone level was significantly ($p < 0.05$) lowered in PCOS group when compared to control (Table 2). The values were less than 5 in 62 cases (37%) between 5 - 10 in 97 cases (57%) between 10 - 15 in 6 cases (4%) and above 15 in 3 cases (2.8%) (Table 5). The testosterone levels were significantly ($p < 0.05$) increased in the PCOS group in comparison to the control (Table 2). The values were between 36 - 50 in 4 patients (2%), 50-86 in 134 patients (80%) and above 86 in 30 patients (18%) (Table 5).

Women with PCOS demonstrated significantly ($p < 0.05$) higher cholesterol levels in PCOS group in comparison to the control (Table 2). The values were below 250 in 88 cases (52%), above 250 in 34 cases (20%) and above 300 in 46 cases (28%) (Table 6). Compared with the corresponding controls, the blood glucose level was significantly ($p < 0.05$) increased in PCOS group (Table 2). The values were between 100 and 115 in 24 patients(14%),between 115 and 130 in 38 patients (23%), between 130 and 145 in 70 patients (42%) and above 145 in 36patients (21%) (Table 6).

DISCUSSION

Polycystic ovary syndrome, although a common disorder, remains poorly understood. Much debate continues regarding its etiology and as yet no universally accepted diagnostic criteria have been identified (Armstrong *et al*., 2001). In this study, we have demonstrated the prevalence of PCOS reproductive aged women of Central Travancore. We have also established the altered hormonal and metabolic profile in PCOS patients. PCOS is highly prevalent in Central Travancore women (33%) due to their unhealthy dietary patterns and life style changes. The socio economic studies carried out in these patients reveal that they belong to high income families and have a high intake of dietary sugar.

In our study, PCOS patients were presented with a wide range of hormonal and metabolic imbalances. An inappropriate gonadotropin secretion was associated with PCOS subjects in this study. For women with PCOS, LH and FSH are about two times or three times when compared to control. Earlier it was shown that woman with PCOS may have an LH level of 18 mL U/mL and a FSH level of about 6 mLU/mL (both levels still fall within the normal range of 5-20 mL U/mL). This elevated LH to FSH ratio may disrupt ovulation ((Taylor *et al*., 1997). An elevated LH/FSH-ratio of 2-3:1 is commonly used to indicate abnormal gonadotropin secretion, which has been established in some of the PCOS patients of the present study. The demonstration of an increased LH pulse frequency in PCOS subjects in our study is important as it indicates that at least a portion of the gonadotropin defect in this disorder occurs at the hypothalamic level.

Insulin resistance and hyperinsulinemia were observed in PCOS subjects of the present study. This insulin resistance was resulted from overconsumption of carbohydrate diet. An estimated 50% to 70% of women with PCOS are insulin resistant and experience weight gain, difficulty in losing weight, hypoglycemic episodes and intense cravings for carbohydrates (Michel more et al., 2001). This insulin resistance and compensatory hyperinsulinemia caused defects in gonadotropin hormone release in PCOS subjects of the present study. Researchers also suggest that the hyperinsulinemia seen in PCOS causes hyperandrogenemia which strongly supported our study with increased level of testosterone in PCOS subjects

A normal TSH levels with lower T_4 in PCOS subjects in the current study indicated non functioning pituitary gland which is not simulating the thyroid gland to produce T_4 (Drumond and Findlay, 1995). Hypothyroidism observed in these PCOS subjects is associated with an increased metabolic production rate of testosterone, diversion of testosterone metabolism from androsterone to etiocholanolone, and reduced binding activity and hepatic production of SHBG (Gordon *et al*., 1969). Hypothyroidism also decreases libido and causes anovulation, infertility, alopecia, and excessive and irregular menstrual bleeding.

High prolactin levels were found in PCOS women in the present study. Hyperprolactinemia can cause symptoms similar to PCOS. Reports have suggested that women with PCOS have elevated prolactin levels, typically falling within the 25-40 ng/ml range which supported the present study. Prolactin excess in PCOS subjects in our study has been associated with hyperandrogenism of PCOS in a variety of circumstances. This increased prolactin may augment adrenal androgen secretion by the inhibition of 3beta-hydroxysteroid dehydrogenase activity or, less often, through selective action on the sulfation of DHEA in adrenal or extra-adrenal sites (Carter *et al*., 1977). However, prolactin inhibits FSH-induced ovarian aromatase, leading to intraovarian hyperandrogenemia. In hyperprolactinemic women (prolactin range, 36 to 991 ng/mL) 40% had androgenic abnormalities of which the most common was elevated free testosterone levels (Longcope, 1986).

Abnormal progesterone secretions were observed in PCOS subjects. If the Progesterone level is high (usually greater than 14 ng/ml) this means that ovulation did indeed occur and the egg was released from the ovary. If the progesterone level is low the egg was probably not released. This test is especially important because sometimes women with PCOS can have some signs that ovulation is occurring however, when the progesterone test is done, it shows that ovulation did not occur. If this happens, the patient's body may be producing a follicle and preparing to ovulate, but for some reason the egg is not actually being released from the ovary. This information helps the physician possibly adjust fertility medication for the next cycle to encourage the release of the egg.

Increased level of testosterone secretion was observed in PCOS subjects. Women with PCOS often have an increased level of both total testosterone and free testosterone. The increased testosterone levels observed in PCOS subjects can suppress normal menstruation and ovulation. Accumulating reports suggested that plasma levels of testosterone, biologically available testosterone (non-SHBG-bound and free), androstenedione, DHEAS, DHEA, and DHT can be elevated in PCOS. By combining the results of a number of studies, it can be seen that there is increased ovarian androgen production in most women with PCOS. Under normal circumstances, more than 90% of serum DHEAS is secreted by the adrenals; (Longcope, 1986) thus, its elevation in women with PCOS indicates that there is an adrenal contribution to androgen excess (Ehrmann *et al*., 1995).

An increased cholesterol level was observed in PCOS subjects. Women with PCOS have a greater tendency to have high cholesterol, a major risk factor for developing heart disease. The levels of good (high-density lipoproteins or HDL) and bad (low-density lipoproteins or LDL) are sometimes more indicative of a PCOS woman's risk for developing heart disease, these levels might also be assessed. Women with PCOS tend to have less good cholesterol and more bad cholesterol. In addition, triglyceride levels, another component of cholesterol, tend to be high in women with PCOS which further contributes to the risk of heart disease. The serum total cholesterol and LDL-cholesterol levels were significantly higher in sisters with PCOS, compared to unaffected sisters or to control women (Sam *et al*., 2005). They associated these abnormalities with hyperandrogenemia.

PCOS subjects demonstrated high blood glucose levels in the current study. A high glucose level in PCOS subjects in our study indicated insulin resistance, a diabetes-related condition that contributes to PCOS. The incidences of Impaired Glucose Tolerance (IGT) and Type II Diabetes Mellitus(T2DM)are significantly increased in women with PCOS. In a study from

the University of Pittsburgh, T2DM was noted in 12.6% of women with PCOS (who had a mean age of 42 years) in comparison with 1.4% of matched control subjects (Talbott *et al*., 2004).

In this study we have demonstrated that PCOS is highly prevalent among the infertile cases of Central Travancore. Altered hormonal and metabolic profile have also been established in the present study. Nutrition for PCOS targets inflammation, as it is the root problem of the condition. Food also has the power to normalize hormone levels in their body, which will help control the symptoms of PCOS. Improving diet and exercise program by making lifestyle changes may reduce their risk for developing chronic diseases associated with PCOS such as diabetes, heart disease and endometrial cancer.

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