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Impact of Headache in Women with Polycystic Ovary Syndrome

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Summary. Polycystic ovary syndrome (PCOS) is one of the most frequent endocrine, metabolic, and androgen excess disorders among reproductive age women. Globally, 46% of the adult population suffer from headache in general. PCOS and migraine pathogenesis are closely associated with insulin resistance. Studies on headache in women with PCOS are scarce. The objective of the study was to evaluate the frequency of headache, its association with metabolic parameters, and impact on daily activities in women with PCOS.

Materials and methods. 114 women with PCOS (according to the Rotterdam criteria) and 80 age-matched control women with regular menses and no clinical or biochemical hyperandrogenism or polycystic ovaries were enrolled in the study. Data on age, height, weight, and blood pressure were collected, the body mass index (BMI) was calculated. Participants were tested for complete blood count, fasting glucose, fasting insulin, lipid profile, and comprehensive hormone panel. An ad-hoc questionnaire was given to the participants to obtain information on headache.

Results. A total of 60.8% of studied women complained of headache attacks. Women with PCOS experienced headache more frequently than control subjects (68.4% vs. 50.0%, p=0.010). Having PCOS increased the odds ratio of headache by 2.17 (CI: 1.20–3.91, p=0.010). Being overweight or obese increased the odds ratio of having headache by 2.5 times for women with PCOS (OR 2.50, CI: 1.11–5.61, p=0.026). 24.6% of women with PCOS compared with 11.2% of control women reported that headache limited their daily housekeeping activities (p=0.020). 31.6% of women with PCOS compared with 18.8% of control women reported that headache had negative impact on their professional life (p=0.046).

Conclusion. Women with PCOS (particularly overweight or obese) in Lithuania are often prone to suffer from headaches; the latter affect their professional life and everyday activities.

Keywords: polycystic ovary syndrome, headache.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most frequent endocrine and metabolic disorders among reproductive age women. PCOS occurs in 3–17.8% of women of various nationalities and involves over 100 million women globally [1, 2]. PCOS is a heterogeneous disorder defined by a combination of symptoms and signs of androgen excess and ovarian dysfunction in the absence of other specific diagnoses. PCOS can be considered the most common metabolic disorder in premenopausal women, and two of the defining characteristics of PCOS – hyperandrogenism and insulin resistance – are closely linked [3, 4].

Globally, 46% of the adult population suffer from headache in general, 11% have migraine, 42% have tension-type headache, and 3% have chronic daily headache [5]. Headache disorders are associated with impaired quality of life [6]. Recent studies have proposed that migraine is primarily a metabolic endocrine disorder and that insulin resistance plays a significant role in the pathophysiology of migraine, as it does in PCOS [7]. The prevalence of PCOS is higher among women with idiopathic intracranial

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hypertension [8, 9]. Studies on headache in women with PCOS are scarce [10, 11].

The objective of the study was to evaluate the frequency of headache, its association with metabolic parameters and the impact on daily activities in women with PCOS.

SUBJECTS AND METHODS

This was a cross-sectional study that was carried out at the Department of Anatomy, Histology and Anthropology (Faculty of Medicine of Vilnius University) in cooperation with the Outpatient Clinics at Vilnius city. The study population included women aged 20–35, residents of Vilnius and Vilnius region. Written informed consent was obtained from participants prior to study entry. The Lithuanian Bioethics Committee gave approval to conduct the study. 114 women with PCOS (according to the Rotterdam criteria) and 80 age-matched women (with regular menses and no clinical or biochemical hyperandrogenism or polycystic ovaries) as controls, were enrolled in the study [12, 13]. Body weight, height and blood pressure were measured. Body mass index (BMI) was calculated as the ratio of weight in kilograms to height in square meter (kg/m^2). Venous blood samples were taken from each study subject after overnight fasting in the morning (between 7 and 9 a.m.). Participants were tested for complete blood count, fasting glucose, fasting insulin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, total testosterone, dehydroepiandrosterone sulphate (DHEAS), sex hormone-binding globulin (SHBG), thyroid-stimulating hormone (TSH), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides (TG). Laboratory measurements were done applying standard methods; intra-assay and inter-assay coefficients of variation for the tests were less than 5%. The Free androgen index (FAI) was defined according to the formula suggested by A. Vermeulen et al.: FAI = (total testosterone (nmol/L) × 100) / sex hormone-binding globulin (SHBG) (nmol/L) [14]. The Homeostasis Model of Assessment Insulin Resistance (HOMA-IR) index was calculated using the formula: HOMA-IR = (insulin (mIU/L)) × (fasting plasma glucose (mmol/L)) / 22.5) [15].

