

Early onset androgenic alopecia: not a cosmetic problem but a sign of life time risk factors. Male phenotypic equivalent of polycystic ovarian syndrome: Is There a Male Phenotype of PCOS

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ABSTRACT

Objective: Polycystic ovarian syndrome (PCOS) was thought to be a gynecologic disorder and then accepted as a general endocrine and metabolic syndrome. The genetic component of PCOS seems to be very important in its etiology. Because of this reason there should be a male PCOS equivalent. Early androgenetic alopecia (EAGA) is a specific pattern of hair loss and it should start before age 30 years and it is claimed to be a male equivalent of PCOS in women.

Materials and Methods: In this study we aimed to investigate the hormonal and metabolic parameters of men with EAGA and compare them with healthy age-matched controls. Thirty men with EAGA and 30 controls were screened for free testosterone, DHEAS, gonadotropins, 17OH progesterone, ACTH, fasting glucose, fasting insulin, homocysteine and metabolic profile. Homeostasis model assessment (HOMA) results were used for the marker of insulin sensitivity. Alopecia classification was made by using the scale of Hamilton with Norwood modification.

Results: Patients with EAGA had higher free testosterone ($25,12 \pm 3,05$ vs $21,3 \pm 1,77$), DHEAS ($634,90 \pm 27,09$ vs $578 \pm 17,82$), LH ($9,16 \pm 0,28$ vs $5,13 \pm 0,40$). The EAGA group had insulin resistance but the control group did not (HOMA results were $3,34 \pm 0,47$ vs $1,43 \pm 0,3$). The homocysteine levels of EAGA group were higher than controls ($12,37 \pm 1,31$ vs $9,33 \pm 2,12$) which is another cardiovascular risk factor. The correlations that we found in our study among HOMA, serum androgen levels, homocysteine and alopecia scores were positive in EAGA patients. We didn't find any correlations among those parameters in control group. Because of these findings men with EAGA can be considered as male synonym to PCOS syndrome. These young men should be followed for the same long time risk profile like PCOS women. Insulin resistance and its results like metabolic syndrome, diabetes and cardiovascular diseases are real risks but there may be even a risk for infertility.

Conclusion: We aimed to investigate whether EAGA can be accepted as the male phenotype of PCOS and if they have elevated risk factors for chronic complications than their age and sex matched controls.

Keywords: insulin resistance, androgenetic alopecia, polycystic ovary syndrome

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) was thought to be a gynecologic disorder and then accepted as a general endocrine and metabolic syndrome. It is characterized by irregular menses caused by anovulation, clinical (hirsutism /acne), with or without biochemical findings of high androgenic hormones, small sized (<8mm) multiple cysts in ovaries and some metabolic abnormalities in women who suffers from the syndrome (1). The evidences for the genetic component in PCOS etiology are strong. In the clinic, we see lots of patients with PCOS who clusters in the same families. It seems to be inherited through a polygenic autosomal type of mechanism.

The role of genetic in PCOS etiopathogenesis gives the scientific basis for a male PCOS equivalent. There is a strong possibility for inheriting the same responsible genes for PCOS in male relatives of those women (2).

Early androgenetic alopecia (EAGA) starts before age of 30 even sometimes before age of 20. It is a specific pattern of hair loss that starts from the temporal and occipital parts of the hair. EAGA and accompanied hypertrichosis in men may be the male synonym of PCOS in women. Men with EAGA mostly show similar abnormalities in their sex hormone profiles like PCOS women. Although this phenotype and androgen abnormalities in men are widely accepted, the metabolic abnormalities and long-term risks are still controversial (3).

MATERIAL and METHODS

This study was a prospective case-control hospital-based one and executed in the endocrinology department of Ege University. The ethics committee approved this study as a graduation thesis, and all participants gave written approval for participating in this study. Thirty men aged 18-30 years that has this specific type of hair loss (according to the classification of alopecia scale of Hamilton with Norwood they all had grade 4 or higher alopecia) were accepted as our study patient group. The most important inclusion criteria of our study group are that the patients should have a first degree female relative with the diagnosis of PCOS. Thirty age-matched men without any evidence of androgenetic alopecia were accepted as control.

