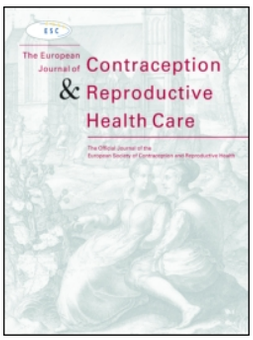

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RESEARCH ARTICLE

Evaluation of different antiandrogenic progestins on clinical and biochemical variables in polycystic ovary syndrome

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ABSTRACT

Objectives: The aim of the study was to update the results of a previous study published 10 years ago and compare the effect on hyperandrogenism of a newer progestin, dienogest (DNG), in a combined oral contraceptive (COC) formulation with ethinylestradiol (EE), with that of COCs containing the same dose of EE in combination with drospirenone (DRSP) and chlormadinone acetate (CMA).

Methods: Sixty women with polycystic ovary syndrome (PCOS) aged between 16 and 35 and requiring antiandrogenic contraceptive treatment were randomised to one of three treatment groups: EE 30 μg/DRSP 3 mg, EE 30 μg/CMA 2 mg, EE 30 μg/DNG 2 mg. We evaluated the effects of the three COCs on sex hormone-binding globulin (SHBG) and biochemical markers of hyperandrogenism.

Results: After 3 months of treatment, serum androgen concentrations were significantly improved in all treatment groups. Serum concentrations of SHBG were significantly increased with all COC treatments ($p < 0.0001$). Interestingly, DRSP had a greater effect (+218%; $p < 0.0001$) on serum SHBG concentrations compared with DNG and CMA ($p < 0.04$ and $p < 0.002$, respectively). Serum concentrations of total testosterone significantly decreased in all groups ($p < 0.0001$). DRSP had a significantly greater effect on total testosterone concentrations compared with DNG ($p = 0.002$) and CMA ($p < 0.0001$).

Conclusion: Our study showed that DNG exerted an important stimulatory effect on SHBG concentrations, which was less than that of DRSP but greater than that of CMA. Similar results were also obtained for dehydroepiandrosterone sulphate and total testosterone.

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Dienogest; hyperandrogenism; oral contraceptives; PCOS; SHBG

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women during their reproductive years and can cause oligomenorrhoea and anovulatory infertility [1]. It is now widely recognised that insulin resistance, which manifests especially in obese and overweight women but also often also in lean women with PCOS, is one of the keys to this complex disorder. Insulin resistance is often thought to be the cause of hyperandrogenism, for example by acting in a synergistic fashion with luteinising hormone on ovarian steroidogenic enzymes in the ovaries and on sex hormone-binding globulin (SHBG) production by the liver. Moreover, insulin resistance is frequently associated with hirsutism, seborrhoea and acne and/or biochemical hyperandrogenism. Furthermore, in a vicious cycle, hyperandrogenism may cause hirsutism, seborrhoea and acne, which together have a strong impact on the life of affected women [1].

The use of combined oral contraceptives (COCs) in women with hyperandrogenism effectively reduces circulating androgens. The key mechanism of COCs is that they inhibit folliculogenesis by suppressing pituitary gonadotropin secretion [2]. COCs are the most widely used treatment for the symptoms of PCOS. Their mechanism of action not only regulates the menstrual cycle but also suppresses the hypothalamic–pituitary–gonadal axis, which ameliorates the hyperandrogenism by suppressing ovarian and adrenal androgen synthesis, inhibiting 5α-reductase [3] and increasing SHBG concentrations [4,5]. COCs effectively treat hirsutism [6], reducing the clinical manifestations of hyperandrogenism within 6–12 months of therapy by significantly lowering the concentrations of circulating androgens and significantly increasing the concentrations of SHBG [7–9].

