




Higher prevalence of clinical cardiovascular comorbidities in postmenopausal women with self-reported premenopausal hirsutism and/or oligo-amenorrhea

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ABSTRACT

Hirsutism is a common condition, being present in about 5–15% of women. It is characterized by the growth of terminal hair in a pattern typical for men, like as hair growth in upper lip, chin, cheek and lower and upper abdomen. Not infrequently, hirsutism is followed by other signs of hyperandrogenism such as alopecia, acne, and seborrhea. The current study evaluated the association between a self-reported history of hirsutism and oligo-amenorrhea during reproductive age and the presence of several comorbidities in women after menopause. A total of 1057 women were investigated in a cross-sectional study, and information on the age at menarche, menstrual history, complaints about excessive hair growth, and disease development was obtained. Participants from the study were postmenopausal women aged >55 y who attended a primary care service at least once during the 24-month period. Exclusion criteria included the presence of cognitive impairment and/or communication difficulties. Main outcomes were the presence of comorbidities after menopause. The prevalence of comorbidities was significantly higher in women with a history of hirsutism and/or oligo-amenorrhea [OR = 1.6 (95% CI 1.1–2.4), $p = 0.002$] or isolated hirsutism [OR 2.0 (95% CI 1.3–3.2), $p = 0.004$]. The prevalence of stroke, angina or myocardial infarction, cardiac failure, chronic obstructive pulmonary disease, and osteoarthritis were significantly higher in postmenopausal women who had experienced hirsutism and/or oligomenorrhea ($p < 0.03$). Limitations of the study came from the absence of a clear differentiation between hirsutism and hypertrichosis. According our results, the presence of hirsutism and oligo-amenorrhea during the female reproductive period may indicate susceptibility to important diseases at old age.

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Introduction



Hirsutism, which is the growth and distribution of male-type terminal hair, is a common condition in women of reproductive age.^{1,2} Women with hirsutism frequently demonstrate increased androgen levels in the blood and/or polycystic ovary syndrome (PCOS).^{1,2} Indeed, reports in the literature show that the prevalence of hirsutism is as high as 60–80% in women with PCOS as against 3–11% in the general population.^{1–3} A correlation between hyperandrogenism and cardiovascular comorbidities in women has also been proposed, but is still being debated because of several conflicting results. Moreover, it is unclear whether hyperandrogenic women are more prone to cardiovascular complications such as angina, myocardial infarction, or stroke.^{4,5} In an attempt to identify women with features of PCOS, we analyzed

separately patients reporting hirsutism and / or oligo-amenorrhea (reasonably suggesting PCOS) and patients with the complaint of hirsutism and regular menstrual cycles (that might potentially comprise the diagnosis of idiopathic or peripheral hirsutism).

Therefore, this study aimed to address whether hirsutism and/or oligo-amenorrhea during menarche were associated with the presence of self-reported key comorbidities (including cardiovascular disorders) after menopause.

Results

Of 1301 women eligible for the study, only 1057 completed the questionnaire (239 declined and 5 did not meet the inclusion criteria).

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The participants' age and BMI were 67.2 ± 7.6 y and 29.3 ± 5.5 kg/m², respectively. Hirsutism during reproductive age was reported by 12.7% of the women, oligo-amenorrhea by 10.6%, and 21.8% of the women reported having both conditions at the same or different time points. Just 1.7% of the women reported simultaneous hirsutism and oligo-amenorrhea during menacme, what cause the exclusion of analysis of this small group of women with stronger manifestations of endocrine disorders.

The women included in our study were overweight and obese. Only 1,3% and 20,6% of them were underweight and normal weight, respectively. However, there was no association between obesity and hirsutism [OR 1,16 (CI 95% 0.79 to 1.70), $P = 0.491$; controls = 29.1 kg/m² (SD 5.3) vs. case = 30.1 kg/m² (SD 6.5), $P = 0.118$] nor between obesity and "hirsutism and/or oligo-amenorrhea" [OR 1,03 (CI 95% 0.72 to 1.46), $P = 0.929$; controls = 29.1 kg/m² (SD 5.4) vs. case = 29.7 kg/m² (SD 6.2), $P = 0.276$] (data not show in the tables).

