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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; Wiegratz *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 (Wiegratz *et al.*, 1995), which is assumed due to observed changes in the concentration of steroids produced primarily by the adrenals, especially

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/m^2, 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, 1993; 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 (Vrbíkovā *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

Study	No. of participants	Body mass index (kg/m^2)	Design	Intervention/ subgroups	Insulin sensitivity	Total cholesterol	HDL cholesterol	Triglycerides
Korytkowski *et al.* (1995)	19	28	CT (PCOS versus × C)	PCOS	↓	↔	↔	↑
				C	↓	↔	↔	↑
Dahlgren *et al.* (1998)	28	<28	CT (COC versus GnRH analogues)	COC	↓	↔	ND	↑
				GnRH analogues	↑	↔	ND	↔
Armstrong *et al.* (2001)	11	<28	Observational	PCOS	↔	ND	ND	ND
Cibula *et al.* (2002)	22	<30	CT (PCOS versus × C)	PCOS	↔	ND	ND	ND
				C	↔	ND	ND	ND
Vrbikova *et al.* (2004)	24	<30	RCT	COC	↓	↑	↑	↑
				TTS-E/CPA	↔	↔	↔	↔
Guido *et al.* (2004)	18	<25	Observational	DRSP	↔	↑	↑	↑

↔ = 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 = drospirenone; 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 gestagens 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 215×10^6 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 (~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; Vrbīkovā *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 ~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, amenorrhoea, 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 progestin (DNG versus LNG; Wiegratz *et al.*, 2003).

In conclusion, from the above data it follows that the most important parameter in the selection of COC is the type of progestin, which determines the changes in SHBG production. The first choice should be gestagens with low 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 (Acien *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 II. Summary of the studies dealing with COC and metformin

Study	No. of participants	Body mass index (kg/m^2)	Design	Intervention	Change in body mass index	Waist:hip ratio	Insulin sensitivity	Total cholesterol	HDL cholesterol	Triglycerides	Free androgens	Androstenedione	DHEAS	Testosterone	SHBG
Morin-Papunen *et al.* (2000)	32	>27	RCT	COC	↕	↕	↕	nd	nd	nd	↓↓	↓	↓	↓	
				M	↕	↓↓	↕[a]	nd	nd	nd	↕	↓	↕	↕	→
Morin-Papunen *et al.* (2003a,b)	20	<25	RCT	COC		↕	↕[b]	nd	↓LDL:HDL		↓↓	↓↓	↓	↓	
				M	↓	↓	↕[b]	nd	↕	↕	↓	↓	↕	↓	↕
Elter *et al.* (2002)	40	<25	RCT	COC	↕	↕	↕		↕	↕	↓	↓	↕	↓	
				COC + M	↓	↓		↕	↕	↕	↓	↓↓	↕	↓	
Cibula *et al.* (2005)	30	<25	RCT	COC	↕	nd	↕				↓	↓	↕	↓	
				COC + M	↕	nd	↕			↕	↓↓	↓	↕	↓	

[a] Increase in hepatic insulin extraction.
[b] Increase in glucose oxidation and decrease in lipid oxidation.
↔ = no significant change; ↓ = $P < 0.05$; ↓↓ = $P < 0.01$.
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

Table III. Summary of the studies dealing with the combination of COC and weight reduction

Study	Design	Number of participants	Body mass index (kg/m^2)	Intervention	Change in body mass index	Waist:hip ratio	Insulin sensitivity	Total cholesterol	HDL cholesterol	Triglycerides	Free androgens	DHEAS	Testosterone	SHBG
Sabuncu *et al.* (2003)	RCT	40	37 ± 5	COC + diet	↓	↕	↕	↕	↑	↑↑	↓↓	↓↓	↓↓	↑↑
				S + diet	↓↓	↓↓	↑↑	↕	↕	↓	↓↓	↓↓	↓↓	↑↑
				COC + S + diet	↓↓	↕	↕	↕	↑↑	↑	↓↓	↓↓	↓↓	↑↑
Wahrenberg *et al.* (1999)	Open	17	35 ± 4	COC	↔	↕	↕	nd	nd	nd	↓	nd	↓↓	↑↑
			38 ± 2	VLCD	↓↓	↕	↑	nd	nd	nd	↓	nd	↓↓	↑

↔ = 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; S = sibutramin; VLCD = very low calorie diet; nd = not done.

(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; Moghetti *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, progestational, 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/m^2)	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	Fl	28	nd	nd	nd	↔	↔	↔	↔	nd	↓	↔	↕
			COC + Fl	24	nd	nd	nd	↔		↔		nd	↓↓	↓	
Ibanez *et al.* (2000)	18	Observ	Fl	<25	nd	nd	↔	↓	↕	↓	↓	↓	↔	↓	
Ibanez *et al.* (2003)	24	RCT	COC	<25	↔	↔	↔	nd		↔	↔	nd	Nd	↓↓	
			COC + Fl + M	<25	↓↓	↔	↔	nd		↓↓	↔	nd	nd	↓↓	
Ibanez *et al.* (2004)	22	RCT	COC	<25			↔	nd		↔		nd	nd	↓↓	
			COC + Fl + M	<25	↓↓	↓↓	↔	nd		↓↓		nd	nd	↓↓	

[a]Decrease in total body fat, no change in abdominal fat, increase in lean body mass in COC + Fl, no change in COC.
[b]Decrease 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.