In women with PCOS, it has been shown that a COC containing 30 μg ethinylestradiol (EE) and 3 mg drospirenone (DRSP) inhibits adrenal steroidogenesis [10] and stimulates liver production of SHBG more effectively compared with COCs with lower doses of EE [9]. Powerful progestins with low androgenic or antiandrogenic activity currently used in COC formulations are cyproterone acetate (CPA), chlormadinone acetate (CMA), dienogest (DNG) and DRSP [2,11,12]. Knowledge of the effects of the progestins contained in the different COC formulations is fundamental to providing personalised therapy for women with PCOS.

CMA is a progesterone derivative which, when combined with EE, improves acne by 59–83% [13]. The antiandrogenic effect of CMA is presumed to be the result of its binding to androgen receptors, thereby competitively inhibiting the effect of endogenous testosterone and dihydrotestosterone, and competitively inhibiting 5α-reductase [13].

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DRSP is derived from spironolactone and is an antiandrogenic and antimineralocorticoid molecule that can be used to treat both acne and hirsutism and avoid the fluid retention associated with some COCs owing to their oestrogen content [14,15].

DNG has a 19-nortestosterone structure but a 17α-cyanomethyl rather than a 17α-ethinyl group and it does not bind to SHBG; the practical advantage of the lack of SHBG affinity is that the active substance does not release any testosterone from its protein bond [16]. DNG's unique chemical structure gives it the pharmacodynamic properties of both C-19 norprogesterone and progesterone derivatives; thus, free serum concentrations of DNG tend to remain high, while free testosterone concentrations remain low [17]. Its antiandrogenic activity has been found to be 40% that of CPA, which is the most potent antiandrogenic progestin currently known [18,19]. An *in vivo* study of DNG in infantile testosterone-treated castrated rats showed that its antiandrogenic activity was less than that of CPA but more pronounced than that of DRSP and CMA [20,21]. These preclinical data have, however, not been confirmed in humans.

Given the importance of knowing how to choose the most suitable COC, the aim of the present study was to update our results of a study published 10 years ago [22] with the introduction of a newer progestin, DNG, to compare the effects of three COCs containing the same quantity of EE (30 μg) in combination with different progestins (DRSP, CMA and DNG) on SHBG and biochemical markers of hyperandrogenism in women with PCOS. We further aimed to confirm or disconfirm the findings of Oettel and colleagues' data analysis on rats [20,21].

Methods

Study design

This was a randomised study of 60 women with PCOS aged between 16 and 35 years, allocated to one of three groups each composed of 20 women. None of the women had contraindications for COCs. The study was approved by the internal ethics committee of the Section of Obstetrics and Gynaecology and all participants gave their written informed consent.

The diagnosis of PCOS was based on the 2003 Rotterdam criteria and included the presence of two out of three of the following features: clinical and/or biochemical hyperandrogenism, chronic anovulation and/or oligomenorrhoea and ultrasonographic evidence of polycystic ovaries [23]. All participants had clinical and/or biochemical hyperandrogenism and polycystic ovaries confirmed by ultrasound. The participants had not used other hormone or drug therapies for at least 4 weeks.

Prior to enrolment the women had undergone routine blood chemistry tests and transvaginal ultrasonography. Basal blood samples were obtained during the early follicular phase of the menstrual cycle. Serum was separated and frozen prior to assays of androstenedione, dehydroepiandrosterone sulphate (DHEA-S), total testosterone, free testosterone and SHBG. After a control cycle, 60 women were randomly assigned, on the basis of a random number scale, to one of three treatment groups: 30 μg EE/3 mg DRSP (Yasmin; Bayer HealthCare Pharmaceuticals, Berlin, Germany), 30 μg EE/2 mg CMA (Belara; Gedeon Richter, Milan, Italy) and 30 μg EE/2 mg DNG (Effiprev; Effik, Milan, Italy). Therapy began on the first day of the cycle. Pills were taken for three cycles of 21 days followed by a 7 day pill-free interval. Blood samples were taken during the early follicular phase after discontinuation of the third treatment cycle. Ten days after the end of treatment, the participants underwent a general assessment including gynaecological examination and transvaginal ultrasonography.

