Combined oral contraceptives in the treatment of polycystic ovary syndrome

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Combined oral contraceptives (COC) are the most often used treatment modality for polycystic ovary syndrome (PCOS). Undisputedly, COC suppress androgen production, thus ameliorating skin androgenic symptoms and improving menstrual dysfunction. On the other hand, there are still many unresolved issues concerning their metabolic effects. COC could decrease insulin sensitivity and deteriorate glucose tolerance, although the negative influence on insulin sensitivity is dependent on other factors (especially obesity) and this need not be expressed in non-obese patients. It is probable that the impairment of glucose tolerance is reversible, as the incidence of diabetes is not increased in past COC users. The effects of COC on the lipid spectrum are dependent on the type of gestagen, but lipid levels usually remain within the reference limits. Combination therapy of COC with weight reduction or insulin sensitizers could further suppress androgen levels and improve metabolic parameters. The establishment of COC after laparoscopic ovarian drilling may further decrease androgen levels. The combination of COC and GnRH analogues is not superior to COC therapy alone. Prospective data about the influence of COC on the risk of diabetes mellitus, coronary artery disease and endometrial cancer in PCOS women are lacking.

Key words: antiandrogens/combined oral contraceptives/insulin/laparoscopic ovarian diathermy/polycystic ovary syndrome

Introduction

To date, combined oral contraceptives (COC) have been the most common treatment for polycystic ovary syndrome (PCOS). They are also used for the symptomatic treatment of hirsutism, acne and irregular menstrual cycles in women, where the cause of their symptoms is as yet undiagnosed PCOS. But surprisingly, in contrast to laparoscopic ovarian drilling (LOD) or metformin, the study of the effect of COC on PCOS has been given less attention.

The aim of this paper is to give a critical review of the data concerning the effects of COC in the treatment of PCOS, not only in monotherapy but also in combination with other treatment modalities, with special focus on the long-term health risks. Due to the limited literature on PCOS, we present data obtained from healthy COC users with potential application for women with PCOS.

Androgen production (ovarian and adrenal steroidogenesis)

Hyperandrogenism is the key endocrine abnormality of PCOS and serves as the essential diagnostic criterion of the syndrome (Dunaif, 1997; Azziz, 2003; Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004). From studies in vitro and in vivo, there are arguments supporting the significant effect of androgens on the metabolism of lipids or insulin sensitivity (Mortola and Yen, 1990; Polderman et al., 1994; Moghetti et al., 1996; Dahlgren et al., 1998). Amelioration of hyperandrogenaemia is essential for symptomatic treatment in patients with skin androgenic symptoms. It is speculated that an interference with the key pathogenic mechanism of the syndrome also beneficially influences the risk of later metabolic disturbances and health complications.

COC have been repeatedly shown to affect androgen synthesis and metabolism at different levels. Several studies with various designs demonstrated significant inhibition of ovarian androgen production during COC use (Porcile and Gallardo, 1991; Wiegartz et al., 1995; Nader et al., 1997; Dahlgren et al., 1998; Wahrenberg et al., 1999; Breitkopf et al., 2003; Rosen et al., 2003). The key mechanism of COC action is the inhibition of folliculogenesis, either as a result of the suppression of pituitary gonadotrophin secretion, or as the direct influence on ovarian folliculogenesis in COC with weaker antigonadotrophic effect (Burkman, 1995; Krattenmacher, 2000; Raudrant and Rabe, 2003). The other mechanism discussed is the influence on adrenal steroidogenesis (Wiegartz et al., 1995), which is assumed due to observed changes in the concentration of steroids produced primarily by the adrenals,
dehydroepiandrosterone sulphate. Even more significant is their influence on androgen binding capacity by stimulating sex hormone-binding globulin (SHBG) synthesis (see ‘Pill choice’).

A higher free androgen index (Ciampelli et al., 1999) and higher testosterone levels (Acien et al., 1999; Ciampelli et al., 1999) were repeatedly found in obese versus lean PCOS patients. Obesity is a known aggravating factor in the pathogenesis of PCOS (see ‘combination of COC with other treatment modalities’). It is surprising that so far, only one study has focused on the possible differences in the effect of COC on lean versus obese patients. The authors found a less pronounced decline in androgens during COC use in the obese subgroup in comparison to the lean one [average body mass index (BMI) of 32 and 20 kg/m², respectively; Cibula et al., 2001].

In summary, the effect of COC on folliculogenesis significantly decreases androgen production. This mechanism was confirmed in both healthy women and PCOS patients. In obese patients, it is likely that the suppression of androgen production is not as significant.

Glucose tolerance

A frequent finding in lean and obese PCOS women is hyperinsulinaemia secondary to increased peripheral insulin resistance, decreased clearance of insulin and abnormal insulin secretion (Chang et al., 1983; Dunaif et al., 1989, 1992; Dunaif and Finegood, 1996). A higher incidence of impaired glucose tolerance (IGT) and type 2 diabetes (DM 2) was found in comparison to healthy women (Ehrmann et al., 1999; Legro et al., 1999). On the other hand, not all women with PCOS are insulin resistant. Several studies did not confirm decreased insulin sensitivity, especially in non-obese patients when the data were carefully adjusted for potential confounding factors (Holte et al., 1994; Ehrmann et al., 1995; reviewed by Cibula, 2004). It is likely that only certain risk groups of PCOS patients are at an increased risk of developing IGT and DM 2 as a result of insulin resistance.

Healthy women

The first studies examining the effect of COC on glucose tolerance were conducted in the 1960s (Phillips and Duffy, 1973; Kalkhoff, 1975). In the era of high-dose contraceptives, most authors found a deterioration in glucose tolerance (Furman, 1981). Those studies comparing healthy users and non-users of low-dose COC found increased levels of both plasma glucose (+15% to +40–60%) and plasma insulin (+12% to +40%) during the oral glucose tolerance test (oGTT; Godsland et al., 1990a, 1993; Simon et al., 1990; Crook et al., 1993; Watanabe et al., 1994; Fruzzetti et al., 1999), and thus a deterioration in glucose tolerance. The relationship between the dose of progestin and the increase in glucose levels after the glucose challenge was documented for both estrane and gonane progestins (Ramcharan et al., 1980). Recently, Gaspard et al. (2003) showed no deleterious effect on glucose tolerance using COC containing the new antiandrogenic progestin drospirenone (DRSP) in a group of 27 users for a period of 13 months. No change in glucose tolerance was documented in a few more studies on a small number of subjects (Kasdorf and Kalkhoff, 1988; Nikschick et al., 1989; Gaspard et al., 2003).

