Pharmacological Reports 69 (2017) 45–49

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original article

The effect of oral contraception on cardiometabolic risk factors in women with elevated androgen levels

Robert Krysiak[a,*], Małgorzata Gilowska[a,b], Bogusław Okopień[a]

[a] Department of Internal Medicine and Clinical Pharmacology, Medical University of Silesia, Katowice, Poland
[b] Department of Cardiology, Provincial Hospital, Bielsko-Biała, Poland

ARTICLE INFO

Article history:
Received 4 August 2016
Received in revised form 12 September 2016
Accepted 14 September 2016
Available online 15 September 2016

Keywords:
Hormones
Hyperandrogenism
Insulin resistance
Polycystic ovary syndrome
Oral contraception

ABSTRACT

Background: In unselected reproductive-aged women, use of combined estrogen-progestin oral contraceptive pills has been linked with an increased risk of vascular disease. The aim of this study was to investigate the effect of oral contraception on cardiometabolic risk factors in a population of women with hyperandrogenism.
Methods: The study included 16 untreated women with elevated testosterone levels and 15 matched healthy women who were then treated with oral contraceptive pills containing ethinyl estradiol (30 μg) and drospirenone (3 mg). Plasma lipids, glucose homeostasis markers, circulating levels of androgens, uric acid, high-sensitivity C-reactive protein (hsCRP), fibrinogen and homocysteine, as well as urinary albumin-to-creatinine ratio (UACR) were assessed at baseline and after 12 weeks of treatment.
Results: Compared to healthy women, women with elevated androgen levels showed increased plasma levels of hsCRP, fibrinogen and homocysteine, as well as a higher value of UACR. Oral contraception reduced androgen levels only in hyperandrogenic women. In healthy women, ethinyl estradiol plus drospirenone increased plasma levels of insulin, hsCRP, fibrinogen and homocysteine, while in women with elevated androgen levels their effect was limited only to a small increase in hsCRP.
Conclusions: Our results suggest that a deteriorating effect of oral contraceptive pills containing ethinyl estradiol and drospirenone in hyperandrogenic women is weaker than in healthy young women and that ethinyl estradiol/drospirenone combination therapy may be safely used in the former group of patients.

Introduction

Hyperandrogenism is characterized by excess production of androgens by the ovaries and/or by the adrenal glands [1]. In women, elevated androgen levels may result in numerous symptoms, including menstrual irregularities, hirsutism, acne, seborrheic dermatitis, male-pattern baldness, clitoral hypertrophy or deepening of voice [1,2]. Oral estrogen-progestin contraceptives, besides anti-androgen agents, are considered the first-line treatment in this condition [2,3]. They exert an anti-androgenic action by decreasing LH production, which inhibits ovarian steroidogenesis, as well as by the increased production of sex hormone-binding globulin (SHBG), leading to the reduction of circulating levels of free testosterone [3,4]. Unfortunately, although effective, combined oral contraceptive pills confer increased risk of venous thromboembolism and arterial thrombosis [5], as well as were found to deteriorate insulin sensitivity [6].

Interestingly, increased cardiometabolic risk is one of the features of women with polycystic ovary syndrome, being by far the most common cause of elevated androgen levels in young women [7,8]. Women suffering from this condition are characterized by an increased risk of insulin resistance, glucose intolerance, lipid abnormalities, subclinical atherosclerosis, endothelial and a prothrombotic state [9–11]. Consequently, patients with polycystic ovary syndrome may be more prone to the development of cardiovascular and cerebrovascular disease, as well as to the development of type 2 diabetes [9–11]. Similarly, women with congenital adrenal hyperplasia, another disorder resulting in hyperandrogenemia, were found to have an increased body mass index and fat mass, the presence of insulin resistance and hypertension [12]. Congenital adrenal hyperplasia seems to be also associated with excess cardiovascular and metabolic morbidity [13], and with increased carotid intima-media thickness [14].

Abbreviations: DHEA-S, dehydroepiandrosterone sulphate; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA; HOMA1-IR, the homeostatic model assessment 1 of insulin resistance ratio; LDL, low-density lipoprotein; SD, standard deviation; SHBG, sex hormone-binding globulin.

* Corresponding author.
E-mail address: r.krysiak@interia.pl (R. Krysiak).

http://dx.doi.org/10.1016/j.pharep.2016.09.013
1734-1140/

Very little is known about the association between oral contraception and cardiometabolic risk in women with elevated androgen levels. The present study was aimed to compare the effect of oral contraceptive pills on plasma lipids, glucose homeostasis markers and cardiometabolic risk factors between hyperandrogenic and healthy women. Elevated levels of C-reactive protein, uric acid, homocysteine and fibrinogen, as well as increased urinary albumin-to-creatinine ratio (UACR), which were determined in our study, may suggest that patients are more susceptible to atherosclerosis and type 2 diabetes and their complications [15–19].

Materials and methods

Patients

The participants (n = 16) were selected among premenopausal women (aged 20–45 years) with elevated testosterone levels, defined as total testosterone above 0.6 ng/mL and free testosterone above 25 pmol/L. The subjects were excluded if they met at least one of the following criteria: acute and chronic inflammatory processes, cardiovascular disease, diabetes, thyroid or any other endocrine disorders, as well as impaired renal or hepatic function. We also excluded patients treated with any drugs within 16 weeks preceding the study and women with contraindications to oral contraception. Fifteen age- and weight-matched women wanting to use oral contraception served as a control group.