1995; Heiner *et al.*, 1995; Vegetti *et al.*, 1996). The data from randomized studies show the same or increased effect of combined therapy on androgen production, SHBG and hirsutism (Carr *et al.*, 1995; Elkind-Hirsch *et al.*, 1995; Heiner *et al.*, 1995). The largest study to date, of 64 patients, documented a significant reduction in total testosterone ($P < 0.001$) and hair shaft diameter ($P < 0.05$) in the combination group only, but a comparable effect on SHBG (Heiner *et al.*, 1995). In the same year, a smaller study (33 randomized women) confirmed a greater reduction of testosterone, and free testosterone, but equal changes in SHBG in combined treatment (Elkind-Hirsch *et al.*, 1995). However, another study found no differences in the decrease of total testosterone, free testosterone or SHBG at the end of 6 and 12 months of therapy in 33 patients, (Carr *et al.*, 1995).

Two randomized studies (Elkind-Hirsch *et al.*, 1995; Genazzani *et al.*, 1997) compared COC monotherapy and COC in combination with GnRH agonists in patients with PCOS. Both were in agreement and found similar changes in testosterone, androstenedione, 17OH-progesterone, free testosterone and SHBG in both groups during 6 and 12 months of therapy in 30 and 48 randomized patients, respectively.

From the available data, it follows that the addition of GnRH agonist to COC therapy in patients with PCOS is not accompanied by a more significant reduction in androgen production. GnRH agonists do not further potentiate the beneficial effect of the estrogen component of COC on SHBG. Nevertheless, it is possible that some subgroups of patients with PCOS, especially if ovarian steroidogenesis does not respond to COC administration, may benefit from combined therapy.

Conclusions

Even though COC are the most common and one of the oldest symptomatic treatment modalities for androgenic skin symptoms and for irregular menstrual cycles caused by hyperandrogenaemia, it is apparent that the data concerning the metabolic effects in PCOS are scarce, inconsistent, and do not fulfil the criteria for evidence-based medicine.

COC interfere with the key endocrine abnormality of the PCOS—hyperandrogenaemia—at several levels. They decrease ovarian androgen production, increase the binding capacity for steroids by stimulating hepatic SHBG production, and some gestagens with antiandrogenic effect compete with androgens for binding to receptors. The effect on skin androgenic symptoms—acne and hirsutism—is considered as proven. Of the long-term effects, we can assume the protective influence of COC against endometrial cancer in PCOS, similarly as it is documented in healthy users. Although COC could decrease insulin sensitivity and worsen glucose tolerance in both healthy users and PCOS women, currently there is no evidence that COC modify the risk of CAD or DM either negatively or positively.

When indicating long-term treatment, at present there is nothing left except to tailor the therapy to the individual patient. It is probable that metabolic abnormalities, especially disturbances in insulin action, occur in only a certain subgroup of patients with PCOS. These include obese patients, women with a family history of DM 2 or a personal history of GDM, and women with a confirmed disturbance of insulin action. These patients are

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

Study	No. of participants	Design	Intervention	Body mass index (kg/m^2)	Waist:hip ratio	Insulin sensitivity	Total cholesterol	HDL cholesterol	Triglycerides	Free androgens	DHEAS	Testosterone	SHBG	LH	FSH	Androstenedione
Carr *et al.* (1995)	35	RCT	GnRHa	Obese	nd	nd	↔	↔		↓	↔	↓	nd	↓ ↓	↔	↓
			COC	Obese	nd	nd	↔	↔		↓ [a]	↔	↓	nd	↓	↔	↓
			GnRHa + COC	Obese	nd	nd	↔	↔		↓ [a]	↔	↓ [a]	nd	↓ ↓	↓ [b]	↓
Heiner *et al.* (1995)	64	RCT	GnRHa + P	Overweight	nd	nd	nd	nd	nd	↔	↔	↓	↔	↔	↔	↓
			GnRHa + COC	Overweight	nd	nd	nd	nd	nd	↓	↔	↓	↑	↔	↓	↓ ↓
			COC + P	Overweight	nd	nd	nd	nd	nd	↓	↔	↔	↑	↓	↔	↓
			P + P	Overweight	nd	nd	nd	nd	nd	↔	↔	↔	↔	↔	↔	↓
Elkind-Hirsch *et al.* (1995)	33	RCT	GnRHa	Obese	nd	↔ [c]	nd	nd	nd	↓ ↓	↔	↓ ↓	↔	↓ ↓	↓	nd
			COC	Obese	nd	↔ [c]	nd	nd	nd	↓	↔	↓ ↓	↑ ↑	↓	↓	nd
			GnRHa + COC	Obese	nd	↔ [c]	nd	nd	nd	↓ ↓	↔	↓ ↓	↑ ↑	↓ ↓	↓	nd
Vegetti *et al.* (1996)	56	RCT	GnRHa + COC	<25	nd	nd	nd	nd	nd	↓	↔	↓	↑	↓ ↓	↓	nd
			COC	<25	nd	nd	nd	nd	nd	↓	↔	↓	↑	↓	↓	nd

a [a]-
[b]Transient decrease.
[c]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 hyperandrogenaemia.

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References

Acien P, Quereda F, Matallin P, Villarroya E, Lopez-Fernandez JA, Acien M, Mauri M and Alfayate R (1999) Insulin androgens and obesity in women with and without polycystic ovary syndrome: a heterogeneous group of disorders. Fertil Steril 72,32–40.

Armstrong VL, Wiggam MI, Ennis CN, Sheridan B, Traub AI, Atkinson AB and Bell PM (2001) Insulin action and insulin secretion in polycystic ovary syndrome treated with ethinyl oestradiol/cyproterone acetate. Q J Med 94,31–37.

