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SPECIAL REPORT

A bitter pill to swallow: adjustments to oral contraceptive pill use in polycystic ovary syndrome

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ABSTRACT

Introduction: This Special Report aims to highlight the importance of tailored therapies in women with Polycystic Ovary Syndrome (PCOS), avoiding prescribing generalized or unsuitable therapies based on oral contraceptive pills (OCPs).

Areas covered: This article discusses the benefits and risks of OCP-based therapy, highlighting the possible undesirable effects, especially in those patients exhibiting risk factors as women with PCOS, and the importance of carefully evaluated tailored therapeutic approaches. Literature searches were performed with the use of PubMed, Google Scholar, and Web of Science between January and February 2024.

Expert opinion: Considering the recent re-analysis of PCOS Rotterdam Criteria by the Expert Group on Inositol in Basic and Clinical Research, and on PCOS (EGOI-PCOS), the traditional Rotterdam phenotypes can be reclassified to achieve more efficacious therapy choices. Using personalized therapies that consider the specific clinical characteristics of the patient allows to improve the management of the syndrome, thus avoiding the generalized use of OCPs, which risk treating only symptoms of PCOS rather than the underlying cause. In cases when contraceptive purpose is desired, patients may benefit from combined therapy with diet or insulin-sensitizer agents, as inositol, to rebalance the metabolic profile, thus reducing the risk of developing future complications.

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Oral contraceptive pills; polycystic ovary syndrome; metabolic alterations; phenotypes; diagnosis; tailored therapies; inositol

1. Introduction

Thanks to the high efficacy, accessibility, and ease of use, the oral contraceptive pills (OCPs) use, or more in general the combined hormonal contraceptive (CHC) use, has spread exponentially since their first approval by Food and Drug Administration (FDA) in 1960 [1,2].

Their mechanism of action interferes with estrogen and progesterone signaling during ovulation, thus disrupting the physiological function of these hormones and preventing pregnancy. Furthermore, they can also increase the viscosity of the cervical mucus and reduce the receptivity of the endometrium to a possible implantation [3]. In particular, the estrogen component of the pill may suppress luteinizing hormone (LH) secretion and reduce the ovarian androgen production, thus increasing sex hormone-binding globulin (SHBG) and reducing free testosterone [4]. Therefore, the combined formulation of hormonal contraceptives guarantees a synergic action, decreasing plasma gonadotropin levels and suppressing ovulation more effectively than either alone. Unsurprisingly indeed, the combined estrogen-progesterone pills are the most prescribed, compared to those based only on progesterone (POP).

Despite the primary indications of CHCs being fertility regulation and preventing pregnancy, they have found applications as 'off-label' medicines. Examples of CHC applications, especially as OCPs, include gynecological conditions, such as menstrual discomforts (pain, irregularity, and related migraine), fibroids, endometriosis pain, and polycystic ovary syndrome (PCOS) with related acne, hirsutism, menstrual alterations [5–7].

Even though OCPs are a safe and effective therapy, over the years OCP users have experienced several drawbacks and received some warnings of the potential risks. OCP treatment may cause various undesirable side effects, which may threaten patient compliance and lower the continuation rate of the therapy [8,9]. In detail, OCP use may increase the likelihood of the development of future complications, such as cardiovascular disease (CVD), obesity, high blood pressure, hemorrhagic

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Article highlights

- Combined hormonal contraceptives are widely used worldwide among young women for birth control, but their use may expose them to different undesirable side effects.
- The use of OCPs requires a revision, notably to take into account the patient's clinical background.
- A large portion of patients with PCOS exhibit metabolic and/or inflammatory alterations that expose them to a higher risk of complications when treated with OCPs.
- In the incidence of OCP treatment for contraceptive purposes in PCOS patients, a combined OCP + inositol approach may represent a safer strategy.
- Patients with PCOS require a specific diagnosis with a defined phenotype, which is mirrored in the therapy choice.

stroke, increasing oxidative stress, risk of cerebral vein thrombosis, and a potential impairment of peak spinal bone mineral density (BMD) that relates to lifetime fracture risk, especially in adolescent CHC users [10,11]. Consequently, it is important to consider these side effects, especially in patients who have already present risk factors for these pathological complications.

