International Journal of Obstetrics and Gynecology Vol. 1 (2), pp. 015-019, October, 2013. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Abnormal blood pressure and hyperandrogenemia in first degree relatives of women with polycystic ovarian syndrome referring to gynecology clinics of Shiraz Medical University

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Accepted 30 September, 2013

In women with polycystic ovarian syndrome (PCOS), increased prevalence of hypertension and abnormal androgen status is common. The study investigated the degree of hypertension (BP) and hyperandrogenemia in the first degree relatives of women with (PCOS) referred to a clinic affiliated to Shiraz University of Medical Sciences. This is a case-control study in which 107 first degree relatives of women with (PCOS) as case group and 107 individuals as control group were interviewed. Then, the first part of a questionnaire including demographic information was filled in, and the blood pressure measurements and blood samples were obtained to evaluate the serum levels of androgens. The data were analyzed through Chi-square. All statistical tests had 95% confidence intervals and alpha coefficient of 0.05. There was a statistically significant relationship between the mean BP of the experimental and control groups (p≤0.001) but no significant relationship was observed among the brothers. The mean testosterone in the experimental groups was significantly higher than the controls (p≤0.001). Testosterone levels in the parents of the experimental group than control group but no significant relationship between them (p≥0.05). The first degree relatives of women with (PCOS) are probably exposed to the risk of high BP and hyperandrogenemia. Screening for hypertension and other risk factors related to increased androgen (Hyperlipidemia, glucose tolerance, etc.) is essential.

Key words: Hypertension, hyperandrogenemia, polycystic ovarian syndrome, hyperlipidemia, androgen.

INTRODUCTION

One of the most common disorders of endocrine glands and the most common cause of elevated androgens and hirsutism is polycystic ovarian syndrome. This disease is specified with bilateral enlarged cystic ovaries, amenorrhea or oligomenorrhea and persistent ovulation, with etiological and clinical manifestation including insulin resistance, hyperinsulinaemia and hyperandrogenemia appear (Novak, 2005). More than 50% of patients with polycystic ovarian syndrome suffer from obesity (Novak, 2005; Speroff and Fritz, 2005).

In this disease, abnormal lipoproteins status, increase in the incidence of hypertension with passing of time and reaching a maximum rate of 40 percent around menopause, increase in the incidence of arthrosclerosis, and cardiovascular diseases and up to 7 times the risk of myocardial infarction are common complications. Other com-

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plications include night apnea, and infertility (Baillargeon, 2005). Polycystic ovarian syndrome is a genetic disease from which about 10-6% of women of reproductive age (45-15 years old) suffer [Baillargeon, 2005; Kavardzhikova and Pechlivanov 2010).

The high familial incidence of this disease suggests its genetic origin but there is limited information about the gene or genes involved. In some studies, a high prevalence of premature baldness in the male first-degree relatives of these women has been observed (Glueck et al., 2003; Vasiljević, 2000) but the findings of other studies were not consistent with these results (Dunaif et al., 1989; Iuorno et al., 2002; Nestler et al., 1999).

Familial aggregation of an ovulation and polycystic ovaries confirming there is a genetic predisposition for this disease. Reported multiple polycystic ovarian syndrome cases in a family indicate the possibility of dominant inheritance transmission by the X chromosome. The incidence rate of hirsutism and oligomenorrhea is twice as much in paternal transmission, but there is a considerable diversity in the phenotypic incidence of this disease. In case mothers suffer from polycystic ovarian syndrome, the risk of the occurrence of disease in individuals is 35%, whereas sisters suffer either, the risk reaches 40%.

The results Yildiz Bulent et al in Turkey on 52 families of patients with PCOS were showed testosterone in pre and postmenopausal higher among the in first-degree female relatives of PCOS compared to the normal population. Also, the sisters of women with PCOS the level of LH, testosterone, androstenedione, and dehydroepiandrosterone sulfate was higher than sister of women non-affected PCOS. Eventually, it was concluded that family screening in women with polycystic ovarian syndrome is essential, (Yildiz et al., 2003) the study is necessary because; the relatively high prevalence of PCOS, to evaluate the hypothesis that first-degree relatives of these patients of affected PCOS have higher hypertension and hyperandrogenemia, and no study has been done in this regard in Iran. The present study entitled “A survey of abnormal blood pressure and hyperandrogenemia in first degree relatives of women with polycystic ovarian syndrome referring to gynecology clinics of Shiraz Medical University in 2009" has been conducted.