Arroyo A, Laughlin GA, Morales AJ and Yen SS (1997) Inappropriate gonadotropin secretion in polycystic ovary syndrome: influence of adiposity. J Clin Endocrinol Metab 82,3728–3733.

Austin H, Austin JM Jr, Partridge EE, Hatch KD and Shingleton HM (1991) Endometrial cancer, obesity and body fat distribution. Cancer Res 51,568–572.

Azziz R (2003) Androgen excess is the key element in polycystic ovary syndrome. Fertil Steril 80,252–254.

Balogh A, Kauf E, Vollanth R, Graser G, Klinger G and Oettel M (2000) Effects of two oral contraceptives on plasma levels of insulin-like growth factor I (IGF-I) and growth hormone (hGH). Contraception 62,259–269.

Barth JH, Cherry CA, Wojnarowska F and Dawber RP (1991) Cyproterone acetate for severe hirsutism: results of a double-blind dose-ranging study. Clin Endocrinol (Oxf) 35,5–10.

Beral V, Hannaford P and Kay C (1988) Oral contraceptive use and malignancies of the genital tract results from the Royal College of General Practitioners' Oral Contraception Study. Lancet 2,1331–1335.

Breitkopf DM, Rosen MP, Young SL and Nagamani M (2003) Efficacy of second versus third generation oral contraceptives in the treatment of hirsutism. Contraception 67,349–353.

Burkman RT, Jr (1995) The role of oral contraceptives in the treatment of hyperandrogenic disorders. Am J Med 98,130S–136S.

Buyalos RP, Pekonen F, Halme JK, Judd HL and Rutanen EM (1995) The relationship between circulating androgens, obesity and hyperinsulinemia on serum insulin-like growth factor binding protein-1 in the polycystic ovarian syndrome. Am J Obstet Gynecol 172,932–939.

Cagnacci A, Paoletti AM, Renzi A, Orru M, Pilloni M, Melis GB and Volpe A (2003) Glucose metabolism and insulin resistance in women with polycystic ovary syndrome during therapy with oral contraceptives containing cyproterone acetate or desogestrel. J Clin Endocrinol Metab 88,3621–3625.

Campo S, Felli A, Lamanna MA, Barini A and Garcea N (1993) Endocrine changes and clinical outcome after laparoscopic ovarian resection in women with polycystic ovaries. Hum Reprod 8,359–363.

Cancer and Steroid Hormone Study (1987) Combination oral contraceptive use and the risk of endometrial cancer. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. J Am Med Assoc 257,796–800.

Carr BR, Breslau NA, Givens C, Byrd W, Barnett-Hamm C and Marshburn PB (1995) Oral contraceptive pills, gonadotropin-releasing hormone agonists, or use in combination for treatment of hirsutism: a clinical research center study. J Clin Endocrinol Metab 80, 1169–1178.

Chang RJ, Laufer LR, Meldrum DR, DeFazio J, Lu JK, Vale WW, Rivier JE and Judd HL (1983a) Steroid secretion in polycystic ovarian disease after ovarian suppression by a long-acting gonadotropin-releasing hormone agonist. J Clin Endocrinol Metab 56,897–903.

Chang RJ, Nakamura RM, Judd HL and Kaplan SA (1983b) Insulin resistance in nonobese patients with polycystic ovarian disease. J Clin Endocrinol Metab 57,356–359.

Chasan-Taber L, Willett WC, Stampfer MJ, Hunter DJ, Colditz GA, Spiegelman D and Manson JE (1997) A prospective study of oral contraceptives and NIDDM among US women. Diabetes Care 20,330–335.

Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy PF 2nd and Fitzpatrick LA (2003) Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. J Clin Endocrinol Metab 88,2562–2568.

Ciampelli M, Fulghesu AM, Cucinelli F, Pavone V, Ronsisvalle E, Guido M, Caruso A and Lanzone A (1999) Impact of insulin and body mass index on metabolic and endocrine variables in polycystic ovary syndrome. Metabolism 48,167–172.

Cibula D (2004) Is insulin resistance an essential component of PCOS?: the influence of confounding factors. Hum Reprod 19,757–759.

Cibula D, Hill M, Fanta M, Sindelka G and Zivny J (2001) Does obesity diminish the positive effect of oral contraceptive treatment on hyperandrogenism in women with polycystic ovarian syndrome? Hum Reprod 16,940–944.

Cibula D, Sindelka G, Hill M, Fanta M, Skrha J and Zivny J (2002) Insulin sensitivity in non-obese women with polycystic ovary syndrome during treatment with oral contraceptives containing low-androgenic progestin. Hum Reprod 17,76–82.

Cibula D, Fanta M, Vrbikova J, Stanicka S, Dvorakova K, Hill M, Skrha J, Zivny J and Skrenkova J (2005) The effect of combination therapy with metformin and combined oral contraceptives (COC) versus COC alone on insulin sensitivity, hyperandrogenaemia, SHBG and lipids. Hum Reprod 20,180–184.

Ciotta L, Cianci A, Giuffrida G, Marletta E, Agliano A and Palumbo G (1996) Clinical and hormonal effects of gonadotropin-releasing hormone agonist plus an oral contraceptive in severely hirsute patients with polycystic ovary disease. Fertil Steril 65,61–67.

Clausen JO, Borch-Johnsen K, Ibsen H, Bergman RN, Hougaard P, Winther K and Pedersen O (1996) Insulin sensitivity index, acute insulin response and glucose effectiveness in a population-based sample of 380 young healthy Caucasians. Analysis of the impact of gender, body fat, physical fitness and life-style factors. J Clin Invest 98,1195–1209.