The exclusion criteria for our study were

- prior diagnosed endocrine disorder,
- cardio-metabolic diseases especially diabetes
- usage any medications that effect skin or hormones for hair loss
- Men with Body mass index ≥ 35 kg/m²
- Usage of medications that effect glucose metabolism
- Special for the control group, men who have relatives with PCOS were also excluded.

Detailed anamneses and family history were saved in their medical records for each participant. All individuals were assessed by the same physician. The weights of the patients were evaluated with the same Tanita BC-418 early in the morning before breakfast, their heights were also measured. The body mass index (BMI) was calculated using these results.

Blood samples were collected after ten hours overnight fast between 8 AM to 9 AM. Serum lipid profiles (total cholesterol, triglyceride, HDL, LDL) were measured by Olympus AU 2700 automated analyzer. The insulin levels in plasma were assessed using 2 site chemiluminescent immunometric assay by Immunolite 2000.

The glucose oxidase technique was used to evaluate plasma glucose levels (Biobak Laboratory Supplies Trade, Ankara, Turkey). Serum liver function tests [Serum glutamic oxaloacetic transaminase (SGOT), Serum glutamic pyruvic transaminase (SGPT) and glutamyl transferase (GGT)], kidney functions (creatinine and urea) and uric acid levels were measured by Olympus AU 2,700 analyzer.

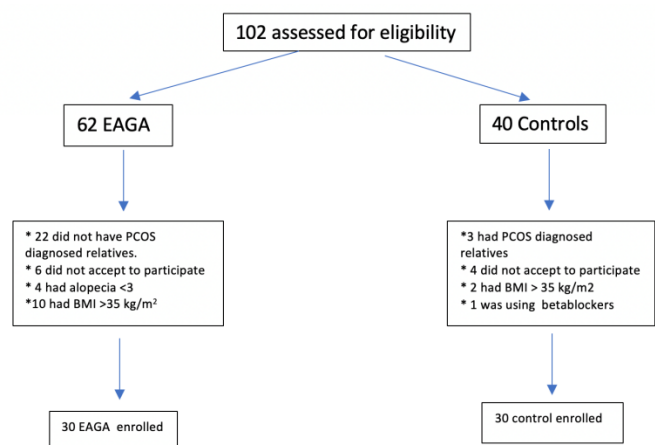
The levels of insulin in plasma were measured by microparticle enzyme immunoassay (Abbott, Wiesbaden-Delkenheim, Germany). Insulin sensitivity was investigated by calculation of [fasting insulin (mU/ml) X fasting glucose (mg/dl)/22.5X18 = HOMA]. Results greater than 1.7 were accepted positive for insulin resistance and >2.7 was a high risk of diabetes mellitus.

Serum homocysteine levels were measured by high-performance liquid chromatography with the Hewlett-Packard 1100 Series System (Waldron, Germany). The serum concentrations of FSH, LH, E2, progesterone, prolactin, and cortisol, were measured by chemiluminescent enzyme immunoassay (ASC 180 (+) Ciba Diagnostics, USA). The blood sample test results of ACTH, 17-OH progesterone, Free Testosterone, DHEA-S, and thyroid hormones were measured with standard radioimmunoassay.

The Statistical Package for the Social Sciences (version 10.0 for Windows; SPSS, Inc., Chicago, IL) was used for statistical analyses. The normality tests were used to test the characteristic distributions of the data. If the distribution of the variables were normal, students two tailed t-test with or without logarithmic transformation was used to compare all parameters. For the variables which didn't show normal disturbance even after log transformation Man-Whitney U test was performed. Relations between insulin sensitivities, degree of alopecia, metabolic and hormonal parameters were analyzed with simple linear regression analysis, and Pearson (r) correlation coefficients were presented. P values smaller than 0.05 were accepted as statistically significant.

Study design: One hundred two patients were evaluated as the outpatient basis in Ege University endocrinology and dermatology departments. Figure 1 shows the patient enrollment protocol. Sixty-two patients with EAGA were evaluated for the patient group. In this group of patients, 22 did not have first degree PCOS relatives, 6 of them did not accept to participate in our study, one had an alopecia score <4 and 10 of them had body mass index (BMI) >35 kg/m². For the control group we evaluated 30 medical students, assistants and fellows without significant alopecia. Among the control group subjects 3 had PCOS relatives, 4 of them did not want to participate, 2 had BMI >35 kg/m² and one of them was using betablockers. The remaining 30 participants became our control group.