MATERIALS AND METHODS

This case control study was conducted in 2009. First, patients with polycystic ovary syndrome whose disease has been proved through clinical and Para-clinical methods by a specialist in gynecology clinics affiliated to Shiraz University of Medical Sciences were identified. Then their first-degree relatives (father, mother, sisters and brothers) with inclusion criteria were interviewed. Inclusion criteria included: 1. all subjects are first degree relatives of women with PCOS, 2. non-smoking, age over 30 years, no history of polycystic ovarian syndrome and no use of drugs for blood pressure and free testosterone. Then, the first part of a questionnaire comprising of demographic information was completed. Provided they had all the inclusion criteria and signed the consent form, they were selected as the experimental group.

The control group consisted of women who own and their first-degree relatives families are not suffering from polycystic ovarian syndrome. To ensure that a complete history (a history of regular menstrual periods, lack of hirsutism, infertility, etc.) was taken and those having all the inclusion criteria were selected as the controls. A sample size of 107 individuals (17 brothers, 34 fathers, 17 sisters and 39 mothers) as the experimental group and 107 patients as the controls were selected. Then the blood pressure and blood samples were measured in both groups.

The participants’ blood pressure was measured after 15 minutes sitting on a chair with no cover while their right arms were in a 45° angle to the chest and their elbows between 3-5 ribs space by means of a sphygmomanometer matched to the arms diameter while the bag pressure gauge had been closed to the 2.5 cm over the elbows. Blood pressure was measured twice within 10 minutes from the right arm and its mean was recorded. The first Korsakov phase was considered as the systolic point and the fifth as a diastole point. Blood pressure of equal or higher than 140/90 was recorded as hypertension.

The following considerations were necessary by the participants before the blood test

No use of drugs affecting blood pressure and androgens (the night before and the morning before the tests), digestible dinner 10-12 hours before the test (that abstinence from eating solid and liquid food except water). A written informed consent was taken from all the participants. Inclusion criteria were: 1-all subjects in the experimental group were of first degree relatives of patients with polycystic ovarian syndrome as diagnosed by a physician. The diagnosis of polycystic ovarian syndrome patients was based on history, clinical examination, laboratory tests, and ultrasound as well as tracking other diseases such as neoplasm, hyperprolactinemia and congenital adrenal hyperplasia. 2 -being over 30 years old 3 -no history of smoking 4- no use of drugs effecting blood sugar, blood pressure, cholesterol and blood testosterone three months prior to the test. 5- no history of polycystic ovarian syndrome.

For blood sampling, a sample was taken between 9-7 am from all the participants and centrifuged 45-30 minutes after that according to the standard protocols. Testosterone was measured by calorimetrically enzymatic

Table 1. Distribution of blood pressure in the study population.

level / group	*Case group(N=107)						**Control group(N=107)					
	Norma l ≤120/80		Pre-hypertension 121/81-139/89		High ≥140/90		Norma l ≤120/80		Pre-hypertension 121/81-139/89		High ≥140/90	
	number	percent	number	Percent	number	percent	number	percent	number	percent	number	percent
father	13	38.23	16	47.1	5	14.7	22	64.7	10	29.4	2	5.8
mother	13	33.33	22	56.4	4	10.2	21	53.8	17	43.6	1	2.5
sister	4	23.5	10	58.2	3	17.65	10	58.82	6	35.3	1	5.9
brother	7	41.17	9	52.9	1	5.9	10	58.82	7	41.17	0	0
	37	34.6	57	53.27	13	12.15	63	58.87	40	37.38	4	3.7

*Mean=12/73 SD=1.39 ** Mean=11/32 SD=1.21 p=o.o4.

Table 2. Comparison of mean (SD) blood pressure (mm / Hg) in in first degree relatives of women with polycystic ovary syndrome and first degree relatives of control women.

Group	Case group(N=107) Mean± Standard deviation	Control group(N=107) Mean± Standard deviation	P value
father	120.85±1.39	110.44± 1.39	P=0.001,t=-3,df=66
mother	122.69±1.31	111.66±1.02	P=0.001,t=-3.8,df=76
sister	120.75±1.2	100.7±0.72	P=0.001,t=-4.7,df=32
brother	110.88±1.43	100.85±1.39	P=0.001,t=-4,df=32

method using test kits Pars (Tehran-Iran). This kit is based on the testosterone over 10 ng/kg for males and more than 0/7 ng/kg are the women who are suffering Hyperandrogenism. To describe the target population, from continuous variables, mean and standard deviation and from extensive variables percentage was used. After the experiments, those who had high androgen were identified and were referred for further investigation to an endocrinologist.

Data collected based on the research objectives were analyzed using the Statistical Package for the Social Sciences (SPSS 16). Measured values are reported as mean ±standard deviation and percentage. The categorical and continuous variables (hypertension, testosterone) between the two groups were compared using the Chi-square test. The statistical tests were performed with reliability of 95% and alpha coefficient of 0.05. In this study, P values less than 0.05 was considered significant.