An ad-hoc questionnaire was given to the participants to obtain information on headache, including type of headache ("tension-type headache", "migraine", "tension-type headache and migraine", "other types of headache"), headache occurrence during the day ("in the morning hours", "in the afternoon", "in the evening", "at sleep" and "undetermined") and during the week ("at the beginning of the week", "in the middle of the week", "at the end of the week", "at weekends"), triggers of headache, impact of headache on everyday life ("negatively impacts quality of life", "negatively impacts professional life", "negatively impacts personal life", "negatively impacts sexual life"), and impact of headache on activities ("limits work activities", "limits daily housekeeping", "limits social activities", "keeps me at home", and "confines me to bed").

Table. **Study subjects' characteristics**

Variable	PCOS	Control
n	114	80
Age, years	27.18±3.87	27.99±3.65
BMI, kg/m^2	27.4±6.96	21.78±2.41*
Systolic blood pressure, mmHg	118.19±13.01	109.93±8.55*
Diastolic blood pressure, mmHg	79.04±9.68	74.53±6.83*
Haemoglobin, g/L	136.39±8.95	132.31±8.47*
FSH, IU/I	5.47±1.49	6.38±1.75*
LH, IU/I	7.87±4.11	6.17±2.16*
Estradiol, pmol/L	168.17±62.85	176.6±66.33
Testosterone, nmol/L	1.98±0.70	0.99±0.36*
DHEAS, μmol/L	8.2±2.96	6.76±2.19*
SHBG, nmol/L	45.39±27.1	73.17±23.1*
FAI	6.10±4.11	1.50±0.73*
TSH, mIU/L	2.22±1.06	1.89±1.02
Glucose, mmol/L	5.12±0.53	4.74±0.47*
Insulin, μU/mL	12.36±10.2	6.4±2.81*
HOMA-IR	2.96±2.77	1.36±0.63*
Total cholesterol, mmol/L	4.85±0.88	4.71±0.74
HDL-cholesterol, mmol/L	1.50±0.4	1.82±0.31*
LDL- cholesterol, mmol/L	2.84±0.76	2.55±0.71*
TG, mmol/L	1.15±0.64	0.77±0.34*

BMI – Body Mass Index; Student's t-test; *p<0.001

Analyses were conducted using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Categorical variables were reported as counts and percentages, and continuous variables were reported as means and standard deviations. The Chi-squared test (^{2}) was used to evaluate relationship between categorical variables. The between group differences were examined with Student's t-test. Logistic regression was used to determine headache status (as the dependent binary variable) and the presence of PCOS or overweight (as the independent variable). Statistical significance was set at $p<0.05$.

RESULTS

The study results are summarized in the Table. A total of 60.8% (n=127) of studied women complained of headache attacks: 35.1% (n=68) experienced tension-type headache, 7.2% (n=14) had migraine, 9.8% (n=19) had tension-type headache and migraine, and 8.8% (n=17) had other types of headache. Women with PCOS experienced headache more frequently than control subjects (68.4% vs. 50.0%, p=0.010) (Fig. 1). Logistic regression analysis was performed on headache status as an outcome and PCOS as a predictor. PCOS reliably predicted headache; having PCOS increased the odds ratio for headache by