Figure 1: Study design chart



RESULTS

The demographic and biochemical features and laboratory results of the studied groups are demonstrated in Table 1. The age in the EAGA group (as mean \pm SD) was 25,33 \pm 2,24 years and it was 24,3 \pm 1,72 years in group 2. The difference was not statically significant (P=0,06). The calculated BMI is significantly high in the EAGA group than the control group 2 (27,42 \pm 3,3 kg/m² vs 24,7 \pm 3,13 kg/m² respectively P=0,02). The systolic blood pressures were similar in both groups but the diastolic blood pressure was high statistically in EAGA group (8,18 \pm 0,41 vs 7,95 \pm 0,29 P=0,01). The blood glucose in the fasting state (FBG) was significantly higher in Group-1 than Group-2 (98,93 \pm 4,49 mg/dl vs 85,96 \pm 4,64 mg/dl respectively P=0,01). There were 6 patients in EAGA group who had impaired fasting glucose (IFG). We performed standard two-hour oral glucose tolerance test with seventy-five grams glucose (OGTT) to those patients and 4 had impaired glucose tolerance and 2 had normal results. None of the control group-participants had IGF. We did not perform an OGTT to the control group as the FBG and HbA1c levels were normal in all control group patients. The HOMA index was higher and it was in insulin-resistant range in all the patients in Group 1. That result was significantly higher than control group (3,34 \pm 0,47 vs 1,43 \pm 0,3 respectively P<0,01). There were only 7 participants whose HOMA index was higher than 1,7 (risky group) and no one had a HOMA index greater than 2,7. The lipid profile parameters except HDL were significantly higher in EAGA but none of them needed antilipidemic treatment.

HDL levels were similar in the two groups. The mean HbA1c value of EAGA was higher than control group (5,91 \pm 0,24 vs 5,29 \pm 0,18 respectively P<0,01). In the EAGA group 1 patient had a diabetic HbA1c value but his OGTT was in IGT range. Homocysteine values were higher in AGAE group than control group (12,37 \pm 1,31 vs 9,33 \pm 2,12 respectively P<0,01).

The hormonal profiles of our study population are demonstrated in Table 2. We found that The EAGA group had significantly higher free testosterone levels than controls. (25,12 \pm 3,05 vs 21,3 \pm 1,77 respectively P<0,01). When we investigate adrenal androgens DHEAS was significantly higher in the EAGE group (634,90 \pm 27,09 vs 578 \pm 17,82 p=0,02) but the 17-hydroxiprogesterone values were not significantly different. (2,31 \pm 0,18 vs 2,22 \pm 0,12 P=0,02).

The ACTH and TSH values were similar in both groups. The prolactin results of EAGA group was significantly lower than controls (12,96 \pm 1,58 vs 14,7 \pm 2,1 respectively p<0,01) The mean LH results were higher in EAGA group (9,16 \pm 0,28 vs 5,13 \pm 0,40 P<0,01) but FSH mean results were similar in both groups (4,20 \pm 0,17 vs 4,29 \pm 0,16 P=0,8). This resulted in the elevation of LH/FSH ratio in the EAGA group. In our investigation we demonstrated that the mean levels of prolactin in the EAGA group were significantly lower than the control group. But all the results of both groups were in the normal range (12,96 \pm 1,58 vs 14,7 \pm 2,1 respectively p<0,01)

Table 1: Demographic and biochemical results of the studied groups.