Most of the above-cited studies were cross-sectional (Godsland et al., 1990a, 1993; Simon et al., 1990; Crook et al., 1993; Watanabe et al., 1994) and thus there could have been many unknown confounders with significant influence on glucose metabolism, such as lifestyle, ethnicity, family history of diabetes mellitus (DM), or socio-economic background of the participants. Moreover, it should be emphasized that the oGTT is poorly reproducible (Mooy et al., 1996; Ko et al., 1998; Eschwege et al., 2001), and its usefulness, even for the diagnosis of DM, is currently under debate (Davidson, 2002).

Thus, it can be summarized that COC may worsen glucose tolerance in healthy users. Based on available data it is speculated that the type of gestagen could play a role. However, this is not yet confirmed by any direct comparative study. Concerning the dose of estrogen, there are no data directly comparing low-dose COC with ultra-low-dose or extremely-low-dose COC.

PCOS

To date, there have been only a few short-term studies (all lasting < 6 months) assessing the effects of different COC on glucose tolerance in PCOS women. Two studies reported increased glucose levels after an oral glucose load (P < 0.05) when using COC containing desogestrel (DSG; Nader et al., 1997) or cyproterone acetate (CPA, P < 0.03; Morin-Papunen et al., 2000) in obese PCOS patients. In non-obese women, no significant changes in glucose tolerance were found in a small (nine PCOS and ten healthy controls) observational study with norethindrone (NET; Korytkowski et al., 1995), and in randomized studies with CPA (nine women with PCOS; Morin-Papunen et al., 2003a,b), and DSG or CPA (both groups with 10 women; Cagnacci et al., 2003). Recently, a 1 year pilot open study with DRSP in 15 PCOS women found no significant change in oral glucose tolerance or in the insulinaemic response during oGTT (Guido et al., 2004).

It is thus possible to hypothesize that the metabolic effects of COC in PCOS could be dependent on body weight, nevertheless, as yet, there is no head-to-head comparison of different COC between lean and obese patients. The above-cited studies are small and not unanimous. New gestagens with minimal metabolic side-effects, such as DRSP, could probably be more advantageous where glucose tolerance is concerned.

Insulin resistance and secretion

Healthy women

Most studies that evaluated only insulin levels (as the simplest measure of insulin resistance), were in agreement and found higher fasting levels and higher levels after oral glucose load in healthy COC users versus non-users (Godsland et al., 1990b; Spellacy et al., 1992; Crook et al., 1993).

The gold standard for the evaluation of insulin sensitivity is the euglycaemic–hyperinsulinaemic clamp (DeFronzo et al., 1979; Wallace and Matthews, 2002). As this method is laborious, so far there have been no population-based studies in healthy women using the clamp and distinguishing the effects of COC on insulin sensitivity. A cross-sectional study in 15 women using COC and 15 non-users (Perseghin et al., 2001) found
an ~40% decrease in insulin sensitivity in users. A similar decrease was found when using COC containing levonorgestrel (LNG) in seven healthy lean women (Kasdorf and Kalkhoff, 1988). In contrast, no deterioration in insulin sensitivity was demonstrated after 12 months of using COC containing CPA in seven women (Scheen et al., 1993). Data from two controlled studies examining the effect of COC in PCOS women found mostly no change in insulin sensitivity in control groups (13 and 9 healthy women) during 3 and 6 months of treatment, respectively (Armstrong et al., 2001; Cibula et al., 2002).

The intravenous glucose tolerance test (IVGTT) with minimal modelling is considered to be more suitable for population studies than the clamp. The drawback of this method is mainly the lower reproducibility (Saad et al., 1994). The advantage of the IVGTT is the possibility of evaluation not only the insulin sensitivity index (Si), but also glucose effectiveness and insulin secretion. Insulin sensitivity and compensatory secretion of insulin are tightly connected (Kahn et al., 1993). The product of insulin sensitivity and β-cell function was found to be a constant value, so-called the disposition index. The results from cross-sectional studies on reasonably sized populations of ~380 and ~390 women, respectively (Godsland et al., 1992; Clausen et al., 1996), found a decreased Si (by between 30 and 40%) in COC users compared to non-users. The lowest Si was shown in users of LNG-containing preparations (P < 0.001). When considering the physiological connection between insulin resistance and secretion, a cross-sectional study of 186 healthy COC users versus non-users revealed an insufficient compensatory increase in β-cell insulin secretion. Values of disposition index in low-dose COC users were ~50% lower than in controls (Watanabe et al., 1994).

It is possible to conclude that COC could decrease insulin sensitivity in healthy users. The observed discrepancies could be due to inadequate adjustment for many confounding factors, which might influence insulin sensitivity, and are difficult to control (lifestyle, dietary composition, ethnicity, etc.). Without doubt, a more important question is whether these changes are irreversible and whether they could have a long-term effect on glucose tolerance (see ‘IGT and DM’). This remains unanswered.

**PCOS**

A significant decrease in insulin sensitivity was found in an observational open study conducted in overweight PCOS women (n = 9) after COC with NET (P < 0.02; Korytkowski et al., 1995). Discrepant data are available for the non-obese subgroup. No significant change in insulin sensitivity was found in a randomized control trial comparing metformin with CPA in 17 non-obese PCOS women (Morin-Papunen et al., 2003b). Observational studies in a small number of non-obese PCOS and healthy women (<20) found no deterioration of insulin sensitivity using CPA (Armstrong et al., 2001) or norgestimate (Cibula et al., 2002). However, all the cited studies are small, with no placebo control group.