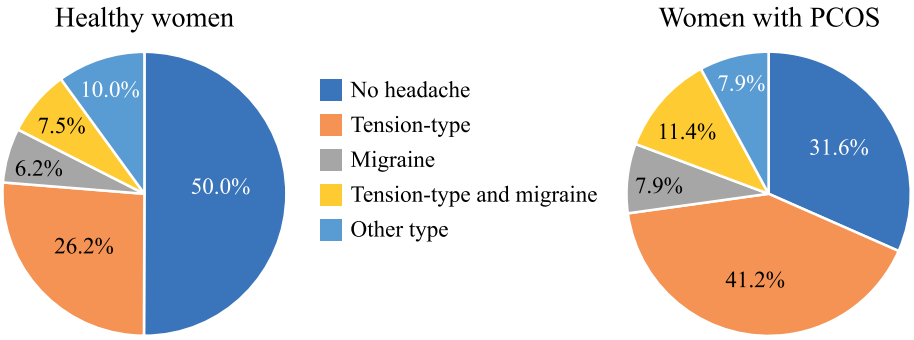

Fig. 1. **Frequency of headache by type in healthy women and women with PCOS**

2.17 (CI: 1.20–3.91, p=0.010). Women with PCOS experiencing headache had lower total cholesterol and high-density lipoprotein cholesterol compared with those without headache (respectively 4.72 vs 5.14 mmol/L, p=0.041, and 1.44 vs. 1.63 mmol/L, p=0.023). In the control group, women with headache, compared with those without headache, had lower hemoglobin (129.38 g/L vs. 135.25 g/L, p=0.002) and higher TSH (2.14 mIU/L vs. 1.64 mIU/L, p=0.030). In the control group, 30.0% of women in the lowest HOMA-IR quartile had headache compared with 67.5% of control women with HOMA-IR in the highest quartile (p=0.02).

43% (n=49) of women with PCOS were of normal weight, 23.7% (n=27) were overweight, and 33.3% (n=38) were obese. Overweight and obese women with PCOS experienced headache more frequently than normal weight women with PCOS (81.5% vs. 61.2%, p=0.016). Being overweight or obese increased the odds ratio of having headache by 2.5 times for women with PCOS (OR 2.50, CI: 1.11–5.61, p=0.026). Among overweight women with PCOS, 40.7% had migraine compared with 12.2% of normal weight women with PCOS (p=0.004) and 13.2% of obese women with PCOS (p=0.011). Tension-type headache frequency did not differ between groups by BMI among women with PCOS. 86.2% (n=69) of control women were of normal weight and 13.8% (n=11) were overweight. There were no obese control women. No significant differences in headache frequency between overweight and normal weight control women were found. Among control women, overweight was not a reliable predictor of headache. Of the group of women with PCOS, 24.1% of women can be classified as suffering from metabolic syndrome [12]. The rate of headache did not differ among women with PCOS having metabolic syndrome and without metabolic syndrome (64.3% vs 69.8%, p=0.59).

Regarding time of the day, 12.4% of women experienced headache in the morning hours, 24.2% in the afternoon, 19.1% in the evening, and 3.5% at sleep; no differences were found in headache occurrence time between women with PCOS and control women. 4.6% of women reported that they had headache in the beginning of the week, 8.8% in the middle of the week, 9.8% at the end of working week, and 4.1% at weekend. The frequency of headache during the week did not differ between women with PCOS and control women. 38.6% of women indicated that stress triggered headaches.

The impact of headache on daily activities is summarized in Fig. 2: 24.6% of women with PCOS compared with 11.2% of control women reported that headache limited their daily housekeeping activities (p=0.020). 40.4% of women with PCOS and 32.5% of control women reported that headache limited their work activities (p=0.265). Headache kept at home 10.5% of women with PCOS and 8.8% of controls (p=0.682).

The impact of headache on quality of life is presented in Fig. 3: 31.6% of women with PCOS compared with

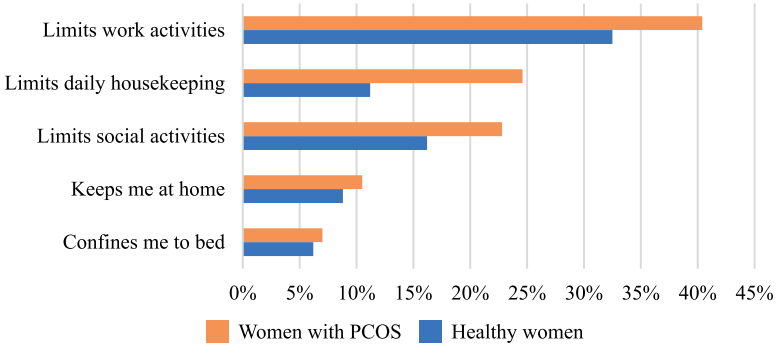

Fig. 2. **Impact of headache on daily activities in women with PCOS and healthy women**

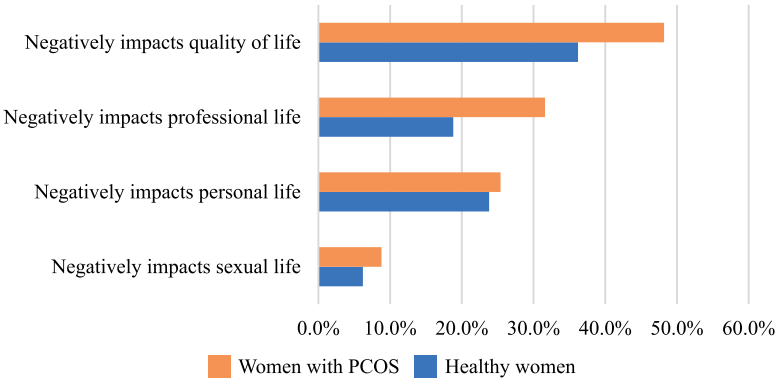

Fig. 3. **Impact of headache on quality of life**

18.8% of control women reported that headache had negative impact on their professional life (p=0.046). No significant differences in the degree of negative impact on quality of life, personal or sexual life were found between women with PCOS and control women.