	GROUP-1	GROUP-2	p
AGE (year)	25,33 \pm 2,24	24,3 \pm 1,72	P=0,06
BMI(kg/m ²)	27,42 \pm 3,3	24,7 \pm 3,13	P=0,02
SYSTOLIC BLOOD PRESSURE (cm/Hg)	12,12 \pm 0,46	11,87 \pm 0,55	P>0,05
DIASTOLIC BLOOD PRESSURE (cm/Hg)	8,18 \pm 0,41	7,95 \pm 0,29	P=0,01
ALOPECIA SCOR	7,93 \pm 1,5	1,47 \pm 0,5	P<0,01
FASTING BLOOD GLUCOSE (mg/dl)	98,93 \pm 4,49	85,96 \pm 4,64	P<0,01
FASTING INSULIN (mIU/ml)	13,53 \pm 1,83	6,8 \pm 1,44	P<0,01
HOMA	3,34 \pm 0,47	1,43 \pm 0,3	P<0,01
T. CHOLESTEROL (mg/dl)	232,96 \pm 14,44	193,63 \pm 15,817	P<0,01
TG (mg/dl)	245,76 \pm 45,92	177,9 \pm 35,48	P<0,01
HDL (mg/dl)	42,16 \pm 4,2	41,83 \pm 6,2	P=0,81
LDL (mg/dl)	141,40 \pm 11,92	118,23 \pm 14,32	P<0,05
URIC ASID (mg/dl)	6,1 \pm 1,19	5,1 \pm 0,55	P=0,83
SGOT (IU/L)	24,42 \pm 6,7	23 \pm 6,1	P=0,76
SGPT (IU/L)	39,6 \pm 9,3	26 \pm 9,1	P<0,05
HOMOCYSTEIN (μ mol/L)	12,37 \pm 1,31	9,33 \pm 2,12	P<0,01
HBA1C	5,91 \pm 0,24	5,29 \pm 0,18	P<0,01

Table 2: The Hormonal Profiles of the Studied Groups

	GROUP-1	GROUP-2	p
F.Testosteron(pg/ml)	25,12 \pm 3,05	21,3 \pm 1,77	P<0,01
DHEAS (μ g/dl)	634,90 \pm 27,09	578 \pm 17,82	P=0,02
17-OHP (ng/ml)	2,31 \pm 0,18	2,22 \pm 0,12	P=0,11
FSH (mIU/ml)	4,20 \pm 0,17	4,29 \pm 0,16	P=0,80
LH (mIU/ml)	9,16 \pm 0,28	5,13 \pm 0,40	P<0,01
ACTH (pg/ml)	26,16 \pm 3,90	26,4 \pm 3,59	P=0,81
TSH (mU/ml)	2,56 \pm 0,51	2,37 \pm 0,52	P=0,73
PROLAKTİN (ng/ml)	12,96 \pm 1,58	14,7 \pm 2,1	P<0,01
AGA SKOR	7,93 \pm 1,5	1,47 \pm 0,5	P<0,01

We investigated the correlation between androgenic hormones and insulin sensitivity. The correlation between HOMA and free testosterone levels were positive and strong in EAGA group as shown in Figure-2 ($r=0,69$ $p<0,001$). The correlation between DHEAS and HOMA was also positive and statistically significant but weaker than free testosterone and HOMA correlation shown as shown in Figure 3. ($r=0,43$ $p=0,17$)

The levels of 17OHP and HOMA were not significantly correlated in our study ($r=0.17$ $p=0.59$). The correlation among homocysteine values and HOMA results were weakly positive but statistically significant ($r=0,37$ $p=0.04$). The correlation was also positive between the alopecia score and free testosterone as shown in Figure-4.