Coulam CB, Annegers JF and Kranz JS (1983) Chronic anovulation syndrome and associated neoplasia. Obstet Gynecol 61,403–407.

Crook D, Godsland IF, Worthington M, Felton CV, Proudler AJ and Stevenson JC (1993) A comparative metabolic study of two low-estrogen-dose oral contraceptives containing desogestrel or gestodene progestins. Am J Obstet Gynecol 169,1183–1189.

Dabelea D and Hamman RF (2004) Epidemiology of type 2 diabetes mellitus. In Le Roith D, Taylor SI and Olefsky JM (eds) Diabetes Mellitus: A Fundamental and Clinical Text. 3rd edn. J.B. Lippincott, Co., Philadelphia, PA, pp 785–796.

Dahlgren E, Johansson S, Oden A, Lindstrom B and Janson PO (1989) A model for prediction of endometrial cancer. Acta Obstet Gynecol Scand 68,507–510.

Dahlgren E, Landin K, Krotkiewski M, Holm G and Janson PO (1998) Effects of two antiandrogen treatments on hirsutism and insulin sensitivity in women with polycystic ovary syndrome. Hum Reprod 13,2706–2711.

Davidson MB (2002) Counterpoint: the oral glucose tolerance test is superfluous. Diabetes Care 25,1883–1885.

Dawood MY, Lewis V and Ramos J (1989) Cortical and trabecular bone mineral content in women with endometriosis: effect of gonadotropin-releasing hormone agonist and danazol. Fertil Steril 52,21–26.

DeFronzo RA, Tobin JD and Andres R (1979) Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 237,E214–E223.

Dejager S, Pichard C, Giral P, Bruckert E, Federspield MC, Beucler I and Turpin G (2001) Smaller LDL particle size in women with polycystic ovary syndrome compared to controls. Clin Endocrinol (Oxf) 54,455–462.

Dodin S, Lemay A, Maheux R, Dumont M and Turcot-Lemay L (1991) Bone mass in endometriosis patients treated with GnRH agonist implant or danazol. Obstet Gynecol 77,410–415.

Dodin S, Faure N, Cedrin I, Mechain C, Turcot-Lemay L, Guy J and Lemay A (1995) Clinical efficacy and safety of low-dose flutamide alone and combined with an oral contraceptive for the treatment of idiopathic hirsutism. Clin Endocrinol (Oxf) 43,575–582.

Donesky BW and Adashi EY (1995) Surgically induced ovulation in the polycystic ovary syndrome: wedge resection revisited in the age of laparoscopy. Fertil Steril 63,439–463.

Donesky BW and Adashi EY (1996) Surgical ovulation induction: the role of ovarian diathermy in polycystic ovary syndrome. Baillières Clin Endocrinol Metab 10,293–309.

Dunaif A (1997) Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 18, 774–800.

Dunaif A and Finegood DT (1996) Beta-cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. J Clin Endocrinol Metab 81,942–947.

Dunaif A, Segal KR, Futterweit W and Dobrjansky A (1989) Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 38,1165–1174.

Dunaif A, Segal KR, Shelley DR, Green G, Dobrjansky A and Licholai T (1992) Evidence for distinctive and intrinsic defects in insulin action in polycystic ovary syndrome. Diabetes 41,1257–1266.

Ehrmann DA, Sturis J, Byrne MM, Karrison T, Rosenfield RL and Polonsky KS (1995) Insulin secretory defects in polycystic ovary syndrome. Relationship to insulin sensitivity and family history of non-insulin-dependent diabetes mellitus. J Clin Invest 96,520–527.

Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK and Imperial J (1999) Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 22,141–146.

Elkind-Hirsch KE, Anania C, Mack M and Malinak R (1995) Combination gonadotropin-releasing hormone agonist and oral contraceptive therapy improves treatment of hirsute women with ovarian hyperandrogenism. Fertil Steril 63,970–978.

Elter K, Imir G and Durmusoglu F (2002) Clinical, endocrine and metabolic effects of metformin added to ethinyl estradiol-cyproterone acetate in non-obese women with polycystic ovarian syndrome: a randomized controlled study. Hum Reprod 17,1729–1737.

Eschwege E, Charles MA, Simon D, Thibult N and Balkau B (2001) Reproducibility of the diagnosis of diabetes over a 30-month follow-up: the Paris Prospective Study. Diabetes Care 24,1941–1944.

Falsetti L and Pasinetti E (1995) Effects of long-term administration of an oral contraceptive containing ethinylestradiol and cyproterone acetate on lipid metabolism in women with polycystic ovary syndrome. Acta Obstet Gynecol Scand 74,56–60.

Falsetti L, Gambera A, Legrenzi L, Iacobello C and Bugari G (1999) Comparison of finasteride versus flutamide in the treatment of hirsutism. Eur J Endocrinol 141,361–367.

Farquhar C, Lee O, Toomath R and Jepson R (2003) Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Cochrane Database Syst Rev CD000194.

Fruzzetti F, Bersi C, Parrini D, Ricci C and Genazzani AR (1999) Treatment of hirsutism: comparisons between different antiandrogens with central and peripheral effects. Fertil Steril 71,445–451.

Furman BL (1981) Impairment of glucose tolerance produced by diuretics and other drugs. Pharmacol Ther 12,613–649.

Gambineri A, Pelusi C, Vicennati V, Pagotto U and Pasquali R (2002) Obesity and the polycystic ovary syndrome. Int J Obes Relat Metab Disord 26,883–896.