Among the adverse effects associated with hormonal combined treatment, increased body weight is common among users, and it may seriously influence the continuation of the contraceptive therapy, reaching a 40% increase in discontinuation in women who gained weight compared to those who demonstrated no weight change [12]. Dyslipidemia and increased body mass index (BMI) may occur during hormonal contraceptive therapy and influence the risk of cardiovascular events [13]. In detail, circulating levels of triglycerides and cholesterol may increase, along with greater insulin resistance (IR) and inflammatory markers, such as C-reactive protein (CRP) [14,15]. To further evaluate the effect of OCPs on CVD risk, Wang and colleagues demonstrated that the use of OCPs increased levels of proteins involved in lipid metabolism, such as the apolipoprotein A and B [16]. Even though changes in OCP formulation have helped to maximize their effect on elevating high-density lipoprotein (HDL) levels whilst minimizing other risks, conflicting evidence on the effects on lipid profile is still reported in literature. A study by Azizi et al. found no significant differences in cholesterol, triglycerides, and low-density lipoprotein (LDL) between OCP users and non-users [17], while another study by Naz and colleagues revealed statistically significant differences in cholesterol, triglycerides, and LDL between the two groups [18]. In addition, a study by Hashemi et al., conducted on 2272 female participants (1549 OCP users, 723 non-users OCs), indicated that the mean lipid profile levels were higher in OCP users than in non-users [19].

Among the OCP-mediated effects, improvement of the androgenic profile is clearly understood, due to increased SHBG content and decreased albumin and testosterone concentrations. However, OCP use may increase thrombotic risk [20]. A work by Horton and colleagues reported that a higher BMI associated with the use of COCs may highly increase the risk of venous thromboembolism (VTE). Even though estimating the absolute risk of VTE among with both of these risk factors is difficult, the absolute risk of VTE is clearly smaller in healthy women of reproductive age [21]. In line with this, a recent study by Rosano and colleagues strongly supported obesity as a strong risk factor for developing VTE in women concomitantly using OCPs. Indeed, women who present both obesity and use of OCPs have a greater risk (between 12 and 24 times) to develop VTE than non-obese non-OCP users [11].

Besides influencing CVD risk, OCP use can cause hypertension in 4–5% of healthy women and exacerbate hypertension in 9–16% of women with preexisting hypertension [22]. For all these reasons, women who have a preexisting cardiovascular condition or smoke, or who are already exposed to metabolic or CVD risks for other concomitant pathologies, should carefully use OCPs under a strict medical control [22]. Indeed, as also reported in a work by Shufelt and colleagues, evaluating cardiovascular risk factors (hypertension, smoke, diabetes, nephropathy) and other vascular disease (migraine) is crucially important before using OCPs [23]. Finally, some of the OCP-induced effects, such as cellulite and water retention, leg swelling, and increase in body weight, may strongly influence the self-perception of body image with psychological implications that may influence self-esteem and contribute to symptoms of depression [24–26]. In addition, the use itself of such contraceptive therapies may expose women to a deficiency of various micronutrients, such as zinc, magnesium, and selenium, whose low levels correlate can contribute to the occurrence of symptoms of depression [24,27].

Overall, the use of OCPs in clinical practice requires proper attention in healthy people, and especially in patients who may be predisposed to, or already exhibit, a higher degree of risk of developing metabolic and/or cardiovascular complications.

2. Polycystic ovary syndrome: far from generalized OCP-based therapies

The general use of OCPs requires a rethink, in no area is this more required than in PCOS. Although the management of PCOS with OCPs has a long and established history, conflicting data have emerged regarding beneficial or adverse metabolic effects, thus making a more careful evaluation of such therapies in this patient population necessary [28,29].