Figure 2: The correlation of F. testosterone and HOMA

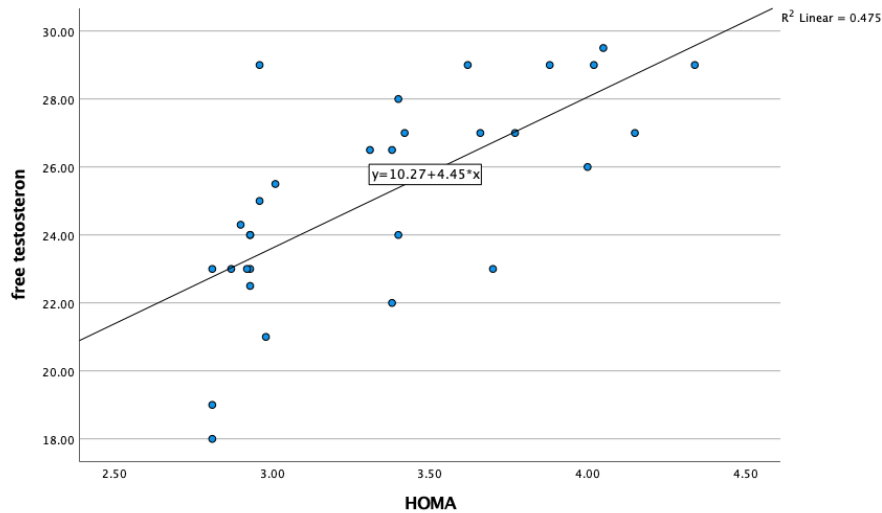


Figure 3: The correlation of Alopecia Score and HOMA

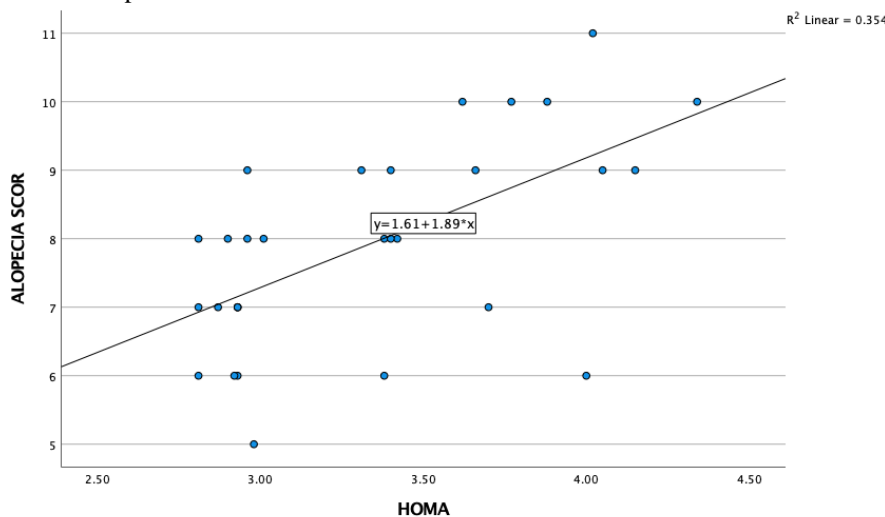
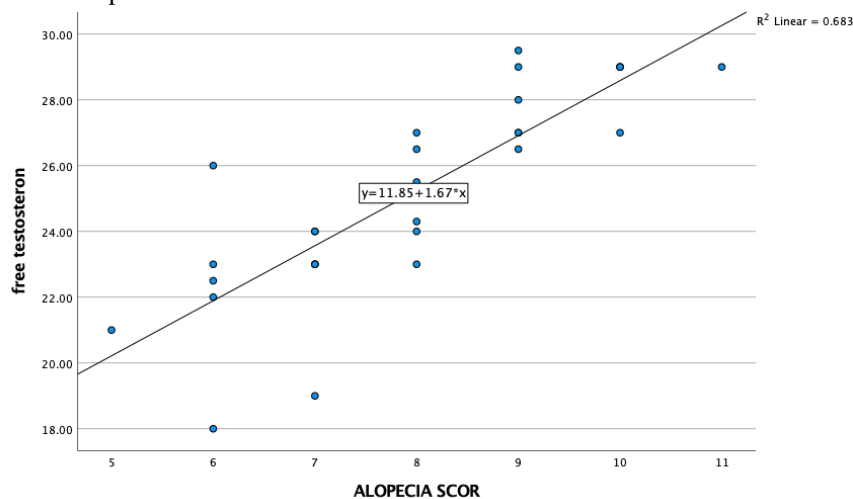


Figure 4: The correlation of Alopecia Score and free testosterone



DISCUSSION

EAGA is like a dance of androgens and gens. Evaluating the testicular and the adrenal gland hormones in these men is necessary to understand the etiopathogenesis of EAGA and to predict the future risks in this problem. Various studies proved the there are lots of similar findings in the hormonal abnormality styles of EAGA men with those women with PCOS. Now EAGA in men is widely accepted to be the phenotypic equivalent of PCOS (4).

There are a lot of studies showing the association of EAGA with insulin resistance and metabolic syndrome (3). Although it is really difficult to compare the results of the sex hormone parameters in male and female patients, there are studies in the literature that reports similar hormonal changes in men affected by the EAGA as seen in PCOS (5). It was found that this characteristic EAGA type is mostly present in male family members of PCOS women. This supports the hypothesis of the genetic component of this syndrome.

In this study we investigated 30 EAGA men who have first-degree relatives with the diagnosis of PCOS and compared them with age-matched men without EAGA and also without any female relatives with the diagnosis of PCOS.