As shown in Table 1, no differences in age, BMI, years after menopause, education, tobacco use, or alcohol consumption were observed in women regarding self-reported hirsutism and/or oligo-amenorrhea. Nevertheless, women who reported hirsutism and/or oligo-amenorrhea had a higher prevalence of comorbidities (78.7%) compared with women without this history (67%) ($p = 0.002$).

When the presence of hirsutism and/or oligo-amenorrhea was considered, a larger association with other cardiovascular comorbidities was noted including

Table 1. Characteristics of women regarding the presence or absence of hirsutism and/or oligo-amenorrhea.

	Without Hirsutism or Oligo-amenorrhea	With Hirsutism and / or Oligo-amenorrhea	<i>P</i>
Age (years)	67.2 (7.6)	66.5 (7.6)	0.21
BMI (kg/m ²)	29.1 (5.3)	29.9 (6.4)	0.11
Years after menopause			
< 10 y	14.7% (115/780)	18.1% (40/221)	0.15
10 – 19 y	40.8% (318/780)	34.4% (76/221)	
20 – 29 y	29.5% (230/780)	34.8% (77/221)	
≥ 30 years	15.0% (117/780)	12.7% (28/221)	
Tabagism	12.4% (98/788)	10.5% (23/220)	0.42
Alcohol use (> 3 un/day)	0.3% (2/786)	0% (0/220)	1.0
Education			
Primary School	75.7% (544/731)	73.8% (150/203)	0.45
Secondary School	16.8% (123/731)	20.0% (41/203)	
Graduation or more	7.3% (54/731)	5.9% (12/203)	
Comorbidities*	67.5% (509/754)	78.7% (166/211)	0.002

*Reported at least one of the following: asthma, COPD, osteoarthritis, rheumatoid arthritis, heart failure, hypertension, ischemic heart disease, Parkinson's disease, multiple sclerosis, cancer, diabetes, inflammatory bowel disease.

Table 2. Comorbidities according to the presence of hirsutism and/or oligo-amenorrhea.

	With Hirsutism and / or Oligo-amenorrhea	<i>P</i>	With Hirsutism	<i>P</i>
Presence of Comorbidities	1.6 (1.1–2.4)	0.02	2.0 (1.3 – 3.2)	0.004
Diabetes Mellitus	1.1 (0.7–1.6)	0.65	1.2 (0.8 – 1.9)	0.36
Hypertension	1.4 (0.9–2.0)	0.07	1.5 (0.99 – 2.2)	0.06
Cardiac Failure	1.8 (1.1–3.1)	0.03	2.2 (1.3 – 3.9)	0.005
Stroke	1.8 (1.04–3.0)	0.03	1.3 (0.7 – 2.5)	0.34
Angina or MI	1.9 (1.2–2.9)	0.006	1.5 (0.9 – 2.4)	0.15
COPD	1.8 (1.1–3.0)	0.02	2.07 (1.2–3.4)	0.006
Asthma	1.3 (0.8–2.2)	0.27	1.57 (0.8–2.8)	0.08
Osteoarthritis	1.5 (1.1–2.1)	0.02	1.6 (1.1–2.3)	0.01
Rheumatoid Arthritis	1.45 (0.9–2.2)	0.08	1.3 (0.8–2.2)	0.14
Inflammatory Bowel Disease	1.67 (0.6–4.4)	0.27	0.7 (0.17–3.3)	1.0
Multiple Sclerosis	0.78 (0.7–0.8)	1.0	0.87 (0.85–0.89)	1.0
Parkinson's Disease	1.3 (0.3– 5.1)	0.7	0.87 (0.85–0.89)	0.38
Cancer	1.4 (0.8–2.5)	0.21	1.28 (0.6–2.5)	0.44
Hyperprolactinemia	3.52 (1.6–7.6)	0.03	3.0 (1.3–7.0)	0.01
Hypothyroidism	1.0 (0.70–1.4)	0.85	1.22 (0.7–1.8)	0.35