Gambineri A, Pelusi C, Manicardi E, Vicennati V, Cacciari M, Morselli-Labate AM, Pagotto U and Pasquali R (2004) Glucose intolerance in a large cohort of mediterranean women with polycystic ovary syndrome: phenotype and associated factors. Diabetes 53,2353–2358.

Gaspard U, Scheen A, Endrikat J, Buicu C, Lefebvre P, Gerlinger C and Heithecker R (2003) A randomized study over 13 cycles to assess the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on carbohydrate metabolism. Contraception 67,423–429.

Genazzani AD, Petraglia F, Battaglia C, Gamba O, Volpe A and Genazzani AR (1997) A long-term treatment with gonadotropin-releasing hormone agonist plus a low-dose oral contraceptive improves the recovery of the ovulatory function in patients with polycystic ovary syndrome. Fertil Steril 67,463–468.

Giudice LC, Dsupin BA and Irwin JC (1992) Steroid and peptide regulation of insulin-like growth factor-binding proteins secreted by human endometrial stromal cells is dependent on stromal differentiation. J Clin Endocrinol Metab 75,1235–1241.

Givens JR, Kurtz BR, Kitabchi AE, Bittle JB, Karas JG, Mitchell JA and Howes JF (1987) Reduction of hyperinsulinemia and insulin resistance by opiate receptor blockade in the polycystic ovary syndrome with acanthosis nigricans. J Clin Endocrinol Metab 64,377–382.

Gjonnaess H (1998) Late endocrine effects of ovarian electrocautery in women with polycystic ovary syndrome. Fertil Steril 69,697–701.

Gjonnaess H (1999) Comparison of ovarian electrocautery and oral contraceptives in the treatment of hyperandrogenism in women with polycystic ovary syndrome. Acta Obstet Gynecol Scand 78,530–533.

Godsland IF, Crook D and Wynn V (1990a) Low-dose oral contraceptives and carbohydrate metabolism. Am J Obstet Gynecol 163,348–353.

Godsland IF, Crook D, Simpson R, Proudler T, Felton C, Lees B, Anyaoku V, Devenport M and Wynn V (1990b) The effects of different formulations of oral contraceptive agents on lipid and carbohydrate metabolism. N Engl J Med 323,1375–1381.

Godsland IF, Walton C, Felton C, Proudler A, Patel A and Wynn V (1992) Insulin resistance, secretion and metabolism in users of oral contraceptives. J Clin Endocrinol Metab 74,64–70.

Godsland IF, Crook D, Worthington M, Proudler AJ, Felton C, Sidhu M and Stevenson JC (1993) Effects of a low-estrogen, desogestrel-containing oral contraceptive on lipid and carbohydrate metabolism. Contraception 48,217–227.

Grant PJ (2003) Beneficial effects of metformin on haemostasis and vascular function in man. Diabetes Metab 29,6S44–6S52.

Guido M, Romualdi D, Giuliani M, Suriano R, Selvaggi L, Apa R and Lanzone A (2004) Drospirenone for the treatment of hirsute women with polycystic ovary syndrome: a clinical, endocrinological, metabolic pilot study. J Clin Endocrinol Metab 89,2817–2823.

Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer HM and Byrd-Holt DD (1998) Prevalence of diabetes, impaired fasting glucose and impaired glucose tolerance in US adults. The Third National Health and Nutrition Examination Survey, 1988-1994. Diabetes Care 21,518–524.

Heiner JS, Greendale GA, Kawakami AK, Lapolt PS, Fisher M, Young D and Judd HL (1995) Comparison of a gonadotropin-releasing hormone agonist and a low dose oral contraceptive given alone or together in the treatment of hirsutism. J Clin Endocrinol Metab 80,3412–3418.

Henderson BE, Casagrande JT, Pike MC, Mack T, Rosario I and Duke A (1983) The epidemiology of endometrial cancer in young women. Br J Cancer 47,749–756.

Holte J, Bergh T, Berne C, Berglund L and Lithell H (1994) Enhanced early insulin response to glucose in relation to insulin resistance in women with polycystic ovary syndrome and normal glucose tolerance. J Clin Endocrinol Metab 78,1052–1058.

Huber-Buchholz MM, Carey DG and Norman RJ (1999) Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab 84,1470–1474.

Hyde CR (1907) Notes on conservative ovarian surgery. Am J Obstet Dis Women Child 56,145–159.

Ibanez L and De Zegher F (2003) Flutamide-metformin therapy to reduce fat mass in hyperinsulinemic ovarian hyperandrogenism: effects in adolescents and in women on third-generation oral contraception. J Clin Endocrinol Metab 88,4720–4724.

Ibanez L and de Zegher F (2004a) Ethinylestradiol-drospirenone, flutamide-metformin, or both for adolescents and women with hyperinsulinemic hyperandrogenism: opposite effects on adipocytokines and body adiposity. J Clin Endocrinol Metab 89,1592–1597.

Ibanez L and De Zegher F (2004b) Flutamide-metformin plus an oral contraceptive (OC) for young women with polycystic ovary syndrome: switch from third- to fourth-generation OC reduces body adiposity. Hum Reprod 19,1725–1727.

Ibanez L, Potau N, Marcos MV and de Zegher F (2000) Treatment of hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia and

hyperinsulinism in nonobese, adolescent girls: effect of flutamide. J Clin Endocrinol Metab 85,3251–3255.