DISCUSSION

In this study, we found that women with PCOS often suffered from headache that affected their professional life and everyday activities. Moreover, in women with PCOS, overweight or obesity was associated with the frequency of headache.

In our study, women with PCOS experienced headache more frequently than control women: 68.4% vs. 50.0%, p=0.010. We found only one study related to headache in women with PCOS that showed lower rates of headache in PCOS and controls compared with our results, respectively 44.9% in women with PCOS and 33.8% in controls [10]. Pourabolghasem et al. also found no significant difference of headache frequency between women with PCOS and controls (OR=0.78, CI: 0.6–1.03, p=0.81) [10]. Our results showed the opposite: PCOS increased the odds ratio for headache by 2.17 (CI: 1.20–3.91, p=0.010). Differences in reporting headache between women with PCOS versus control subjects could be attributed to variations in their respective hormonal milieu, particularly of estradiol, which may have cerebral vascular effects [11]. The results of this study are at variance with those of another study on the status of PCOS and headache [10]. Although a concrete etiology is lacking, ethnic, racial, and cultural differences in headache pain threshold have been noted worldwide and may explain this discrepancy [16–19].

Available data on headache in women with PCOS are limited, so exploring the pathogenesis mechanisms in migraine and idiopathic intracranial hypertension may lead to better understanding of headache in women with PCOS. Hyperinsulinemia and insulin resistance are highly prevalent in women with PCOS. Overall, 75% of lean women and 95% of obese women with PCOS have insulin resistance [20]. Several clinical studies have confirmed the presence of hyperinsulinemia and insulin resistance in migraine [21–23]. Hyperinsulinemia was associated with a 5.67-fold higher risk of migraine when comparing the lowest and the highest quartile of HOMA-IR [21] and with a 10.62-fold higher risk of migraine when comparing the lowest and the highest quartile of insulin in non-obese women [22]. Significant prevalence of insulin resistance was observed in women with chronic migraine compared with controls, and prevalence of metabolic syndrome was higher in the group of chronic migraineurs [23]. Rainero et al. suggested that alteration of insulin receptor response was characteristic of migraine and that activation of these receptors in the central nervous system through any form of hypoglycemia, e.g., long periods of fasting or intravenous injections of insulin, induced headache attacks in people with affinity for migraine [7]. In contrast, the results of the study by Sacco et al. did not support the association of migraine and insulin resistance [24]. Our results did not show any association of headache and HOMA-IR among women with PCOS, although the frequency of headache in control subjects in the lowest HOMA-IR quartile was higher compared with those in the highest HOMA-IR quartile.

Recent literature has consistently shown an association between obesity and headache [23, 25–27]. Keith et al. have conducted a cross sectional analysis of over 200,000 women drawn from 11 large general population databases. Obesity (BMI of 30 kg/m^2) comparing to BMI of 20 kg/m^2 was associated with an increase in the odds of reporting the presence of headache from 31% to 65%, and severe obesity (BMI of 40 kg/m^2) was associated with an increase in the odds of reporting the presence of headache from 49% to 118% [25]. Obesity has been shown to be a risk factor for migraine and has common overlapping pathophysiological mechanisms regulating feeding [26, 27]. Our results showed that being overweight or obese increased the odds ratio of having headache by 2.5 times in women with PCOS; no such association was found among control women.

Literature data on the association of metabolic syndrome and migraine is controversial. Guldiken et al. reported that 19.5% of patients with metabolic syndrome had migraine headache and the metabolic syndrome components were found more frequent in migraineurs [28]. Another study reported migraine and metabolic syndrome association in 31.9% of patients [29]. No correlation between metabolic syndrome and migraine was found by Salmasi et al., but the group of migraineurs had lower levels of high-density lipoprotein cholesterol [30]. Our results were somewhat in line with M. Salmasi et al., since the rate of headache did not differ among women with PCOS with and without metabolic syndrome, and women with PCOS suffering from headache had lower total cholesterol and high-density lipoprotein cholesterol compared with those without headache.