MI = myocardial infarction

stroke [OR 1.8 (95% CI 1.04–3.0), $p = 0.03$], angina or myocardial infarction [OR 1.9 (95% CI 1.2–2.9), $p = 0.006$], and cardiac failure [OR 1.8 (95% CI 1.1–3.1) $p = 0.03$]. Interestingly, results show that women with just refer the presence of hirsutism as a complaint during the reproductive life also evidenced a higher frequency of some clinical comorbidities (Table 2). In particular, these women were more affected by the cardiac failure [OR 2.2 (95% CI 1.3 – 3.9) $p = 0.005$], COPD [OR 2.07 (95% CI 1.2–3.4) $p = 0.006$], osteoarthritis [OR 1.6 (1.1–2.3) $p = 0.01$], and hyperprolactinemia [OR 3.0 (1.3–7.0) $p = 0.01$] (Table 2).

Discussion

Our study, performed in a multiracial population in south Brazil, provided evidence that self-reported hirsutism and/or oligo-amenorrhea during menacme was associated with the presence of comorbidities during the postmenopausal period.

The commonest cause of hirsutism is PCOS.² Nevertheless, the identification of PCOS is only possible during the reproductive period, and even so, a putative phenotype of PCOS based on the history of menstrual cycles during menacme and the presence of clinical signs of hyperandrogenism has been used for research purposes.⁶ Another disorder that is associated with increased cardiovascular risk is congenital adrenal hyperplasia (CAH), highlighting the key role of excessive androgen secretion in the development of some comorbidities.⁷ Although hirsutism is directly related

to hyperandrogenism, other features such as insulin resistance, glucose intolerance, dyslipidemia, increased inflammation, and oxidative stress status are commonly present in PCOS and should be put in perspective.

In addition to cardiovascular comorbidities, our results showed that women with a history of hirsutism and/or oligo-amenorrhea in menacme more significantly reported diseases like chronic obstructive pulmonary disease (COPD) and osteoarthritis. Although the mechanisms involved in both disorders are unknown, the role of androgens (testosterone) in the worsening of COPD or development of abnormal knee cartilage thickness in women have been described.^{8,9}

Most of population in our study (including controls) were above the healthy parameters (BMI under 25 kg/m²). Indeed, obesity paradox in elderly subjects is an interesting topic. Some studies have described no association between mortality and be overweight in this population while there was an increased risk of death for those with a BMI under 23 kg/m².¹⁰ Nonetheless, these findings could be due to confounding effects such as baseline illness.¹¹ Moreover, the WHO current recommendation still is that the BMI values were age-independent and the same for both sexes (http://apps.who.int/bmi/index.jsp?introPage=intro_3.html).¹²

The strengths of this study include the representative sampling of individuals attending the primary care, which comprises more than 90% of women living in the city, and the evaluation of a multiracial population, with the exception of Asians. These mean that the results of this study can be extrapolated to other postmenopausal women worldwide. Globally, PCOS remains under-recognized in primary care. In the UK, the primary care system indicates that the incidence of PCOS (2004–2014) was up to 50% of the expected cases.¹³ Similar figures have been described in Australia.¹⁴ The use of a questionnaire allowed us to include clinically hyperandrogenic women not formally diagnosed with PCOS in the study.