RESULTS

The average age of the parents participating in the two groups of the study was not significantly different (p>0.05). Optimal blood pressure in the experimental group (≤120/ 80) was seen in 34.6 percent of the participants while 58.78 percent of the controls were in this range of blood pressure. The risk of high blood pressure in the experimental group (high ≥ 140/90) was 12.15% and it was 7.3 percent in the control group. 53.27% of the experimental group and 37.38% of the control group were in the pre-hypertension status (121/81-139/89). A statistically significant relationship was observed between the risk of blood pressure higher than normal in both groups of control and experimental (p = 0.07), (Table 1)

Incidence rate of hypertension in the mothers, brothers and sisters in the experimental group (12.15%) showed no significant correlation with the control group (3.7%) (p > 0.05). But in the fathers of the experimental (14.7%) and control groups (5.8) this correlation was statistically significant (p<0.04). Average blood pressure of the fathers, mothers, and sisters of the experimental group was higher than the control group, being statistically significant (p =0.001) but the difference was not significant in the brothers (Table 2). The average house hold's testosterone was significantly higher than the control group (p =0.001) (Table 3). The incidence rate of high testosterone was higher in the mothers and fathers of the controls but it was not statistically significant (p>0.05). (Table 4)

DISCUSSION

This study showed no significant relationship in the incidence rate of hypertension between mothers, brothers

Table 3. Comparison of mean (SD) Blood testosterone levels in first degree relatives of women with polycystic ovary syndrome and first degree relatives of control women.

Group / Testosterone level	Case group(N=107) Mean± Standard deviation	Control group(N=107) Mean± Standard deviation	P value
father	7.9±1.66	4.6±2.14	P=0.001,t=-1.7,df=66
mother	0.7±1.03	0.4±2.01	P=0.001,t=-9.2,df=76
sister	0.60.18	0.3±0.11	P=0.001,t=-7.2,df=32
brother	8.9±1.67	3.30±1.78	P=0.001,t=-9.5,df=32

Table 4. incidence rate of high testosterone levels in first degree relatives of women with polycystic ovary syndrome and first degree relatives of control women.

Group / Testosterone level	Case group)		Control group		P value
	N	%	N	%	
Father(each group=34 people)	3	8.8	2	5.8	0.6
mother(each group=39 people)	2	5.1	1	2.5	0.5
sister(each group=14 people)	4	23.5	1	5.9	0.07
brother(each group=14 people)	0	0	1	5.9	0.06

and sisters of the experimental and control groups, but this relationship was significant in the fathers of both groups. Moreover, the average testosterone of the experimental group was significantly higher than the controls. Epidemiology has shown that increased incidence of cardiovascular diseases in diabetic patients is associated with impaired metabolism of lipoproteins and hypertension (Gaillard et al., 1997). In some studies, the factors causing cardiovascular diseases including diabetes type 2, hyperglycemic, hypertension and high testosterone were higher in the first degree relatives of women with PCOS compared with the control group (Yildiz et al., 2003).

The studied groups' age was homogeneous and this similarity confirms the homogeneity of data. In similar studies conducted by Benitez (Sir-Petermann et al., 2002) and Sir-Peterman (Legro et al., 2002), the individuals were also matched for age since age is highly related to chronic diseases such as obesity, diabetes, hypertension and hyperlipidemia (Stalenhoef, 1999).

Average blood pressure of the fathers, mothers and sisters of the experimental group was higher than the control group and this difference was statistically significant. Also, this finding confirms the results of the previous studies. In a similar study in Turkey in 2005, the fathers' average blood pressure of women with PCOS (polycystic ovarian syndrome) was significantly associated with the control group (Benítez, 2001). In another study in 2007, the brothers' blood pressure in women with polycystic ovarian syndrome was significantly higher than the controls (Baillargeon, 2007).

In a study by Sam, the mean level of blood pressure in the brothers of women with PCOS had a statistically significant relationship with the control group (Sam and sung 2008).

In similar studies conducted by Baillargeon (Baillargeon 2007), on suffering from high blood pressure, no significant correlation was observed between the experimental and control groups. It seems that differences in the findings of the various studies are due to the low sample size and lifestyle and genetics of different subjects as well.

In similar studies in the past, blood pressure in sisters of women with polycystic ovarian syndrome has not been measured and compared with the control group. But due to the importance of blood pressure in cardiovascular disease in the current study this was included and considered.