PCOS is a multifactorial disorder involving both the reproductive and the endocrine system. Patients with PCOS may exhibit a wide heterogeneity of clinical manifestations, including fertility problems, metabolic alterations, and/or endocrine unbalances. The current diagnostic criteria for PCOS were defined in 2003 by the Rotterdam Criteria [30] and have subsequently been updated by the international clinical guidelines; however, these guidelines have come under constant critique and discussion [31,32]. Indeed, a new reading of the existing Rotterdam Criteria by members of the Expert Group on Inositol in Basic and Clinical Research, and on PCOS (EGOI-PCOS), highlighted the definition of four different phenotypes of PCOS, three of which classified as endocrine metabolic syndrome (EMS) with metabolic and androgenic alterations (A, B, C), while the fourth norm androgenic and classified as PCOS, with only ovarian and menstrual alterations (D) (Figure 1) [33,34]. In line with this, the need of re-defining the name 'PCOS' is

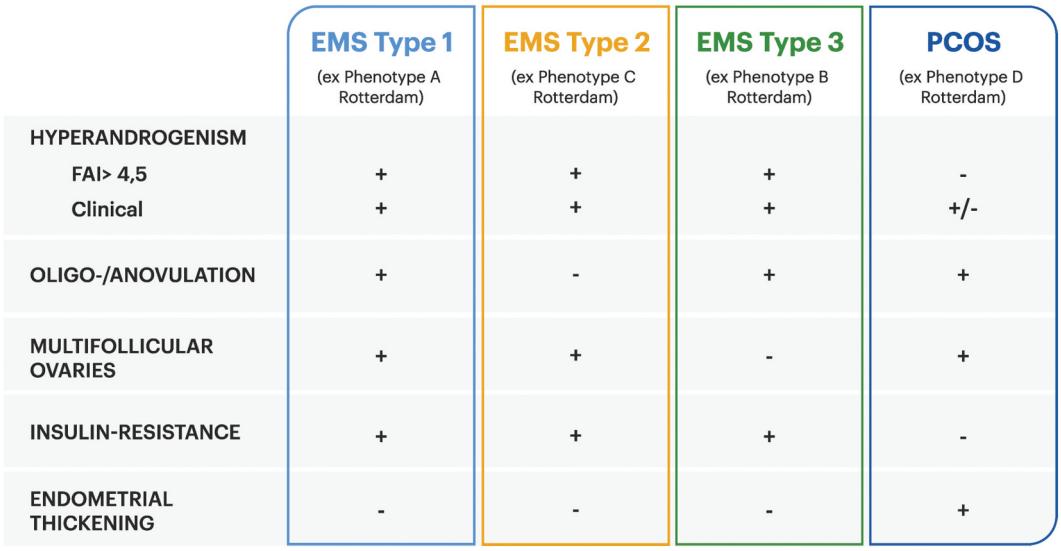

Figure 1. New classification of PCOS diagnostic criteria by the Expert Group on Inositol.

PCOS (polycystic ovary syndrome), EMS (endocrine – metabolic syndrome), FAI (Free Androgen Index). The novelty of this reclassification consists of considering the ex-phenotypes A, B, C of PCOS as an endocrine-metabolic syndrome characterized by hyperandrogenism (defined as FAI and clinical) and metabolic alterations. Instead, the fourth phenotype exhibits a norm androgenic profile with alterations referred to an ovarian origin such as oligo/anovulation, multifollicular ovaries, and endometrial thickening.

emerging more and more within the scientific community. Indeed, even though originally seen as a gynecological disease with menstrual abnormalities and subfertility, PCOS is now recognized as a reproductive, cardiometabolic, dermatologic, and psychological condition, and above all recent evidence reported how different pathogenesis underlying different phenotypes [35]. Interestingly, the only phenotype that properly shows an ovarian origin and that can still be classified as 'PCOS' is the phenotype D, as widely explained in a recent work in which the authors shined a spotlight on this phenotype, gathering various reports of how phenotype D is differentiated from the other PCOS phenotypes [36].