Study design

The study protocol was approved by the local review board. Before enrollment, both groups of patients were informed about the benefits and harms of androgen therapy and gave written, informed consent to participate in the study. All patients were then treated for 12 weeks with oral contraceptive pills containing ethinyl estradiol (30 μg) and drospirenone (3 mg). Compliance was assessed every two weeks by tablet counts and was regarded as satisfactory if the number of tablets returned ranged from 90% to 100%.

Laboratory assays

Laboratory assays were performed at the beginning and at the end of the study. Venous blood samples were collected from the antecubital vein at 8 a.m. (to avoid possible circadian fluctuations in the parameters studied) after an overnight 12-h fasting, while all assays were performed in duplicate to minimize analytical errors. Plasma lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides), glucose and uric acid, as well as urinary albumin and creatinine were assayed by routine laboratory techniques using reagents purchased from Roche Diagnostics (Basel, Switzerland). LDL-cholesterol levels were measured directly. Plasma levels of insulin, total testosterone, free testosterone, dehydroepiandrosterone sulfate (DHEA-S) and androstenedione were measured by enzyme-linked immunosorbent assay (DRG Instruments GmbH, Marburg, Germany). To calculate the homeostasis model assessment 1 of insulin resistance index (HOMA1-IR) the following equation was used: [fasting plasma glucose (mg/dL) × fasting insulin level (μU/mL)]/405. Plasma levels of C-reactive protein were evaluated using a high-sensitivity monoclonal antibody assay (hsCRP) (MP Biomedicals, Orangeburg, NY, USA). Plasma fibrinogen levels were determined with a semi-automated blood coagulation analyzer OPTION 2 Plus using reagents obtained from bioMerieux (Marcy l'Etoile, France). Plasma homocysteine levels were determined with the use of enzyme immunoassay (Diazyme, San Diego, CA, USA). UACR was calculated as follows: UACR (mg/g) = urine albumin (mg/dL)/urine creatinine (g/dL). Intra- and interassay coefficients of variation were less than 6.4 and 8.5%, respectively.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate data normality. Outcomes for triglycerides, HOMA1-IR, androgens, hsCRP, fibrinogen, homocysteine and UACR were natural-log transformed to normalize the distributions. Between-group comparisons were performed by the *t* test for independent samples. Student's paired *t* test was used to compare differences between the means of variables within the same treatment group. Qualitative variables were compared using the χ^2 test. Correlations were calculated using Pearson's *r*-tests. Probability values of *p* below 0.05 was considered statistically significant.

Results

There were no significant differences in the age, weight and smoking status between both study groups (Table 1). Both groups differed in the number of women with polycystic ovary syndrome and metabolic syndrome. At baseline, insulin, total testosterone, free testosterone, androstenedione, DHEA-S, triglycerides, HOMA1-IR, hsCRP, fibrinogen and homocysteine were higher while HDL cholesterol lower in hyperandrogenic women than in healthy controls.

Oral contraceptive pills were well tolerated and all patients completed the study period.

In healthy women, ethinyl estradiol plus drospirenone reduced plasma levels of HDL cholesterol by 13% ($p < 0.05$), increased circulating levels of triglycerides by 39% ($p < 0.05$), increased plasma insulin by 62% ($p < 0.01$), increased HOMA1-IR by 68% ($p < 0.05$), increased plasma total testosterone by 80% ($p < 0.001$), as well as increased plasma levels of uric acid by 44% ($p < 0.01$), hsCRP by 130% ($p < 0.01$), fibrinogen by 23% ($p < 0.05$) and homocysteine by 80% ($p < 0.05$), and UACR by 61% ($p < 0.05$). In this group of patients, oral contraception did not affect total and LDL cholesterol, glucose and the remaining androgens (Table 2).

In women with elevated androgen levels, oral contraceptive pills reduced plasma levels of total testosterone by 23% ($p < 0.05$), free testosterone by 58% ($p < 0.001$), androstenedione by 23% ($p < 0.01$), and DHEA-S by 38% ($p = 0.01$). Moreover, the treatment increased hsCRP by 36% ($p < 0.05$). However, the treatment produced no effect on glucose, insulin, HOMA1-IR, uric acid, fibrinogen, homocysteine and UACR (Table 2).

At the end of the study, both groups differed in the mean values of free testosterone ($p < 0.001$), androstendione ($p < 0.01$), hsCRP ($p < 0.01$), fibrinogen ($p < 0.05$) and homocysteine ($p < 0.05$) (Table 2).

In women with elevated androgen levels, baseline HOMA1-IR showed a weak correlation with baseline circulating levels of total testosterone, free testosterone, androstenedione and DHEA-S (r values between 0.26 [$p < 0.05$] and 0.37 [$p < 0.01$]), as well as with uric acid, hsCRP, fibrinogen, homocysteine and UACR (r values between 0.28 [$p < 0.05$] and 0.39 [$p < 0.01$]). In hyperandrogenic women, baseline androgen levels correlated with hsCRP, fibrinogen and homocysteine (r values between 0.30 [$p < 0.05$] and 0.35 [$p < 0.01$]). No other correlations between baseline values were found.

In healthy women, treatment-induced changes in hsCRP, fibrinogen and homocysteine correlated with the effect of oral contraceptive pills on HOMA1-IR (r values between 0.25 [$p < 0.05$] and 0.38 [$p < 0.01$]). In hyperandrogenic women, the impact of oral contraceptive pills on hsCRP correlated with its effect on HOMA1-IR ($r = 0.26$, $p < 0.05$). In neither group of women, the effect of oral