The data currently available examining insulin secretion after COC in PCOS are sparse and discrepant. Either elevation of the late phase of insulin secretion during the hyperglycaemic clamp after COC with NET (Korytkowski et al., 1995) or no change in insulin pulse frequency after COC containing CPA (Armstrong et al., 2001) was reported. Our group examined both insulin sensitivity and secretion together using an arginine stimulation test, and found a significant decrease (P < 0.0001) in the disposition index (see ‘Insulin resistance and secretion’, ‘Healthy women’) after EE-CPA treatment (Vrbiková et al., 2004).

In conclusion, the available data (Table I) demonstrate that insulin sensitivity may worsen during COC use in PCOS. However, the effect could be modified primarily by the degree of obesity. A decrease in insulin sensitivity is not a necessary consequence of COC use, especially in non-obese women where the influence may be neutral. As yet, the data about changes in insulin secretion are not sufficient to draw any conclusion. Studies comparing different products are sparse, and therefore it is not possible to conclude whether some combinations are superior to the others. It should be emphasized that all available studies are limited in the duration of hormone use and long-term effects are not known.

### Table I. Summary of the studies dealing with insulin sensitivity during COC treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of participants</th>
<th>Body mass index (kg/m²)</th>
<th>Design</th>
<th>Intervention/ subgroups</th>
<th>Insulin sensitivity</th>
<th>Total cholesterol</th>
<th>HDL cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korytkowski et al. (1995)</td>
<td>19</td>
<td>28</td>
<td>CT (PCOS versus × C)</td>
<td>PCOS</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Dahlgren et al. (1998)</td>
<td>28</td>
<td>&lt;28</td>
<td>CT (COC versus GnRH analogues)</td>
<td>COC</td>
<td>↓</td>
<td>↔</td>
<td>ND</td>
<td>↑</td>
</tr>
<tr>
<td>Armstrong et al. (2001)</td>
<td>11</td>
<td>&lt;28</td>
<td>Observational</td>
<td>GnRH analogues</td>
<td>↑</td>
<td>↔</td>
<td>ND</td>
<td>→</td>
</tr>
<tr>
<td>Cibula et al. (2002)</td>
<td>22</td>
<td>&lt;30</td>
<td>CT (PCOS versus × C)</td>
<td>PCOS</td>
<td>↔</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Vrbikova et al. (2004)</td>
<td>24</td>
<td>&lt;30</td>
<td>RCT</td>
<td>COC</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

* ↔ = no significant change; ↑, ↓ = significant change (P < 0.05).

* HDL = high-density lipoprotein; R/CT = randomized/controlled trial; PCOS = polycystic ovary syndrome; C = controls; TTS-E = transdermal estrogens; CPA = cyproterone acetate; DRSP = drosperone; nd = not done.
Lipid levels

Dyslipidaemia has commonly been reported in PCOS women, although the findings are not fully consistent. The most common type is the pattern of metabolic syndrome X, i.e. a decrease in high-density lipoprotein (HDL) cholesterol and increase in triglyceride levels or elevation in small dense low-density lipoprotein (LDL; Dejager et al., 2001). However, the clinical significance of these findings is uncertain. Only in rare cases of reproductive age females affected with PCOS do the lipid levels reach abnormal levels, as defined for example by NHANES III (Legro, 2001).

Healthy users

In healthy users, COC modify the lipid spectrum; however reached concentrations usually remain within the reference limits. Estrogens cause the elevation of HDL cholesterol and this effect is reversed by the antiestrogenic (androgenic) influence of the accompanying gestagen. COC containing less androgenic gestagens, such as DSG, gestodene or dienogest could significantly elevate HDL cholesterol levels when compared to COC with the more androgenic LNG (Crook et al., 1993). The different effects of gestagenses were well documented in a randomized study with an exceptional crossover design (van Rooijen et al., 2002). COC containing an equal dose of ethinyl estradiol (EE) and either DSG or LNG did not significantly change LDL cholesterol, both COC increased triglycerides, to a greater degree with DSG. The level of HDL cholesterol was significantly increased only in the COC containing DSG.

It can be concluded that the changes in the lipid spectrum during COC use are partially modified by gestagens, but more importantly in the vast majority of healthy users the changes remain within reference limits, and it is unlikely that this could have a clinically significant effect on the risk of cardiovascular diseases (Khader et al., 2003).

PCOS

An optimal COC should either be neutral as regards metabolic risk parameters for arterial disease or should change them in the direction expected to reduce the risk. So far, little attention has been given to the influence of different COC on lipid levels in PCOS women. Most of the studies are flawed by the design (non-randomized and open studies), conducted on a small number of participants, and the results are not fully consistent.

COC with CPA is one of the most often used preparations in Europe in women with hyperandrogenaemia. COC with EE 35 μg/CPA 2 mg (Diane 35) was shown to increase total cholesterol ($P < 0.001$), LDL cholesterol ($P < 0.05$) and triglycerides ($P < 0.01$), with no significant changes in HDL cholesterol (Prelevic et al., 1990). In a 3 year observational study the same COC led to a significant increase in triglycerides, HDL cholesterol and apoprotein B, LDL cholesterol and the LDL cholesterol:HDL cholesterol ratio were reduced (all $P < 0.05$; Falsetti and Pasinetti, 1995). Adolescents with PCOS were randomized for either DSG- or CPA-containing COC, and both were associated with an increase in total cholesterol, LDL cholesterol, and HDL cholesterol levels, with no change in the total cholesterol:HDL cholesterol and LDL cholesterol:HDL cholesterol ratios (Mastorakos et al., 2002). Treatment was associated with a tendency towards increase in triglycerides. Treatment with higher doses of CPA (up to 100 mg/day) was found to be equally effective such as the COC containing 2 mg concerning hirsutism (Barth et al., 1991), but triglycerides increased more markedly in the high-dose regimens (Vermeulen and Rubens, 1988).

One recently introduced gestagen, DRSP, was used in PCOS in two open pilot studies. DRSP was shown to induce changes similar to those in healthy women, e.g. an increase in triglycerides, in HDL cholesterol (both $P < 0.01$), and no significant shift in HDL:LDL ratio (Guido et al., 2004). It was found to elevate fasting insulin (Palep-Singh et al., 2004). In comparison with gestodene, DRSP was more beneficial concerning body composition in young women with functional ovarian hyperandrogenism (Ibanez and de Zegher, 2004). In conclusion, as in healthy users the effect of COC on the lipid spectrum is dependent on the type of gestagen, with a beneficial change in the atherogenic index (HDL:LDL) in low-androgenic gestagens, accompanied with a simultaneous increase in triglycerides. These changes usually do not go beyond the reference limits.