The prevalence of PCOS has been found higher among patients with idiopathic intracranial hypertension compared with the general population (up to 57% compared with 5–10%) [31]. Some recent studies have indicated that headaches in idiopathic intracranial hypertension meet the International Headache Society criteria for either episodic migraine, chronic migraine, or tension-type headache [32]. As a result, headaches due to intracranial hypertension may not be detected using a self-reported questionnaire. Epidemiological studies indicated that up to 70% of people with chronic headache had medication-overuse headache [33, 34]. A register-based study in Denmark revealed that women with PCOS had a twofold higher risk of migraine/headache compared with the control group, and this corresponded to a 1.7 times higher rate of prescriptions for painkillers and migraine medications [35].

Studies around the world have confirmed that PCOS adversely affects physical, psychological, and social func-

tioning, overall quality of life and life satisfaction of patients [36–39]. In our study, women with PCOS were twice as likely as controls to report a negative impact of headache on daily activities. Headache limited work activities for more than one third of women in both groups. One third of women with PCOS reported a negative impact of headaches on their professional performance, almost twice as high as in controls.

Our study has limitations such as the fact that we did not register medications used to relieve every headache episode. Also, women with PCOS and control women were not perfectly matched for blood pressure and BMI. It would make sense to take these differences into account in further research.

In conclusion, women with PCOS (especially overweight or obese) in Lithuania are frequently prone to suffer from headaches that negatively affect their professional life and everyday activities.

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GALVOS SKAUSMO POVEIKIS MOTERIMS, SERGANČIOMS POLICISTINIŲ KIAUŠIDŽIŲ SINDROMU

Santrauka

Policistinių kiaušidžių sindromas (PKS) yra viena dažniausių vaisingo amžiaus moterų endokrininių, metabolinių ir androgenų perteklių sukeliančių ligų. Pasaulyje 46 % suaugusiųjų vargina galvos skausmas. PKS ir migrenos patogenezė glaudžiai susijusi su atsparumu insulinui. Tyrimų, nagrinėjančių moterų, sergančių PKS, galvos skausmų sąsajas, nėra daug. Šio tyrimo tikslas buvo įvertinti pacienčių, sergančių PKS, galvos skausmo dažnį, jo sąsajas su medžiagų apykaitos rodikliais ir poveikį kasdienei veiklai.

Tyrimo metodai. 114 moterų, sergančių PKS (pagal Roterdamo kriterijus), ir 80 sveikų moterų, kurios neturėjo klinikinių ar biocheminių hiperandrogenizmo požymių, policistinių kiaušidžių ir kurių mėnesinės buvo reguliarios, buvo įtrauktos į tyrimą. Tiriamosioms buvo išmatuotas ūgis, svoris, kraujospūdis, apskaičiuotas kūno masės indeksas (KMI), atliktas bendras kraujo tyrimas, gliukozės, insulino koncentracijos nevalgius tyrimas, lipidograma, išsamūs hormonų tyrimai. Dalyvės užpildė klausimyną apie galvos skausmą.

Rezultatai. 60,8 % tirtų moterų skundėsi galvos skausmu. Moterys, sergančios PKS, galvos skausmą patyrė dažniau nei kontrolinės grupės pacientės (atitinkamai 68,4 ir 50,0 %, p = 0,010). Sirgimas PKS galvos skausmo šansų santykį padidino 2,17 karto (95 % PI: 1,20–3,91, p = 0,010), o sergančioms PKS moterims antsvoris ar nutukimas galvos skausmo šansų santykį padidino 2,5 karto (95 % PI: 1,11–5,61, p = 0,026). 24,6 % moterų, sergančių PKS, ir 11,2 % sveikų moterų teigė, kad galvos skausmas riboja jų kasdienę veiklą (p = 0,020). 31,6 % PKS sergančių moterų ir 18,8 % sveikų moterų nurodė, kad galvos skausmas neigiamai veikia jų profesinį gyvenimą (p = 0,046).

Išvados. Policistinių kiaušidžių sindromu sergančias moteris, ypač turinčias antsvorį ar nutukusias, dažnai vargina galvos skausmas, kuris neigiamai veikia jų profesinį gyvenimą ir kasdienę veiklą.

Raktažodžiai: policistinių kiaušidžių sindromas, galvos skausmas.

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