Limitations of the study came from the absence of a clear differentiation between hirsutism and hypertrichosis and the type of study design. Hypertrichosis is a condition that can be benign but also may be linked a variety of harmful disorders such as porphyria cutanea tarda, anorexia nervosa, neoplasia, and iatrogenic induced by drugs (use of minoxidil, cyclosporine, phenytoin, diazoxide, glucocorticosteroids).^{15,16} Therefore,

the lack of identification of hypertrichosis may be considered a bias to some reported endpoints. Another weakness derived from the study cross-sectional design and self-reported used data. Moreover, recall bias, about the questionnaire sections concerning hyperandrogenism and/or oligo-amenorrhea, could not be excluded. Finally, information about affected body locations by hirsutism and its connections with systemic disorders could also be helpful but were not explored in the present study.

The increase in hyperprolactinemia was observed in both groups (hirsutism with and without oligo-amenorrhea). Although the rise of prolactin is expected in PCOS (and therefore in the group of women with hirsutism ad oligo-amenorrhea), the influence of other situations including pituitary tumors, constitutional diseases and use of many different drugs could not be easily performed. In this context, caution is necessary to the interpretation of this result.

In conclusion, the co-occurrence of hirsutism and oligo-amenorrhea during the reproductive period of a woman seems to be predictive of important cardiovascular diseases such as angina/myocardial infarction, stroke, and cardiac failure at old age. Further observational studies including women with established diagnosis of PCOS and those with peripheral hirsutism, as well identifying those with hypertrichosis, will be helpful to validate the associations identified in our report.

Material and methods

Study and Population

A cross-sectional survey was performed in the municipality of Santa Maria (south Brazil) between 10th March and 31st August 2013. This study included postmenopausal women aged >55 y who attended the Brazilian primary care service at least once during the 24-month period. Exclusion criteria included the presence of cognitive impairment and/or communication difficulties. The estimated ethnic composition of the population comprised 63.5% Caucasians, 29.5% mixed, 6.6% Africans, and 0.4% other, according to the Brazilian Institute of Geography and Statistics.¹⁷

Variables

Data were collected using a standard questionnaire for comorbidities established and authorized by the GLOW study and The Center for Outcomes

Research, University of Massachusetts Medical School, as previously published.¹⁸ This questionnaire obtained data regarding demographic characteristics including lifestyle (alcohol and tobacco use), menopause, medications, falls, and comorbidities (type 2 diabetes mellitus, asthma, stroke, inflammatory intestinal disease, cardiac failure, angina, myocardial infarction, cancer, Parkinson's disease, multiple sclerosis, osteoarthritis, and rheumatoid arthritis). In addition, other questions concerning hirsutism, oligo-amenorrhea, abortion and treatment of hypothyroidism, infertility due to congenital adrenal hyperplasia, and Cushing's Syndrome or hyperprolactinemia were included, based on previous reports in the literature.^{17,19} The questions regarding hirsutism and oligo-amenorrhea were modified from the study with north european caucasian women by Koivunen *et al.* and consisted of the following questions: 1) "Do you remember if your menstrual cycles occurred at intervals greater than 35 d at least twice a year?" 2) "Do you usually have less than 8 cycles per year or do not menstruate?" 3) "Do you remember if in the past you had problems with the excessive growth of body hair?"²⁰ Oligo-amenorrhea was considered present when question one or 2 had a positive answer. Hirsutism was considered present when question 3 had a positive answer. Moreover, anthropometric measures including weight and height were obtained in all participants.

Informed consent was obtained from all participants. This study was approved by the municipality of Santa Maria, Brazil, and the Ethics Committee of the Federal University of Santa Maria (CAAE 11166012.6.0000.5346).

Statistical analysis

Description of data included mean \pm SD, median (IQR 25, 75), and frequency (n/total n). To address differences between groups, the Fisher's Exact, Chi-square, Student's t, and Mann-Whitney U-tests were used.

The results of these models were expressed in odds ratios and 95% confidence intervals [OR (95% CI)]. A statistically significant association was noted when $P < 0.05$. The analyses were performed using the statistical program IBM SPSS for Windows (version 19.0, IBM Brazil, São Paulo, Brazil).

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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