Long-term health risks in PCOS

IGT and DM

The global prevalence of DM 2 has been increasing in recent years and it is supposed to reach $215 \times 10^6$ affected individuals in the year 2010. The highest prevalence is seen in the Pacific region, reaching 10–20%. In the USA, African Americans, Hispanic and Asian and Pacific Islander groups mostly have a higher prevalence of DM 2 (13, 20 and 8%, respectively) than non-Hispanic white Americans ($\sim 3–8$%). Worldwide, the lowest prevalence is seen in rural populations such as Tanzania, Chile or mainland China (<3%). White populations mostly have moderate prevalence: 2–4% in Central and Eastern Europe and 1–2% in the UK (Dabelea and Hamman, 2004).

In women with PCOS, a greater prevalence of IGT and DM 2 was shown independently by two groups in the USA. Among obese patients, IGT and DM 2 were found in 30 and 10%, respectively (Ehrmann et al., 1999; Legro et al., 1999). These data were confirmed in different populations (Weerakiet et al., 2001) with variations in prevalence in different ethnic groups. In non-obese or only overweight women with PCOS, the prevalence of IGT and DM 2 ranged between 10 and 2%, respectively (Legro et al., 1999; Vrbíková et al., 2003; Gambineri et al., 2004). A higher rate of conversion from normal glucose tolerance to IGT or to DM 2 was described by two groups (Ehrmann et al., 1999; Wang and Norman, 2004), but both studies have a high number of drop-outs (80 and 50%), and so it is difficult to draw any definite conclusion. Globally, the risk of glucose intolerance among PCOS subjects seems to be $\sim 5–10$-fold higher than for the entire population. The exact factors responsible for this excess risk have not been identified; family history of DM 2, obesity, insulin resistance, β cell secretory dysfunction and hyperandrogenaemia are possible candidates (Legro, 2001; Norman et al., 2001). It is debatable whether PCOS itself creates a risk or whether only certain subgroups of patients (e.g. obese) are at an increased risk of DM.
It was discussed previously that COC in healthy women could lead to a temporary deterioration of glucose tolerance (see ‘Glucose tolerance’). Concerning the long-term use of COC, there are few data available, as published studies lasted 1 year at most. A deterioration of glucose tolerance by COC is probably reversible, as was shown even for high-dose COC and reviewed by Kalkhoff (1975). Most importantly, there is no evidence about a consequently increased risk of frank DM among former or current users of COC (Rimm et al., 1992; Chasan-Taber et al., 1997), with the exception of the small increase in risk for COC users in the distant past (Rimm et al., 1992). On the other hand, we must take into account that the women examined were relatively young (with a range of 25–44 years) and the incidence of undiagnosed DM in this age group is as low as 1% (Harris et al., 1998). Another drawback is the short follow-up of the cohort, which reached only 4 years.

Concerning women with pre-existing risk factors for DM, in the largest retrospective cohort study to date comparing COC with non-hormonal contraception, COC did not increase the risk of DM 2 in Latino women with previous gestational diabetes mellitus (GDM; Kjos et al., 1998).

In another threatened group, women with PCOS, the data are very sparse. Only one prospective long-term study evaluated glucose tolerance in a small group of PCOS users versus non-users of COC. This showed a slight decrease in post-load glucose levels in users, but significant deterioration of hyperinsulinaemia in non-users (Pasquali et al., 1999). However, it should be emphasized that the study enrolled 37 women with a lack of adjustment for possible confounders.

To summarize, although some studies demonstrate worsening of glucose tolerance in healthy COC users, at present there is no evidence showing an increased risk of DM in past or present users. Even in women with a history of GDM, COC use did not alter the risk. Only one study, although not controlled, evaluating the risk in patients with PCOS, actually found better values of glucose tolerance in COC users in comparison with non-users. Therefore, the available data do not confirm a potentially increased risk of DM in PCOS women as a consequence of COC use. An attractive concept of improving glucose tolerance by long-term use of COC by lowering hyperandrogenaemia remains only speculative.

Coronary artery disease

Some of the proven risk factors for coronary artery disease (CAD) occur with greater likelihood in women with PCOS. Besides dyslipidaemia, the risk of CAD might also be increased by hyperinsulinaemia and a higher prevalence of IGT and DM 2. In small groups of patients, CAD was found to be more frequent, more extensive, or manifested earlier in life in PCOS patients (Talbott et al., 1998; Talbott et al., 2000; Paradisi et al., 2001; Christian et al., 2003). In contrast, Pierpoint et al. (1998) evaluated cardiovascular (CV) mortality in women with PCOS. A total of 786 patients diagnosed in the UK between 1930 and 1979 were traced from hospital records. The standardized mortality ratio was then calculated based on 59 deaths. The study found a higher mortality from DM but no increased average mortality from circulatory disease. Based on available data, recent reviews concluded that the evidence for PCOS as an independent risk factor for CAD is currently weak (Wild, 2002a,b).

It is generally accepted that COC does not modify the absolute risk of CAD in healthy users <35 years of age with no CV risk factors, who do not smoke, and who have had their blood pressure checked before starting COC use. The effect of smoking on CAD risk is greater than the effect of COC alone. The World Health Organization Collaborative Study (1997) found odds ratios for acute myocardial infarction among current healthy COC users to be 5.01 (95% CI 2.54–9.90) in European centres and 4.78 (95% CI 2.52–9.07) in developing countries. More recently, a case–control study based on a similar number of cases showed an odds ratio for myocardial infarction among any type of COC users to be 2.0 (95% CI 1.5–2.8), and 1.3 (95% CI 0.7–2.5) for pills with low androgenic progestin as compared to non-users (Tanis et al., 2001).