Hormone assays

Plasma concentrations of DHEA-S, total testosterone, androstenedione, free testosterone and SHBG were assayed. We used Immulite 2000 immunoassay systems (Siemens, Milan, Italy) to measure SHBG, androstenedione and DHEA-S; and Access immunoassay systems (Beckman Coulter, Milan, Italy) to measure total and free testosterone. Samples were analysed twice at two dilutions. Quality controls at low, medium and high hormone concentrations were included in each test. Detection limits were 0.35 nmol/L for testosterone, 1.0 nmol/L for androstenedione, 0.02 nmol/L for SHBG and 0.08 μmol/L for DHEA-S. Variations within a given sample and between samples were 3.4% and 4.6% for total testosterone, 3.2% and 3.4% for free testosterone, 5.6% and 6.4% for androstenedione, 6.9% and 13% for SHBG and 4.9% and 7.2% for DHEA-S. The methods used were highly specific for each hormone and had low crossreactivity (<0.05%) with other hormones or drugs that could have been present in the blood samples.

Statistical analysis

The variables were analysed by comparing means and their variations in sequential samples. Within-group differences were evaluated by the Friedman χ^2 test, and between-group differences by the Kruskal–Wallis test. Within-group changes with respect to the control cycle were evaluated by the Wilcoxon test. Data are presented as mean ± standard deviation (SD) and were considered significant if $p < 0.05$.

Results

The three groups did not differ in age or body mass index (BMI). BMI was <25 kg/m^2 and did not change significantly during the treatment period. The study population was homogeneous (Table 1). No participants interrupted therapy and side effects were registered as minor: one case of menstrual spotting (with DNG), five cases of headache (three with DRSP, two with CMA) and four cases of breast pain (one with DRSP, two with DNG, one with CMA).

After 3 months of treatment, all studied COCs significantly improved serum androgen concentrations, in

Table 1. Basal evaluation of DHEA-S, total testosterone, SHBG and androstenedione in the three treatment groups.

Biochemical marker	EE/DRSP	EE/CMA	EE/DNG	*p*-value
DHEA-S, μmol/L	6.08 ± 1.22	6.89 ± 1.0	6.57 ± 1.22	0.88
Total testosterone, nmol/L	3.17 ± 0.3	3.1 ± 0.28	3.14 ± 0.29	0.79
SHBG, nmol/L	28.2 ± 6.52	29.35 ± 6.77	30.2 ± 7.69	0.31
Androstenedione, nmol/L	7.61 ± 1.11	8.13 ± 1.15	7.54 ± 1.11	0.74

Data are presented as mean ± SD.