In our study, the mean free testosterone and DHEAS levels in the EAGA group were significantly elevated than the levels of Group 2. The findings of free testosterone were similar to studies by Sanke et al (6), Narad et al (7) and some others. (8, 9) In contrast with those studies, some investigators found just slightly lower than normal levels of testosterone among their EAGA patients (10, 11). For the high DHEAS levels in EAGA, our findings were similar to the findings of some of the authors (10, 12). But again some authors published normal values of DHEAS (7, 8) in their study group EAGA men. The high DHEAS value is an important finding as DHEAS has some special features such as it has a long half-life and it doesn't have any pulsatility. It is widely accepted as a useful marker of hyperandrogenism in men (5, 13). In this study, we didn't define any correlation between the DHEAS - ACTH levels but there correlation between F. testosterone and DHEAS was significant and positive. This indicates that pituitary-adrenal ax stimulation may not be the main reason of DHEAS elevation (5). But we did not investigate ACTH stimulated DHEAS response. Studies with PCOS women found the increased response to ACTH stimulation even the basal DHEAS values were not correlated to ACTH (13, 14). Additional new studies are needed to estimate the effect of ACTH stimulation on DHEAS levels in EAGA men.

In our study, we found elevated LH/FSH levels than the control group due to the elevation of LH levels in men with EAGA. There are conflicting data in the literature about the high LH/FSH levels and LH elevations in EAGA men (7, 15). We think that elevation in LH is an important finding in EAGA men with PCOS family members as elevated LH/FSH ratio is a significant finding of PCOS. (13) An increase in LH levels results in increased testosterone levels and the finding in our study of significant correlation among those values supports this theory. As far as we know this is the first study that evaluated the correlation among them. In our study, we found decreased levels of prolactin in EAGA group; it is the

opposite of the study by Sanke et al (6) as they found increased levels. But in our study all the results of both the EAGA and control group were in the normal range. More research is needed for determining the role of prolactin in this syndrome.

In our study, we found significant increases of fasting blood glucose, fasting insulin, HOMA and HbA1c results in EAGA men than the control group. Insulin resistance was reported frequently in men affected by the EAGA in the literature (16). The brothers of PCOS women are shown to suffer from some metabolic problems such as a higher risk of insulin resistance, elevation in triglyceride levels, and elevation in blood pressure (17, 18). We found insulin resistance and other problems not only in brothers but in all first degree male EAGA relatives of PCOS women. The combination of lower SHBG with higher free testosterone and metabolic problems in the EAGA men were reported in some studies. A case-control study on a Finnish population made of 125 men with EAGA and 104 controls, aged 19–50 years, found patients with early EAGA had elevated BMI with a twofold higher risk of developing insulin resistance when compared to controls (19). In our study, we found higher BMI in the group of EAGA than controls. The interesting finding is that the insulin resistance was significantly higher than the control group even if the BMI effect is eliminated. According to this EAGA may be accepted as one of the predictors for the future diagnosis of hyperglycemia, insulin resistance then type 2 DM in young patients. Framingham Offspring Study has demonstrated that insulin resistance and serum homocysteine level elevations are associated and may partially be the reason for increased risk of CVD (20). The reason for elevated homocysteine is insulin inhibits the hepatic cystathionine β synthetase activity. In our study, we found significantly increased levels of homocysteine in the EAGA group and it was correlated with insulin levels this was similar to the study of AGA and coronary artery heart disease risk (21).

The correlation was not strong but homocysteine levels can be affected by nutrition factors like vitamin B12 and folic acid. It may be the reason for the weak correlation of our results as we did not investigate the nutritional status of our patients. There were few problems in our study; the parameters that we asses alopecia grade were subjective and our study group had a small sample size.

CONCLUSIONS

We found significantly increased LH, free testosterone, DHEAS levels in our EAGA group. The LH/FSH ratio was higher in men with EAGA. These hormonal test results are nearly the same of the profile of women with PCOS. We also found significantly increased levels of fasting blood glucose, fasting insulin and HbA1c levels in EAGA group. These biochemical parameters are also similar to the metabolic abnormality of PCOS women. So we suggest that these men could be accepted as a phenotypic synonym of PCOS women. These young men may have the same increased risks as women with PCOS, including insulin resistance, metabolic syndrome, diabetes, cardiac and vascular diseases and also may be for infertility. These risks need to be confirmed by some multicentered, large studies. And long term follow-up study results of men with EAGA are also needed to confirm these findings.

Author contributions: DDA, CY; Literature search and study design, statistical analyzes, DDA; Writing article and revisions

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Ethical issues: All authors declare originality of research.

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