It must be emphasized that past COC use was not found to be a CAD risk factor, nor was a tendency shown towards an increased risk with the duration of COC use. Unfortunately, until now, no data are available evaluating modification of CAD risk in PCOS in relation to COC use.

Endometrial cancer

An increased risk of endometrial cancer is often presented as one of the health consequences of PCOS. A higher prevalence of obesity, irregular menstrual cycles, amenorrhea, infertility, or hirsutism was repeatedly found in patients with endometrial cancer in the general population (Coulam et al., 1983; Henderson et al., 1983; Dahlgren et al., 1989; Austin et al., 1991; Parslov et al., 2000). PCOS women cluster many of these risk factors.

In PCOS, the most commonly presented cause of increased risk is unopposed estrogens due to long-term anovulation. However, this mechanism does not coincide with the finding of a thin endometrium in most women with PCOS or with the low frequency of dysfunctional uterine bleeding as a result of endometrial hyperproliferation.

It is likely that in women with PCOS, there are other mechanisms involved, including hyperandrogenaemia or the increased concentration of free insulin-like growth factor-I (IGF) (Giudice et al., 1992).

It is generally accepted that COC prevent endometrial cancer in the healthy population. A number of case–control and a few cohort studies have demonstrated an apparent protective effect (World Health Organization Collaborative Study Cancer and Steroid Hormone Study, 1987, 1988; Beral et al., 1988). This is supported by the observations showing a tendency towards a risk reduction with the duration of use and, on the other hand, an increased risk with increasing interval since last COC use (Stanford et al., 1993). The mechanism of the protective effect is unknown. Besides the antiestrogenic effect of gestagens, there can only be speculation about the role of decreased free IGF concentration due to estrogen-stimulated increased synthesis of insulin-like growth factor binding protein-1 (Westwood et al., 1999; Balogh et al., 2000; Cibula et al., 2001).

Unfortunately, no data are available evaluating the prevalence of endometrial cancer in PCOS women in relation to current or past COC use. It is questionable whether data from the healthy population, in terms of endometrial safety, might be applied to
PCOS. Based on the known risk factors, it is probable that the underlying mechanisms in the general population do not differ from specific risk subgroups in PCOS patients. However, the only conclusion which might be made is that a preventive effect of COC on the risk of endometrial cancer is highly likely, dependent on duration of use, but has not yet been proven specifically in PCOS.

Pill choice

One of the key aspects for clinical practice is the choice of an optimal product from the available COC. The criteria for selection have not been objectively balanced, due to marketing interests especially in the treatment of acne. Currently, the spectrum of COC differs in three basic parameters: (i) dose of EE; (ii) composition; (iii) choice of gestagen.

Dose of EE

All currently available COC contain the same estrogen, EE, whose daily dose ranges from 15 to 50 μg. The dose of estrogen influences the activity of the pituitary–ovarian axis and as a result also the residual ovarian activity. The likelihood of follicular growth up to the size of a dominant follicle is greater with a daily dose of 20 μg in comparison to a dose of 30 μg (van Heusden and Fauser, 1999). Residual follicular activity is responsible not only for ovarian estradiol synthesis but also for androgen production. Moreover, the dose of EE in combination with the same dose and type of gestagen correlates with the final concentration of SHBG (Wiegratz et al., 2003). This is a critical factor for the level of the circulating free fraction of androgens.

Composition

The composition of the product (monophasic, biphasic or triphasic) does not influence the mechanisms by which COC affect the metabolism of androgens. Nevertheless, monophasic COC might be argued as the first choice due to the easier transition to continuous use. During the 7-day pill-free interval, an increase in gonadotrophin levels stimulates the ovarian synthesis of androgens. Testosterone levels are significantly lower during the continuous regimen in comparison to the cyclic one with an 86% increase in testosterone after 7 days of placebo (Ruchhoft et al., 1996).

Progestin

The antiestrogenic (androgenic) effect of progestin in a combined preparation is decisive for the influence on the production of binding proteins. With increasing antiestrogenic activity, a stimulatory effect of COC on SHBG synthesis is decreased. Significant differences in SHBG changes among preparations with various gestagens using the same dose of EE were repeatedly presented (van der Vange et al., 1990; Wiegratz et al., 2003). In healthy users after six cycles the mean changes in SHBG reached +270% versus +80% if COC contained low or higher antiestrogenic (androgenic) activity, which do not decrease estrogen-stimulated overproduction of binding proteins, especially SHBG. A daily dose of 30–35 μg of EE guarantees sufficient suppression of ovarian follicular activity as well as effective stimulation of SHBG production. The monophasic composition might be advantageous due to easy transition to a continuous regimen.

Combination of COC with other treatment modalities

Combination of COC and metformin

Metformin was used in PCOS for the first time in 1994 (Velazquez et al., 1994) and 51 clinical trials were performed until the end of 2003. A recent meta-analysis comparing all randomized controlled studies (Lord et al., 2003) concluded that metformin is effective in achieving ovulation with odds ratios of 3.88 (CI 2.25–6.69) for metformin versus placebo, and that metformin has a significant effect in reducing fasting insulin levels (weighted mean difference –5.37, CI –8.11 to –2.63), blood pressure and LDL cholesterol. There was no evidence of an effect on BMI or waist:hip ratio. In the general population, use of metformin delayed manifestation of DM 2 in patients at high risk for diabetes (Knowler et al., 2002), beneficially influenced CV risk factors (see, e.g. Palumbo, 1998) and reduced CV morbidity and mortality in DM 2 patients (Grant, 2003). These beneficial effects of metformin on CV risk factors and on insulin sensitivity could justify the combination of metformin with COC in PCOS patients.