Ibanez L, Valls C, Cabre S and De Zegher F (2004) Flutamide-metformin plus ethinylestradiol-drospirenone for lipolysis and antiatherogenesis in young women with ovarian hyperandrogenism: the key role of early, low-dose flutamide. J Clin Endocrinol Metab 89,4716–4720.

Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP *et al.* (1993) Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 42,1663–1672.

Kalkhoff RK (1975) Effects of oral contraceptive agents on carbohydrate metabolism. J Steroid Biochem 6,949–956.

Kasdorf G and Kalkhoff RK (1988) Prospective studies of insulin sensitivity in normal women receiving oral contraceptive agents. J Clin Endocrinol Metab 66,846–852.

Kelestimur F and Sahin Y (1998) Comparison of Diane 35 and Diane 35 plus spironolactone in the treatment of hirsutism. Fertil Steril 69, 66–69.

Khader YS, Rice J, John L and Abueita O (2003) Oral contraceptives use and the risk of myocardial infarction: a meta-analysis. Contraception 68,11–17.

Kjos SL, Peters RK, Xiang A, Thomas D, Schaefer U and Buchanan TA (1998) Contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes mellitus. J Am Med Assoc 280,533–538.

Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA and Nathan DM (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346,393–403.

Ko GT, Chan JC, Woo J, Lau E, Yeung VT, Chow CC and Cockram CS (1998) The reproducibility and usefulness of the oral glucose tolerance test in screening for diabetes and other cardiovascular risk factors. Ann Clin Biochem 35(Pt1),62–67.

Korytkowski MT, Mokan M, Horwitz MJ and Berga SL (1995) Metabolic effects of oral contraceptives in women with polycystic ovary syndrome. J Clin Endocrinol Metab 80,3327–3334.

Krattenmacher R (2000) Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. Contraception 62,29–38.

Legro RS (2001) Diabetes prevalence and risk factors in polycystic ovary syndrome. Obstet Gynecol Clin North Am 28,99–109.

Legro RS, Kunselman AR, Dodson WC and Dunaif A (1999) Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women [see comments]. J Clin Endocrinol Metab 84,165–169.

Lemieux S, Lewis GF, Ben-Chetrit A, Steiner G and Greenblatt EM (1999) Correction of hyperandrogenemia by laparoscopic ovarian cautery in women with polycystic ovarian syndrome is not accompanied by improved insulin sensitivity or lipid-lipoprotein levels. J Clin Endocrinol Metab 84,4278–4282.

Lord JM, Flight IH and Norman RJ (2003) Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database Syst Rev CD003053.

Mastorakos G, Koliopoulos C and Creatsas G (2002) Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. Fertil Steril 77,919–927.

Moghetti P, Tosi F, Castello R, Magnani CM, Negri C, Brun E, Furlani L, Caputo M and Muggeo M (1996) The insulin resistance in women with hyperandrogenism is partially reversed by antiandrogen treatment: evidence that androgens impair insulin action in women. J Clin Endocrinol Metab 81,952–960.

Moghetti P, Tosi F, Tosti A, Negri C, Misciali C, Perrone F, Caputo M, Muggeo M and Castello R (2000) Comparison of spironolactone, flutamide and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. J Clin Endocrinol Metab 85,89–94.

Mooy JM, Grootenhuis PA, de Vries H, Kostense PJ, Popp-Snijders C, Bouter LM and Heine RJ (1996) Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn Study. Diabetologia 39,298–305.

Morales AJ, Laughlin GA, Butzow T, Maheshwari H, Baumann G and Yen SS (1996) Insulin, somatotropic and luteinizing hormone axes in lean and obese women with polycystic ovary syndrome: common and distinct features. J Clin Endocrinol Metab 81,2854–2864.

Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK and Tapanainen JS (2000) Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab 85,3161–3168.

Morin-Papunen L, Rautio K, Ruokonen A, Hedberg P, Puukka M and Tapanainen JS (2003a) Metformin reduces serum C-reactive protein levels in women with polycystic ovary syndrome. J Clin Endocrinol Metab 88,4649–4654.

Morin-Papunen L, Vauhkonen I, Koivunen R, Ruokonen A, Martikainen H and Tapanainen JS (2003b) Metformin versus ethinyl estradiol-cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab 88,148–156.

Mortola JF and Yen SS (1990) The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. J Clin Endocrinol Metab 71,696–704.

Muderris II, Bayram F and Guven M (2000) Treatment of hirsutism with lowest-dose flutamide (625 mg/day). Gynecol Endocrinol 14,38–41.

Nader S, Riad-Gabriel MG and Saad MF (1997) The effect of a desogestrel-containing oral contraceptive on glucose tolerance and leptin concentrations in hyperandrogenic women. J Clin Endocrinol Metab 82,3074–3077.

Nikschick S, Kohler G and Mannchen E (1989) Carbohydrate metabolism during treatment of endometriosis with the progestin dienogest. Exp Clin Endocrinol 94,211–214.

Norman RJ, Masters L, Milner CR, Wang JX and Davies MJ (2001) Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. Hum Reprod 16,1995–1998.

Palep-Singh M, Mook K, Barth J and Balen A (2004) An observational study of Yasmin in the management of women with polycystic ovary syndrome. J Fam Plann Reprod Health Care 30,163–165.

Palumbo PJ (1998) Metformin: effects on cardiovascular risk factors in patients with non-insulin-dependent diabetes mellitus. J Diabetes Complications 12,110–119.

Paradisi G, Steinberg HO, Hempfling A, Cronin J, Hook G, Shepard MK and Baron AD (2001) Polycystic ovary syndrome is associated with endothelial dysfunction. Circulation 103,1410–1415.