OCPs are often chosen as a first mode of treatment in women with PCOS due to their effects on androgen profile, along with inflammatory acne and menstrual irregularities. Indeed, the estrogen component of OCPs suppresses LH secretion, reduces the ovarian androgen production, and increase SHBG, thus reducing free testosterone. In line with this, a clinical study revealed that OCP-treated women with PCOS exhibit a significant decrease in LH, testosterone, and Ferriman-Gallwey (FG)-score compared to PCOS patients who did not undergo treatment [37]. However, OCPs may negatively influence metabolic and inflammatory profiles in such patients. A clinical study on 50 women with PCOS reported a worsening of biochemical parameters like oral glucose tolerance test (OGTT), lipid profile, fasting insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI) in PCOS patients treated with OCPs compared to the non-treated group [37]. It was also demonstrated that, in OCP-treated patients with PCOS, total cholesterol, waist-hip circumference, and BMI significantly increased compared to non-treated women with PCOS, along with a worsening of hepatic lipid accumulation, which is closely associated with exacerbated inflammation. In addition, the alteration of OGTT, lipid profile, and insulin function can expose patients to increased long-term risk of various metabolic diseases including obesity, Type 2 Diabetes mellitus (T2DM), IR, and CVD.

More generally, metabolic issues, inflammation, increased coagulability, visceral obesity, IR, and androgen excess are among features commonly observed in PCOS [38–40]. As a consequence of the hyperandrogenism and insulin-resistant metabolic milieu, patients with PCOS are also predisposed to prothrombotic state and endothelial dysfunctions [38,41,42]. Indeed, hyperinsulinemia and obesity induce an increased production of some adipocytokines (adiponectin, visfatin, resistin) that can lead to a pro-inflammatory response. Furthermore, in this syndrome, IR may promote hyperandrogenism, and these two conditions may interfere with the hemostatic fibrinolytic system, thus altering fibrinolysis and impairing the coagulation process [43,44]. Considering the link between OCP use and coagulation process (as well as the inflammatory cytokine profile of women using OCPs) is crucial, particularly in the case of women with PCOS. Yosuf and colleagues demonstrated that inflammatory cytokine profile changed in PCOS affected women following OCP-based therapy; they also observed a significant decrease in adiponectin levels in OCP treated women with PCOS compared to untreated patients [37]. Interestingly, low levels of adiponectin in literature correlate with T2DM, obesity, dyslipidemia, hypertension, and CVD [45,46]. In addition, interleukin 1β (IL-1β) increased in women with PCOS using OCP, which is in line with evidence that correlates increased secretion of IL-1β with various autoimmune and auto-inflammatory diseases, along with metabolic alterations related to T2DM and impaired β cell function [47]. Finally, visfatin and resistin, two molecules linking inflammation and weight gain, are increased in women with PCOS undergoing OCP treatment; furthermore, visfatin levels are raised in various metabolic disorders like obesity, IR, and T2DM [47,48]. Another study reported increased levels of

a predictor of subclinical inflammation, as the logarithmic ratio between CRP and albumin, in women with PCOS using OCPs compared to non-user women with PCOS [49].

Women living with PCOS are also more prone to developing migraines, which is linked to metabolic and hormonal aspects, and which is an adverse effect frequently associated with OCP treatment. A recent narrative review by Sarahian and colleagues highlighted that along with genetic factors, levels of sex hormones (including estrogen and progesterone) and serotonin may also contribute to the pathogenesis of migraines [50]. Serotonin seems to be the interface ring between PCOS and migraine and reduced serotonin levels in both conditions may partly explain this association. In particular, estrogens may affect serotonin synthesis and absorption and, on the other side, serotonin, the activity of which is reduced in people with PCOS and migraines, may regulate pain threshold.