There are two studies randomizing PCOS women for EE/CPA or metformin in obese or non-obese groups of patients. The first study evaluated 32 obese PCOS women during 6 months treatment with either 1–2 g of metformin daily or EE + CPA (Diane Nova). In the metformin group, a significant decrease was observed in the waist:hip ratio (P < 0.01), fasting blood glucose (P < 0.04) and insulin levels (P < 0.02), increase in fasting glucose oxidation (P < 0.06) and decrease in lipid oxidation (P < 0.02). Insulin sensitivity, as measured by the euglycaemic–hyperinsulinaemic clamp, and free androgen index did not change significantly. In the Diane group, there was a worsening of glucose tolerance, not accompanied by a deterioration of insulin sensitivity (clamp), and a significant decrease in androgen levels (P < 0.001; Morin-Papunen et al., 2000). Altogether 20 non-obese patients were enrolled into another study with the same design (Morin-Papunen et al., 2000). In the metformin group, BMI decreased significantly (P < 0.05), with no change in the waist:hip ratio. Fasting glucose and insulin decreased (P < 0.05), with no change in insulin sensitivity, and with an improvement in hepatic insulin extraction (P < 0.01). Serum androgen levels decreased (P < 0.05) and the menstrual pattern improved in ~50% of the patients. Diane significantly ameliorated hyperandrogenism (P < 0.001), and did not influence glucose tolerance and insulin sensitivity. The decrease in the LDL:HDL ratio (P < 0.02), increase in triglycerides (P < 0.001) and increase in C-reactive protein (P < 0.001) was observed in the EE/CPA-treated group in contrast to the metformin-treated patients (Morin-Papunen et al., 2003a).

So far, there have been two studies directly comparing COC and the combination therapy of COC with metformin. In the first
study, 40 lean PCOS women were randomized for the above two treatments for a limited period of 3 months (Elter et al., 2002). Metformin added to COC led to a greater decrease in androstenedione ($P < 0.04$) and to a more pronounced increase in SHBG ($P < 0.02$). A decrease in BMI, waist:hip ratio, and in glucose:insulin ratio was observed only in the metformin group, but the difference between both treatment groups did not reach significance. Recently, we randomized 31 non-obese PCOS women for COC or for COC + metformin (Cibula et al., 2005). Insulin sensitivity was evaluated directly using the euglycaemic–hyperinsulinaemic clamp. Addition of metformin only slightly modified the treatment effect of COC. There was no change in insulin sensitivity in either group, and the only significant difference between both groups was a greater decrease in androstenedione after combined treatment.

The results of available studies suggest a positive effect of metformin in monotherapy on both endocrine and metabolic disturbances in PCOS (Table II). There are only two studies dealing with the combination of metformin + COC. This combination led to a greater decrease in androstenedione; but insulin sensitivity was not modified and the changes in adiposity (BMI, waist:hip ratio) were not fully consistent. Therefore, we conclude that the available data do not offer enough evidence to advocate the standard use of COC in combination with metformin in the long-term treatment of PCOS. It should be emphasized that the potential benefit of combined treatment with metformin for specific subgroups of women with PCOS (especially the obese ones) should be addressed by future studies.

### Combination of COC and weight reduction

About 50% of the women suffering from PCOS are obese (Gambineri et al., 2002). Obesity is not a diagnostic criterion of PCOS, but, if present, is a significant factor modifying the clinical phenotype of the patients. Obesity itself suppresses the synthesis of SHBG, increases androgen production (Givens et al., 1987), and decreases insulin sensitivity (Pasquali et al., 1993). In obese PCOS women, higher levels of androgens (Acién et al., 1999) and more pronounced insulin resistance were demonstrated compared to lean and obese healthy women (Dunaif et al., 1989). The higher levels of androgens and insulin stimulate the synthesis of insulin-like growth factor-I and suppress SHBG and insulin-like growth factor binding protein-1 production in the liver (Buyalos et al., 1995; Morales et al., 1996) with resulting higher levels of free IGF-1. A negative correlation between gonadotrophin secretion (LH) and BMI was repeatedly described (Arroyo et al., 1997; Taylor et al., 1997).

Weight reduction alone can significantly influence the phenotype of the disease. Open observational non-controlled studies showed that after a 6–12 month hypocaloric regimen, a mean weight loss of $-2$–$-10\%$ was followed by a decrease in testosterone and by ovulation resumption (Pasquali et al., 1989; Huber-Buchholz et al., 1999).

An observational non-randomized study (Wahrenberg et al., 1999) compared 3 months of weight reduction using a very low calorie diet (VLCD; $n = 9$) with the use of COC ($n = 8$) containing norethisterone in PCOS women. Improved insulin sensitivity (determined by significantly lower levels of fasting insulin

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of participants</th>
<th>Design</th>
<th>Intervention</th>
<th>Change in body mass index</th>
<th>Waist:hip ratio</th>
<th>Insulin sensitivity</th>
<th>Triglycerides</th>
<th>Total cholesterol</th>
<th>HDL cholesterol</th>
<th>LDL:HDL</th>
<th>Androstenedione</th>
<th>DHEAS</th>
<th>Testosterone</th>
<th>SHBG</th>
</tr>
</thead>
</table>

- $\rightarrow$ Increase in hepatic insulin extraction.
- $\rightarrow$ Increase in glucose oxidation and decrease in lipid oxidation.
- $\rightarrow$ Increase in glucose oxidation and decrease in lipid oxidation.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; RCT = randomized controlled trial; M = metformin; nd = not done.
and glucose; both $P < 0.05$) was seen in the VLCD group, but not in the COC group. The SHBG level rose significantly in both groups, but more markedly in the COC group ($P < 0.01$), whereas total serum testosterone decreased equally in both groups. Subcutaneous fat tissue biopsy was performed in both groups before and after treatment. After VLCD, the lipolytic sensitivity to noradrenalin increased 10-fold, whereas COC lowered the lipolytic sensitivity to noradrenalin and isoprenaline. COC therapy thus reduces hyperandrogenicity, but fails to improve insulin sensitivity and intensifies catecholamine resistance in adipose tissue.

Recently, a prospective controlled study randomized 40 obese PCOS women for either COC ($n = 14$) or sibutramine ($n = 12$) or for the combined treatment of COC + sibutramine ($n = 14$). All three groups were advised to follow a hypocaloric diet. A significant decrease in the waist:hip ratio ($P < 0.01$), diastolic blood pressure ($P < 0.05$), serum triglyceride level ($P < 0.001$) and higher insulin Si derived from oGTT ($P < 0.001$) were shown only after sibutramine; on the other hand, improvement in androgen levels and in the degree of hirsutism was similar in all groups (Sabuncu et al., 2003).