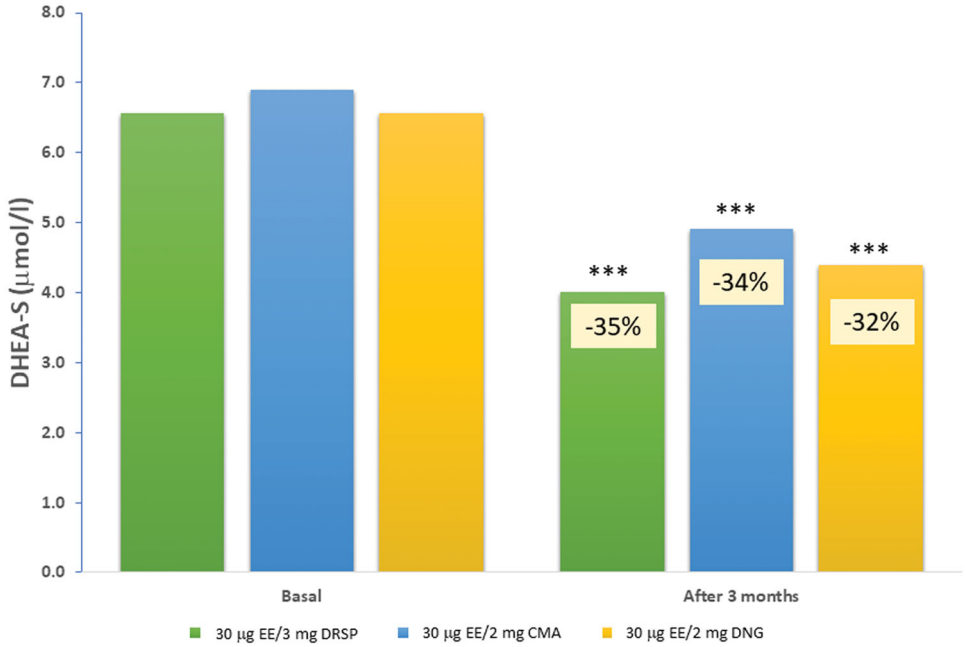

Figure 1. Comparison of the effects of three COCs (30 µg EE/3 mg DRSP, 30 µg EE/2 mg CMA and 30 µg EE/2 mg DNG) on serum concentration of DHEA-S before and after 3 months of therapy (***$p < 0.001$).

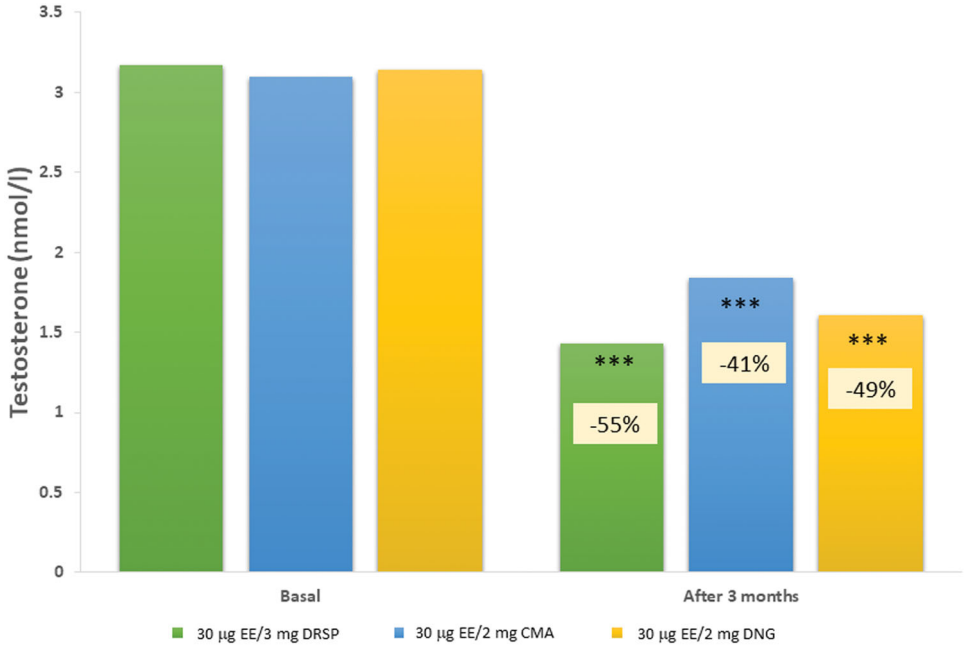

Figure 2. Comparison of the effects of three COCs (30 µg EE/3 mg DRSP, 30 µg EE/2 mg CMA and 30 µg EE/2 mg DNG) on serum concentration of testosterone before and after 3 months of therapy (***$p < 0.001$).

particular by decreasing DHEA-S: by 32.03% in the EE/DNG group (from 6.57 ± 1.22 µmol/L to 4.39 ± 0.81 µmol/L), by 33.87% in the EE/CMA group (from 6.89 ± 1.0 µmol/L to 4.91 ± 0.65 µmol/L) and by 35.06% in the EE/DRSP group (from 6.08 ± 1.22 µmol/L to 4.01 ± 1.25 µmol/L) ($p < 0.0001$ in all study groups) (Figure 1).