Parslov M, Lidegaard O, Klintorp S, Pedersen B, Jonsson L, Eriksen PS and Ottesen B (2000) Risk factors among young women with endometrial cancer: a Danish case–control study. Am J Obstet Gynecol 182,23–29.

Pasquali R, Antenucci D, Casimirri F, Venturoli S, Paradisi R, Fabbri R, Balestra V, Melchionda N and Barbara L (1989) Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss. J Clin Endocrinol Metab 68,173–179.

Pasquali R, Casimirri F, Cantobelli S, Labate AM, Venturoli S, Paradisi R and Zannarini L (1993) Insulin and androgen relationships with abdominal body fat distribution in women with and without hyperandrogenism. Horm Res 39,179–187.

Pasquali R, Gambineri A, Anconetani B, Vicennati V, Colitta D, Caramelli E, Casimirri F and Morselli-Labate AM (1999) The natural history of the metabolic syndrome in young women with the polycystic ovary syndrome and the effect of long-term oestrogen–progestagen treatment. Clin Endocrinol (Oxf) 50,517–527.

Perseghin G, Scifo P, Pagliato E, Battezzati A, Benedini S, Soldini L, Testolin G, Del Maschio A and Luzi L (2001) Gender factors affect fatty acids-induced insulin resistance in nonobese humans: effects of oral steroidal contraception. J Clin Endocrinol Metab 86,3188–3196.

Phillips N and Duffy T (1973) One-hour glucose tolerance in relation to the use of contraceptive drugs. Am J Obstet Gynecol 116,91–100.

Pierpoint T, McKeigue PM, Isaacs AJ, Wild SH and Jacobs HS (1998) Mortality of women with polycystic ovary syndrome at long-term follow-up. J Clin Epidemiol 51,581–586.

Polderman KH, Gooren LJ, Asscheman H, Bakker A and Heine RJ (1994) Induction of insulin resistance by androgens and estrogens. J Clin Endocrinol Metab 79,265–271.

Porcile A and Gallardo E (1991) Long-term treatment of hirsutism: desogestrel compared with cyproterone acetate in oral contraceptives. Fertil Steril 55,877–881.

Prelevic GM, Wurzburger MI, Trpkovic D and Balint-Peric L (1990) Effects of a low-dose estrogen-antiandrogen combination (Diane-35) on lipid and carbohydrate metabolism in patients with polycystic ovary syndrome. Gynecol Endocrinol 4,157–168.

Ramcharan S, Pellegrin FA, Ray RM and Hsu JP (1980) The Walnut Creek Contraceptive Drug Study. A prospective study of the side effects of oral contraceptives. Volume III. An interim report: a comparison of disease occurrence leading to hospitalization or death in users and nonusers of oral contraceptives. J Reprod Med 25,345–372.

Raudrant D and Rabe T (2003) Progestogens with antiandrogenic properties. Drugs 63,463–492.

Rimm EB, Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, Hennekens CH and Speizer FE (1992) Oral contraceptive use and the risk of type 2 (non-insulin-dependent) diabetes mellitus in a large prospective study of women. Diabetologia 35,967–972.

Rosen MP, Breitkopf DM and Nagamani M (2003) A randomized controlled trial of second- versus third-generation oral contraceptives in the treatment of acne vulgaris. Am J Obstet Gynecol 188,1158–1160.

Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 19,41–47.

Ruchhoft EA, Elkind-Hirsch KE and Malinak R (1996) Pituitary function is altered during the same cycle in women with polycystic ovary syndrome treated with continuous or cyclic oral contraceptives or a gonadotropin-releasing hormone agonist. Fertil Steril 66,54–60.

Saad MF, Anderson RL, Laws A, Watanabe RM, Kades WW, Chen YD, Sands RE, Pei D, Savage PJ and Bergman RN (1994) A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. Insulin Resistance Atherosclerosis Study. Diabetes 43,1114–1121.

Sabuncu T, Harma M, Nazligul Y and Kilic F (2003) Sibutramine has a positive effect on clinical and metabolic parameters in obese patients with polycystic ovary syndrome. Fertil Steril 80,1199–1204.

Scheen AJ, Jandrain BJ, Humblet DM, Jaminet CB, Gaspard UJ and Lefebvre PJ (1993) Effects of a 1-year treatment with a low-dose combined oral contraceptive containing ethinyl estradiol and cyproterone acetate on glucose and insulin metabolism. Fertil Steril 59,797–802.

Simon D, Senan C, Garnier P, Saint-Paul M, Garat E, Thibult N and Papoz L (1990) Effects of oral contraceptives on carbohydrate and lipid metabolisms in a healthy population: the Telecom study. Am J Obstet Gynecol 163,382–387.

Spellacy WN, Tsibris JC, Hunter-Bonner DL, Smalling S, Chez RA, Angel JL and O'Brien WF (1992) Six-month carbohydrate metabolism studies in women using oral contraceptives containing gestodene and ethinyl estradiol. Contraception 45,533–539.

Stanford JL, Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD and Hoover RN (1993) Oral contraceptives and endometrial cancer: do other risk factors modify the association? Int J Cancer 54,243–248.

Talbott E, Clerici A, Berga SL, Kuller L, Guzick D, Detre K, Daniels T and Engberg RA (1998) Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: results of a case-control study. J Clin Epidemiol 51,415–422.

Talbott EO, Guzick DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE and Kuller LH (2000) Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women [in process citation]. Arterioscler Thromb Vasc Biol 20,2414–2421.