It might be concluded that weight reduction could have a beneficial effect, especially on insulin sensitivity and CV risk factors, in patients with PCOS (Table III). This positive trend is maintained even with simultaneous COC treatment. Weight reduction in overweight patients during COC treatment is highly recommended although compliance with this treatment modality is extremely poor.

**COC versus LOD**

A surgical procedure on the ovaries is the oldest treatment modality for PCOS (Hyde, 1907). Several authors presented a significant decrease in LH and androgens, and a resumption of regular ovulatory cycles following the procedure (Campo et al., 1993; Donesky and Adashi, 1995, 1996; Lemieux et al., 1999). These induced changes may be long lasting, as documented in the classic paper by Stein (1956) and confirmed more recently (Gjonnaess, 1998). The maintenance of regular ovulatory cycles and a significant decrease in androgens and gonadotrophins were presented in a group of 51 women 18–20 years following ovarian electrocautery. Surprisingly there has been limited attention to the metabolic consequences of surgical treatment. The euglycaemic–hyperinsulinaemic clamp was used in 17 women with PCOS who had failed to ovulate with clomiphene citrate. Insulin sensitivity as well as lipid levels remained unaltered. However, a significant limitation of the study is the short follow-up for three cycles after the procedure (Lemieux et al., 1999). It might be speculated that substantial endocrine changes cause beneficial metabolic effects after a longer period of time.

Taskin et al. (1996) published a randomized but small study on 17 women with PCOS, which compared the effect of either laparoscopic ovarian cautery or GnRH agonist in combination with COC. Not surprisingly, a more significant decrease in LH (70% versus 59%) and an increase in SHBG (13.5 versus 5.9%) were found in the combined treatment, while there were comparable changes in both groups in testosterone and androstenedione. Similar results were confirmed in another non-randomized study.
(Gjonnaess, 1999). The decrease in LH, testosterone and androstenedione, similar to the increase in SHBG, were significantly more pronounced after COC. It should be emphasized that in both the above studies, the parameters evaluated were measured within a short interval after the procedure.

For our purpose, the more significant question is whether there is an indication for the administration of COC after the procedure. Gjonnaess (1999) compared 18 women using COC and 23 women who were started on COC after establishing regular ovulatory cycles following ovarian electrocautery. The addition of COC caused a further decline in LH, testosterone and androstenedione, and an increase in SHBG. Finally, androgens and SHBG reached comparable changes in both groups; in other words, performing the procedure prior to COC administration did not increase the endocrine effect of COC treatment.

From the limited data published, it follows that COC have a more pronounced effect on androgens and SHBG than ovarian surgery. As long as it is possible to use COC, there is little reason to perform LOD prior to the beginning of treatment. On the other hand, if the procedure is performed, COC may further increase the effect on androgens and SHBG after the surgery.

**Combination of COC with antiandrogens**

Antiandrogens are divided into steroidal (CPA; spironolactone, SP), non-steroidal (flutamide) and 5α-reductase inhibitors (finasteride). As their mechanism of action is different from COC (blocking the androgenic receptor), they could act synergistically with COC.

There is a paucity of randomized controlled studies comparing treatment with different antiandrogens, and those studies mostly include mixed women with PCOS and with idiopathic hirsutism. A recent meta-analysis found SP (100 mg/day) more effective than finasteride (5 mg/day) or low-dose CPA for reduction in the Ferriman–Gallwey score; nevertheless, all study populations were small and confidence intervals were wide (Farquhar et al., 2003). Flutamide (250–500 mg/day) was shown to be superior to finasteride (5 mg/day) in few studies (Falsetti et al., 1999; Venturoli et al., 1999; Muderris et al., 2000) but similar effects of both antiandrogens in the same doses (finasteride 5 mg versus flutamide 500 or 250 mg/day) on hirsutism were described in other studies (Fruzzetti et al., 1999; Mognetti et al., 2000). Addition of SP (Kelestimur and Sahin, 1998) or finasteride (Tartagni et al., 2000) to COC containing 2.5 mg of CPA was superior, in terms of decreasing the degree of hirsutism, to the use of COC alone. However, it should be emphasized that insulin sensitivity, glucose tolerance or lipid levels were not examined in any of the above studies.

It can be concluded that there is some evidence showing more pronounced and faster improvement of skin androgenic symptoms, especially hirsutism, using a combination treatment of COC with antiandrogens. Little is known about whether this combination could have any beneficial metabolic or hormonal effects.

**Combination of COC with flutamide**

Flutamide is the only antiandrogen that specifically blocks the androgen receptor without any glucocorticoid, gestational, androgenic or estrogenic activity. This pure antiandrogen was shown to have beneficial effects on the lipid spectrum (a decrease in triglycerides, total and LDL cholesterol) in young girls with functional ovarian hyperandrogenism (Ibanez et al., 2000). The combination of flutamide with COC could thus theoretically have metabolic benefits besides better antiandrogenic activity.

An open study conducted in women with idiopathic hirsutism compared COC with the combination of flutamide (250 mg/day) with COC (Dodin et al., 1995). The authors found a significant increase in the HDL cholesterol in the combined therapy, and a similar effect of both treatments on hirsutism.

Recently, the combination of very-low-dose flutamide (62.5 mg/day) with metformin was compared with flutamide + metformin + COC in hyperinsulinaemic women suffering from functional ovarian hyperandrogenism. Both groups had a similar decrease in testosterone and increase in SHBG and HDL cholesterol; the only significant difference was a reduction in total body fat in the group (Ibanez and de Zegher, 2003). In an open-labelled study, the same authors randomized 22 young women with PCOS for either COC (containing DRSP) alone or for the combination of COC + metformin with a very low dose of flutamide (62.5 mg/day). Body composition and pro- and anti-inflammatory cytokines (interleukin-6 and adiponectin) were evaluated. Abnormal adipocytokine levels present already at the beginning remained unimproved and body adiposity further increased (P < 0.05) in women on COC alone. In the group on combination treatment, adiponectin increased, and interleukin-6 (both P < 0.01) together with body fat decreased (P < 0.001). The increase in SHBG and decrease in LDL cholesterol were more pronounced in the combination group (P < 0.05; Ibanez and de Zegher, 2004).