Also In a study by Sam et al, Systolic blood pressure in Brothers of Women with PCOS was similar, but diastolic blood pressure was significantly higher in brothers compared with control men (Sam and Coviello, 2008). Research results of Anderson et al also supported the hypothesis that the F First-degree relatives of women with PCOS are at increased risk of Cardiovascular Disease [Yilmaz etal,(2005)].

Our findings support the hypothesis that hypertension features of PCOS are heritable and high prevalence of

hypertension in female and male first-degree relative may represent an important new risk factor for cardiovascular disease in both women and men.

The mean testosterone in the mothers, brothers and sisters of the experimental group was significantly higher than the controls (p = 0/001). This result confirms similar findings in 2007. In that study, the anderstandiol rate, total testosterone and DHEAS in the family of the experimental group were higher than the control group (Yildiz et al., 2003).

In a study in 2007 on the first degree female relatives of women with polycystic ovarian syndrome, blood total testosterone levels in Maternal of the experimental group were higher than the control group (Unlühizarci et al., 2007).

In Richard et al study, to investigate the state of androgens in the brothers of women with PCOS, significantly higher free testosterone levels were observed in comparison with the similar group of the controls (Legro et al, 2002).

In another study in 2007, similar results were obtained. The mean free testosterone serum in the experimental group was significantly associated with the control group (Unlühizarci et al., 2007). Testosterone levels have not been investigated in other studies. Testosterone in central obesity, insulin resistance, cardiovascular diseases or some forms of breast cancer play an important role (Freedman et al, 1990). In women with polycystic ovarian syndrome, testosterone increases. These studies demonstrated that serum levels of free testosterone in the first-degree relatives of PCOs women, serum levels of total testosterone and DHEAS in the experimental group were higher than the control group. Testosterone levels in the fathers and mothers of the experimental group were higher than the control group but this was not statistically significant (p>0.05). Also, in Yildes Bulent's study, the incidence rate of testosterone above the normal in parents of women with polycystic ovarian syndrome was higher than the control group but it was not statistically significant (Yildiz et al., 2003).In Sam's study also no significant difference was observed between the controls and the experimental group in having higher levels of testosterone (p> 0.05). But in other studies this difference has not been studied (Sam et al., 2008).

The risk of testosterone levels higher than normal was in sisters of the experimental group, but cases of this disorder were not observed in the control group. But the difference was not significant between the two groups (p =0.07). But in a study by Lergo et al in 2005 to investigate the genetic evidence of hyperandrogenemia in families of patients with polycystic ovarian syndrome, they examined 115 sisters of 80 probands with PCOS from unrelated families, which Sisters did not report any history of menstrual disorders and 70 healthy women with no history of menstrual disorders participated. The amount of free circulating testosterone in the experimental group was higher than the control group (Legro et al., 1998). Lack of significant correlation between the risk of testosterone higher than normal in this study may partly be due to the small sample size and genetic diversity of the research community. Further studies with larger sample size are recommended in this field.

The past research has emphasized the role of excessive secretion of luteinizing hormones (LH), (Abbott et al., 2005) that leads to an increase in androgen production by ovarian theca cells (Tasoula Tsilchorozidou et al., 2004). The morphological changes in the ovaries, dysfunction, may be an indication of a genetic basis for PCOS, causing the ovary to overproduce androgen (Tasoula Tsilchorozidou et al., 2004; Jakubowski, 2008; Bremer and Miller, 2008). So, abnormal theca cell activity seems to be a primary source for excess androgens in PCOS women [28] and both female and male first degree relatives PCOS women are at higher risk for developing cardiovascular disease.

CONCLUSION

According to the latest studies, less than one third of patients with hypertension have been under treatment in the United States. One reason was lack of individual awareness about affliction with high blood pressure. Also, lack of effective monitoring and treatment of these people has its root in being asymptomatic. The importance of this issue today is characterized by being aware that the risk of morbidity and mortality from cardiovascular diseases increases by high blood pressure.

Therefore, the aim of this study was making families of the patients with polycystic ovarian syndrome sensitive if the complications are not yet serious and in case of occurrence of complications this study might be helpful in diminishing the effects. If the disease is in its early stages of progression (incubation phase) be diagnosed and treat immediately.

ACKNOWLEDGEMENT

This article is extracted from the thesis written by Moradi F. with proposal No. 3958 in Shiraz University of Medical Sciences financially supported by vice-chancellery of research in this university. Hereby I would like to thank community based nursing and midwifery research center and also gynecologic clinic managers of Zaynab (P.B.U.H.) Hospital for their cooperation. The Research Improvement Center of Shiraz University of Medical Sciences, as well as Ms A Keivanshekouh, are thanked for improving the manuscript's grammar.

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