Similarly, serum concentrations of total testosterone were significantly decreased in all groups ($p < 0.0001$): by 54.9% (from 3.17±.03 nmol/L to 1.43 ± 0.21 nmol/L) in the EE/DRSP group, by 40.82% in the EE/CMA group (from 3.1 ± 0.28 nmol/L to 1.84 ± 0.34 nmol/L) and by 48.9% in the EE/DNG group (from 3.14 ± 0.29 nmol/L to 1.61 ± 0.27 nmol/L) (Figure 2). A comparison of the difference in percentage decrease between the three groups revealed that DRSP produced the best improvement in total testosterone ($p = 0.002$ vs DNG; $p < 0.0001$ vs CMA).

Serum concentrations of SHBG were significantly increased in all groups ($p < 0.0001$): by 218% (from 28.2 ± 6.52 nmol/L to 89.7 ± 12.55 nmol/L) in the EE/DRSP group, by 190% (from 29.35 ± 6.77 nmol/L to 85.4 ± 9.37 nmol/L) in the EE/CMA group and by 210% (from 30.2 ± 7.69 nmol/L to 90.9 ± 17.68 nmol/L) in the EE/DNG group (Figure 3). DRSP significantly improved SHBG compared with DNG ($p = 0.04$) and CMA ($p = 0.002$) and significantly improved SHBG compared with CMA ($p = 0.03$).

Serum concentrations of androstenedione significantly decreased in all groups ($p < 0.0001$): by 11.12% (from 8.13 ± 1.15 nmol/L to 7.19 ± 0.80 nmol/L) in the EE/CMA

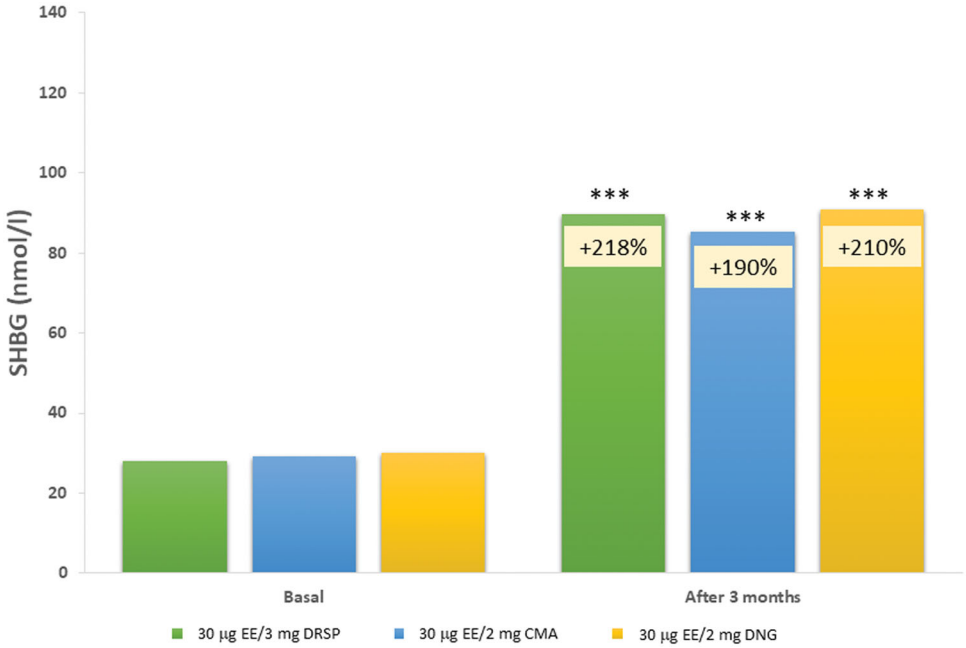

Figure 3. Comparison of the effects of three COCs (30 µg EE/3 mg DRSP, 30 µg EE/2 mg CMA and 30 µg EE/2 mg DNG) on serum concentration of SHBG before and after 3 months of therapy (***$p < 0.001$).