From the published data (Table IV) it is difficult to conclude whether a more rapid and sustained effect of COC in combination with flutamide might be expected on skin androgenic symptoms, especially on hirsutism. It should be emphasized that the price of combination treatment is substantially higher. Until now, the suggested beneficial effects of this combination treatment on lipids, SHBG and body composition have largely been presented by the only one group of authors.

**COC and GnRH agonists**

The rationale for combining COC with GnRH agonists is based on the assumption of more extensive suppression of ovarian steroidogenesis, including the production of androgens. The administration of GnRH agonists has been shown to suppress LH and ovarian androgen production in hirsute women (Chang et al., 1983a; Heiner et al., 1995; Genazzani et al., 1997). However, treatment is accompanied by vasomotor symptoms and its duration is limited due to loss of bone mineral density (Dawood et al., 1989; Dodin et al., 1991). These negative consequences are fully prevented by add-back therapy with COC (Heiner et al., 1995; Ciotta et al., 1996), which makes long-term treatment possible.

Several studies have directly compared COC monotherapy and COC in combination with GnRH agonists (Table V). Most of these focused on the treatment of hirsutism; however, from the characteristics of the populations it is apparent that a large portion of the patients fulfilled the criteria for PCOS (Carr et al.,
Table IV. Summary of the studies dealing with a combination of flutamide and COC

| Study          | No. of participants | Design  | Intervention | Body mass index (kg/m²) | Fat mass | Abdominal fat mass | Insulin sensitivity | Total cholesterol | HDL cholesterol | LDL cholesterol | Triglycerides | Free androgens | DHEAS | Testosterone | SHBG |
|----------------|---------------------|---------|--------------|-------------------------|----------|-------------------|-------------------|-------------------|-----------------|----------------|---------------|---------------|--------------|--------|-------------|------|
| Dodin et al. (1995) | 33                  | Open    | COC + Fl     | 28                      | nd       | nd                | nd                | ++                | ++              | ++             | ++            | ++            | ++       | ++          | ++   |
| Ibanez et al. (2000) | 18                  | Observ  | Fl + Fl      | 24                      | nd       | nd                | nd                | ++                | ++             | ++            | ++            | ++            | ++       | ++          | ++   |
| Ibanez et al. (2003) | 24                  | RCT     | COC          | < 25                    | ++       | ++                | ++                | ++                | ++             | ++            | ++            | ++            | ++       | ++          | ++   |
| Ibanez et al. (2004) | 22                  | RCT     | COC + Fl + Fl| < 25                    | ++       | ++                | ++                | ++                | ++             | ++            | ++            | ++            | ++       | ++          | ++   |

aDecrease in total body fat, no change in abdominal fat, increase in lean body mass in COC + Fl, no change in COC.
bDecrease in total body fat, abdominal fat and increase in lean body mass in COC + Fl + M, increase in total and abdominal fat and decrease in lean body mass in COC.

= no significant change; \( P < 0.05 \); \( P < 0.01 \).

HDL = high-density lipoprotein; LDL = low-density lipoprotein; RCT = randomized controlled trial; M = metformin; Fl = flutamide; nd = not done.

Conclusions

Even though COC are the most common and one of the oldest symptomatic treatment modalities for androgenic symptoms—acne and hirsutism—is considered as proven. The effect on skin androgenic symptoms— acne and hirsutism—is considered as proven. Of the long-term effects, COC could be new in evidence-based medicine, but it is apparent that the data concerning the metabolic effects in PCOS are scarce, inconsistent, and do not fulfill the criteria for evidence-based medicine. The effect on skin androgenic symptoms—acne and hirsutism—is considered as proven.

When indicating long-term treatment, endometrial cancer occurs in only a certain subgroup of patients with PCOS. These patients are women currently receiving oral contraceptives. The effect on skin androgenic symptoms—acne and hirsutism—is considered as proven.

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Table V. Summary of the studies dealing with combination of GnRH analogues and COC

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of participants</th>
<th>Design</th>
<th>Intervention</th>
<th>Body mass index (kg/m²)</th>
<th>Waist:hip ratio</th>
<th>Insulin sensitivity</th>
<th>Total cholesterol</th>
<th>HDL cholesterol</th>
<th>Triglycerides</th>
<th>Free androgens</th>
<th>DHEAS</th>
<th>Testosterone</th>
<th>SHBG</th>
<th>LH</th>
<th>FSH</th>
<th>Androstenedione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carr et al. (1995)</td>
<td>35</td>
<td>RCT</td>
<td>GnRHa</td>
<td>Obese</td>
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<tr>
<td>Heiner et al. (1995)</td>
<td>64</td>
<td>RCT</td>
<td>GnRHa + P</td>
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<td>GnRHa + COC</td>
<td>Overweight</td>
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<td>56</td>
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<td>GnRHa + COC &lt;25</td>
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</table>

a Transient decrease.
b Transient increase.
^ Fasting insulin.
* ↔ = no significant change; ↓ = P ≤ 0.05; ↑ = P < 0.01.
HDL = high-density lipoprotein; DHEAS = dehydroepiandrosterone sulphate; SHBG = sex hormone-binding globulin; RCT = randomized controlled trial; GnRHa = GnRH agonist; P = placebo; nd = not done.
burdened with a high risk of developing DM 2. It might be speculated that specifically in these patients other treatment options are preferable, especially weight reduction and metformin. However, it should be emphasized that there are no prospective studies in any of the above-mentioned treatments confirming their effect on the risk of DM or CAD in PCOS patients.

We assume that in patients without the above-mentioned risk factors, the definite advantages of COC treatment outweigh the speculative disadvantages. Similarly, we can only speculate whether the combination of COC with weight reduction, LOD or metformin would be beneficial regarding metabolic aspects.

The conclusions should motivate further studies in many areas. Several significant questions remain unanswered: the long-term effect of COC on insulin action; the possibility of combining COC with metformin in subgroups of women at risk of DM; influencing the risk of endometrial cancer with long-term COC use; the possible positive effect on the risk of pathological glucose tolerance and DM as a consequence of reducing hyperandrogenenaemia.

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