It is also crucial to consider that OCPs may potentially influence thyroid function by significantly modulating serum concentration of thyroid hormones; indeed, the long-term use of OCPs can correlate with a fourfold higher risk of hypothyroidism [51]. A clinical study with a large sample size indicated that treatment with OCPs may be an independent risk factor for the development of thyroid disease in women with PCOS due to the altered profile of autoimmunity, inflammation, IR, and weight gain typically observed in these patients [52].

Therapies based on OCPs may expose individuals to physical changes that can modify body self-perception, thus increasing the likelihood of low self-esteem, which may lead to symptoms of depression. A recent review by Cantelmi and colleagues investigated this psychological aspect in women with PCOS, demonstrating that such patients are more likely to develop psychological symptoms, such as depression or anxiety disorders; furthermore, other features of PCOS such as infertility, weight gain, hirsutism, and acne may contribute to a worsening of psychological conditions [53].

Reported studies strongly support the evidence according to which OCPs may be a successful treatment in terms of regularizing menstrual cycles and improving hyperandrogenism, thus reducing clinical signs such as hirsutism, alopecia, and acne. However, at the same time, such therapies may expose the treated individuals to a potential worsening of anthropometric, glucose, lipid, inflammation, and coagulation parameters, thus exposing such women to a higher risk of developing several future complications. Indeed, due to the interaction between OCPs and metabolic pathways, OCP use may potentially increase the risk of the development of obesity, T2DM, and CVD.

Overall, considering the emerging definition of four different PCOS phenotypes and the need of having a specific diagnosis, using personalized therapies is highly important. A recent work by Unfer and colleagues demonstrated that using the same treatment – based on the natural molecule of Inositol as insulin sensitizer – does not equally improve the parameters of PCOS in each sub-group of patients, thus highlighting the importance of distinguishing various phenotypes to properly select the effective therapeutical approach [54].

When contraception is not required and the patient with PCOS exhibits clinical manifestation related to EMS, lifestyle changes and/or insulin-sensitizer agents have a crucial therapeutic role [55–57]. A recent publication compared the relationship between IR and hyperandrogenism in PCOS to the dance of the tango, which has the roles of a leader and a follower, revealing that IR plays a leading role in this pathogenesis. Indeed, in cases where androgen excess is predominant, a marked reduction of androgen levels (with OCPs for instance) should be followed by a net reduction of correlated IR, but actually such reduction fails to occur. On the other hand, considering IR as the leader, an insulin-sensitizing intervention should be followed by a net fall of free androgenemia, as is indeed consistent with the case [58]. Therefore, insulin-sensitizer-based approaches may also have positive effects on hormonal aspects, as androgen levels, in those PCOS phenotypes reflecting an EMS [54].

Instead, for patients who require contraception in addition to PCOS care, the combination of OCPs with molecules with a metabolic mechanism of action may reduce the risk associated with OCPs. One such example of this is the use of Inositol, a natural molecule widely used in the management of PCOS, which has demonstrable beneficial effects on the metabolic and hormonal profile of PCOS patients. Inositol is a second messenger of several hormones, including follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH) and insulin, and it is used in PCOS therapy as an insulin sensitizer which restores androgen levels back to a tolerable range [59]. As demonstrated in a recent clinical study by Pkhaladze and colleagues, the combination of myo-Inositol (myo-Ins) with OCPs in adolescents with PCOS significantly improved both metabolic and hormonal parameters; in detail, those treated with OCPs plus myo-Ins exhibited a significant decrease in weight and BMI vs those treated with OCPs alone [60]. Another study reported beneficial effects of combining OCP treatment with another insulin-sensitizer, as metformin, in overweight women with PCOS. The combination of this latter with OCPs improved vascular endothelial function to a greater extent than OCPs alone [61].

In light of this, reclassification of PCOS criteria by the EGOI-PCOS is not only theoretical or educational, but it gains a therapeutic significance. Indeed, it appears clear that in patients with EMS (hyperandrogenic phenotypes), OCPs cannot be the first-line treatment, if not in cases of contraception. However, even in these cases, physicians and patients should combine OCPs with changes in diet, lifestyle and with the use of insulin sensitizer agents, as inositol or metformin.