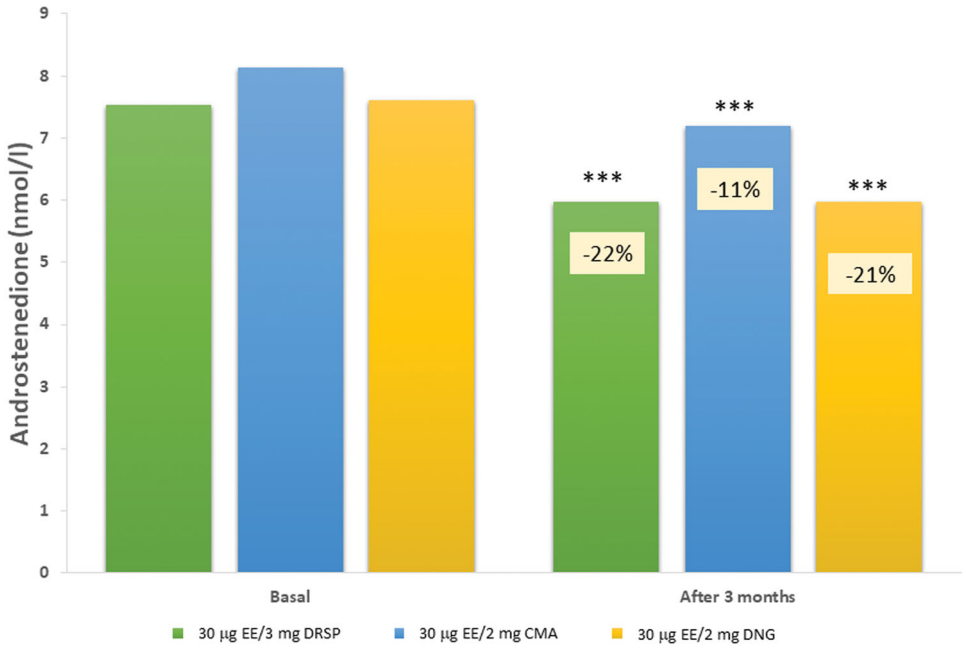

Figure 4. Comparison of the effects of three COCs (30 µg EE/3 mg DRSP, 30 µg EE/2 mg CMA and 30 µg EE/2 mg DNG) on serum concentration of androstenedione before and after 3 months of therapy (***$p < 0.001$).

group, by 20.73% (from 7.54 ± 1.11 nmol/L to 5.97 ± 0.90 nmol/L) in the EE/DNG group and by 21.63% (from 7.61 ± 1.11 nmol/L to 5.97 ± 0.94 nmol/L) in the EE/DRSP group (Figure 4). A comparison of the differences in percentage decreases between the three groups revealed that DNG and DRSP showed significantly better improvements in androstenedione compared with CMA (DNG vs CMA, $p = 0.0005$; DRSP vs CMA, $p < 0.0001$).

Discussion

Findings and interpretation

Our study aimed to evaluate the increase in SHBG caused by three COCs containing antiandrogenic progestins. We believe the data will be useful for gynaecologists when prescribing antiandrogenic COCs in hyperandrogenic women with PCOS. In 2004, SHBG was investigated as marker for risk of venous thromboembolism (VTE). Although SHBG concentrations were found to correlate with changes in various haemostatic factors [24], the data were not subsequently confirmed [25]; therefore, oral contraceptive prescriptions continued to follow the World Health Organisation medical eligibility criteria for contraceptive use [26]. There are both hereditary and acquired risk factors for VTE, which alone or in combination may enhance risk. These factors must be taken into account during contraceptive counselling and when prescribing COCs. Although a positive family history of VTE has a low

predictive value [14,27], it may nevertheless be used in preliminary screening.

The present study was conducted to contribute data on a newer COC containing EE 30 μg and DNG 2 mg. As this COC is a more recent introduction to the Italian market, we wanted to study its impact on SHBG in comparison with that of two other COCs containing the same dose of EE and type of antiandrogenic progestin (DRSP 3 mg and CMA 2 mg).