Tanis BC, van den Bosch MA, Kemmeren JM, Cats VM, Helmerhorst FM, Algra A, van der Graaf Y and Rosendaal FR (2001) Oral contraceptives and the risk of myocardial infarction. N Engl J Med 345,1787–1793.

Tartagni M, Schonauer LM, De Salvia MA, Cicinelli E, De Pergola G and D'Addario V (2000) Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. Fertil Steril 73,718–723.

Taskin O, Yalcinoglu AI, Kafkasli A, Burak F and Ozekici U (1996) Comparison of the effects of ovarian cauterization and gonadotropin-releasing hormone agonist and oral contraceptive therapy combination on endocrine changes in women with polycystic ovary disease. Fertil Steril 65,1115–1118.

Taylor AE, McCourt B, Martin KA, Anderson EJ, Adams JM, Schoenfeld D and Hall JE (1997) Determinants of abnormal gonadotropin secretion in clinically defined women with polycystic ovary syndrome. J Clin Endocrinol Metab 82,2248–2256.

van der Vange N, Blankenstein MA, Kloosterboer HJ, Haspels AA and Thijssen JH (1990) Effects of seven low-dose combined oral contraceptives on sex hormone binding globulin, corticosteroid binding globulin, total and free testosterone. Contraception 41,345–352.

van Heusden AM and Fauser BC (1999) Activity of the pituitary-ovarian axis in the pill-free interval during use of low-dose combined oral contraceptives. Contraception 59,237–243.

van Rooijen M, von Schoultz B, Silveira A, Hamsten A and Bremme K (2002) Different effects of oral contraceptives containing levonorgestrel or desogestrel on plasma lipoproteins and coagulation factor VII. Am J Obstet Gynecol 186,44–48.

Vegetti W, Testa G, Maggioni P, Motta T, Falsetti L and Crosignani PG (1996) An open randomized comparative study of an oral contraceptive containing ethinyl estradiol and cyproterone acetate with and without the GnRH analogue goserelin in the long-term treatment of hirsutism. Gynecol Obstet Invest 41,260–268.

Velazquez EM, Mendoza S, Hamer T, Sosa F and Glueck CJ (1994) Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 43,647–654.

Venturoli S, Marescalchi O, Colombo FM, Macrelli S, Ravaioli B, Bagnoli A, Paradisi R and Flamigni C (1999) A prospective randomized trial comparing low dose flutamide, finasteride, ketoconazole and cyproterone acetate-estrogen regimens in the treatment of hirsutism. J Clin Endocrinol Metab 84,1304–1310.

Vermeulen A and Rubens R (1988) Effects of cyproterone acetate plus ethinylestradiol low dose on plasma androgens and lipids in mildly hirsute or acneic young women. Contraception 38,419–428.

Vrbĭkovā J, Cifkova R, Jirkovska A, Lanska V, Platilova H, Zamrazil V and Starka L (2003) Cardiovascular risk factors in young Czech females with polycystic ovary syndrome. Hum Reprod 18,980–984.

Vrbĭkovā J, Stanicka S, Dvorakova K, Hill M, Vondra K, Bendlova B and Starka L (2004) Metabolic and endocrine effects of treatment with peroral or transdermal oestrogens in conjunction with peroral cyproterone acetate in women with polycystic ovary syndrome. Eur J Endocrinol 150,215–223.

Wahrenberg H, Ek I, Reynisdottir S, Carlstrom K, Bergqvist A and Arner P (1999) Divergent effects of weight reduction and oral anticonception treatment on adrenergic lipolysis regulation in obese women with the polycystic ovary syndrome. J Clin Endocrinol Metab 84,2182–2187.

Wallace TM and Matthews DR (2002) The assessment of insulin resistance in man. Diabet Med 19,527–534.

Wang JX and Norman RJ (2004) Risk factors for the deterioration of glucose metabolism in polycystic ovary syndrome. Reprod Biomed Online 9,201–204.

Watanabe RM, Azen CG, Roy S, Perlman JA and Bergman RN (1994) Defects in carbohydrate metabolism in oral contraceptive users without apparent metabolic risk factors. J Clin Endocrinol Metab 79,1277–1283.

Weerakiet S, Srisombut C, Bunnag P, Sangtong S, Chuangsoongnoen N and Rojanasakul A (2001) Prevalence of type 2 diabetes mellitus and impaired glucose tolerance in Asian women with polycystic ovary syndrome. Int J Gynaecol Obstet 75,177–184.

Westwood M, Gibson JM, Pennells LA and White A (1999) Modification of plasma insulin-like growth factors and binding proteins during oral contraceptive use and the normal menstrual cycle. Am J Obstet Gynecol 180,530–536.

World Health Organization Collaborative Study (1988) Endometrial cancer and combined oral contraceptives WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Epidemiol 17,263–269.

World Health Organization Collaborative Study (1997) Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet 349,1202–1209.

Wiegratz I, Jung-Hoffmann C and Kuhl H (1995) Effect of two oral contraceptives containing ethinylestradiol and gestodene or norgestimate upon androgen parameters and serum binding proteins. Contraception 51,341–346.

Wiegratz I, Kutschera E, Lee JH, Moore C, Mellinger U, Winkler UH and Kuhl H (2003) Effect of four different oral contraceptives on various sex hormones and serum-binding globulins. Contraception 67,25–32.

Wild RA (2002a) Long-term health consequences of PCOS. Hum Reprod Update 8,231–241.

Wild RA (2002b) Polycystic ovary syndrome: a risk for coronary artery disease? Am J Obstet Gynecol 186,35–43.

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