3. Conclusion

Combined hormonal contraceptives have spread exponentially in their use among young women, extending their therapeutic effects toward 'off-label' targets. However, despite their wide use, caution should be taken when prescribing OCPs, especially when their adverse effects overlap with risk factors commonly seen in PCOS patients. In detail, multiple phenotypes of PCOS present metabolic and hormonal alterations, which result in metabolic and cardiovascular complications that might be worsened through a generic one-size-fits-all approach to OCP therapy. Indeed, these drugs risk treating only symptoms of PCOS rather than the underlying cause of the syndrome. Therefore, when contraception is not the

primary goal in PCOS patients, the use of OCPs should take into account the metabolic profile of the patient in addition to the presented phenotype of PCOS.

4. Expert opinion: the importance of tailored therapies in PCOS

PCOS is a complex disorder with a complex pathogenesis, that is still not entirely understood. Considering its wide heterogeneity, standardizing specific criteria for a more precise diagnosis and treatment have been at the center of medical research in PCOS. This is reflected in the clinical environment, where tailored treatment is becoming increasingly necessary and possible to avoid exposing patients to higher risk of future complications. With this aim, the EGOI-PCOS has proposed a new set of classifications for the diagnosis of PCOS, which fully considers the metabolic aspect of PCOS. This recent classification aims to reclassify the hyperandrogenic PCOS phenotypes (A, B, and C according to the Rotterdam criteria) as an EMS due to the frequent metabolic disturbances which are strongly suspected to be the root cause of this syndrome. Therefore, much care is taken when prescribing OCPs to this subset of patients, as OCP use may worsen these metabolic factors. In contrast, the remaining phenotype (phenotype D) was still classified as PCOS, as it is thought the etiopathogenesis for this condition is ovarian in origin, and these patients do not show metabolic disturbances. As such, the standardization of the diagnostic criteria is crucial to better define effective and personalized therapies.

Based on reported evidence on the potentially adverse cardiometabolic effects of OCPs in healthy subjects and in women with PCOS, clinicians should pay attention when prescribing OCP therapies in those patients with metabolic and hormonal alterations. Indeed, such patients could be more prone, possibly also due to genetic predisposition, to develop concomitant pathologies. To counteract this, the combination of OCPs with lifestyle changes and/or insulin-sensitizer agents such as metformin or inositol is advised, particularly in women with hyperandrogenic PCOS.

Usually, in the management of PCOS women who exhibit hyperandrogenism, metabolic alterations, and high BMI, diet and lifestyle changes usually have a crucial role and should be combined with insulin sensitizers, rather than with OCPs, if no contraceptive purpose is required. Indeed, as mentioned above, the real leader in PCOS pathogenesis is IR rather than hyperandrogenism, therefore correcting insulin alteration may recover also androgen levels. Moreover, considering the complexity of PCOS pathogenesis, the use of OCPs may be considered symptomatic against the hormonal and metabolic symptoms, without treating the entire syndrome.

Given the extensive use of OCPs, it is difficult to change the prescription habits of doctors within the field. Therefore, further larger studies will help to evaluate the metabolic risk in patients with different phenotypes of PCOS, in addition to how these may be alleviated. These larger studies will help inform the medical community and move toward a personalized approach for PCOS, treating the underlying pathology rather than a symptomatic approach, as OCP-based therapies.

In our opinion, in the next 5 years, the standardization of diagnostic criteria for PCOS will be crucial for developing new personalized therapies in these patients, also considering the PCOS phenotypes and related risk factors. In this way, it will be possible to tackle each phenotype of PCOS individually, thus stimulating a more selective use of OCPs. For this to be fully realized, further research is required that investigates the underlying biological mechanisms at play, so that the pathogeneses of this traditionally misdiagnosed and misunderstood syndrome can be more accurately treated.

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