We found that DNG stimulated SHBG concentrations to a lesser extent compared with DRSP, but to a greater extent compared with CMA. We obtained similar results with regard to serum concentrations of DHEA-S, total and free testosterone and androstenedione, which were significantly improved in all participants, showing a stronger effect in the EE/DRSP group, followed by the EE/DNG group.

Differences and similarities in relation to other studies

In contrast to the literature, where DNG is described as the antiandrogenic progestin of first choice, our clinical results showed that DNG exerted weaker antiandrogenic activity on circulating androgens and SHBG compared with DRSP [18,19]. The present study demonstrated that formulations containing 30 μg EE combined with DRSP, CMA or DNG caused a large increase in serum concentrations of SHBG in all participants, especially those treated with DRSP and DNG.

In recent years the introduction to the market of a number of COCs containing 30 μg EE and 2 mg DNG has seen gynaecologists also prescribe this COC formulation for therapeutic purposes and particularly for the treatment of hyperandrogenic symptoms related to PCOS. DNG is an excellent progestin for cycle control due to its marked antiproliferative activity on the endometrium [28]. There are numerous studies concerning the efficacy of DNG in the treatment of endometriosis and in particular in reducing and blocking endometriosis-related pain [29,30]. Regarding safety, various studies agree on the low prevalence of minor side effects: in particular, Zimmermann et al. [28] found a prevalence of only 1.4% breast pain, 1.1% weight gain and 0.3% libido loss. Only 3.2% of women in their study discontinued therapy. Serious side effects occurred only in 0.03% of women (two cases of thrombosis, one of suspected lung embolism, two of liver dysfunction). The contraceptive efficacy of the EE/DNG combination is due to numerous mechanisms, in particular the action of DNG at its effective dose of 2 mg [30]. The presence of EE is useful to block the release of gonadotropin from the pituitary and consequently follicular development; furthermore, it guarantees good pituitary tropism [17]. The 30 μg content of EE is also useful for the release of some liver proteins such as SHBG. This protein has different actions, one of which is to bind most steroid hormones, including androgens, to reduce the free portion, which would otherwise have an androgenic effect on the pilosebaceous glands. Comparison of the three COCs containing the most used antiandrogenic progestins showed that EE/DRSP was the most effective combination to increase serum SHBG concentrations, in contrast to previous findings in animal studies [20,21].

The antiandrogenic efficacy of a COC exerts different actions: blocking ovarian activity, exerting anti-insulinaemic activity through the antiandrogenic progestin component and reducing circulating androgen concentrations through binding to SHBG. DNG proved particularly effective at increasing serum SHBG concentrations, placing itself in an intermediate position between DRSP and CMA. This new finding confirms its antiandrogenic effect and places it among the first therapeutic choices in the treatment of PCOS.

The findings of our study further confirm the anti-insulinaemic activity of COCs reported by other authors [31,32]. Our data inform a better choice of contraceptive for the treatment of hyperandrogenism and hyperinsulinaemia in women with PCOS. Women with PCOS should also be treated with inositol, to induce an improvement in hyperinsulinaemia and insulin resistance; inositol phosphoglycans are putative mediators in the non-classical insulin-signalling cascade for glucose uptake and use and have gained increasing attention because of their safety profile and effectiveness in effecting this metabolic change [33–36].

Strengths and weaknesses

In the field of hormonal evaluations, even a study with a limited number of cases, such as ours, can provide important information on contraceptives activity. We therefore expect that the results of our study will encourage other research groups to analyse a wider range of PCOS cases treated with COCs.

Despite much progress in the field of contraception, discontinuation of the pill and switching to other methods is common, often because of minor side effects [37]. It is therefore fundamental to understand every COC combination to better personalise the choice of contraceptive, improve compliance and reduce fears about taking hormonal contraception.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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