Low-dose flutamide-metformin therapy for hyperinsulinemic hyperandrogenism in non-obese adolescents and women

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Polycystic ovary syndrome (PCOS) is a variable disorder that is characterized in adolescents and young women by a broad spectrum of anomalies, including hyperandrogenemia, insulin resistance, dyslipidemia, body adiposity and low-grade inflammation. At present, there is no approved therapy for PCOS. Recent studies indicate that a low-dose combination of flutamide (Flu; a generic androgen-receptor blocker) and metformin (Met; a generic insulin-sensitizer) normalizes the adolescent PCOS spectrum more than an oral contraceptive (OC); in young women, the PCOS spectrum was found to be more normalized by OC plus Flu-Met than by OC alone. Within the pathophysiological cascade of PCOS, Flu-Met seems to counter upstream anomalies like hyperinsulinemia or hyperandrogenism, thereby preventing or reversing downstream effects. In contrast, an OC essentially masks downstream symptoms like hirsutism, acne or irregular menses, whereas the upstream aberrations remain unaltered or may even be worsened. The available experience with Flu-Met is limited but promising. We emphasize that Flu-Met may (as part of its efficacy) induce ovulation but is contra-indicated post-conception because of potential embryotoxicity; therefore, it seems wise to combine Flu-Met with an oral or a transdermal oestro-progestagen or with a non-endocrine method of contraception. May this update prompt further research into Flu-Met’s therapeutic potential in patients with PCOS. Until the abovementioned effects have been broadly confirmed, Flu-Met should not be regarded as a standard therapy for widespread clinical practice.

Key words: drospirenone/flutamide/metformin/oral contraception/polycystic ovary syndrome

Introduction

It is now 70 years ago that the entity of ‘amenorrhea associated with bilateral polycystic ovaries’ was described (Stein and Leventhal, 1935). This condition was later broadened into polycystic ovary syndrome (PCOS), the main features of which are currently considered to be oligo- or anovulation, hyperandrogenism and a polycystic appearance of the ovaries (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). The latter appearance may essentially be a late epiphenomenon of an early-onset disorder that includes endocrine, metabolic and inflammatory components. Indeed, PCOS is now recognized as the most prevalent endocrine-metabolic disorder of adolescents and young women; it is a condition that represents a major health-care challenge, partly because of its co-morbidities including subfertility, dyslipidemia and cardiovascular disease (Asunción et al., 2000; Dunai and Thomas, 2000; Azziz et al., 2004a, 2005; Buggs and Rosenfield, 2005). Acne and hirsutism are among the classic symptoms of PCOS; other features include a deficit of lean mass and an excess of fat, in particular of abdominal fat, even in the absence of obesity (Kirchengast and Huber, 2001; Ibáñez and de Zegher, 2003a; Ibáñez et al., 2003; Azziz et al., 2004a,b). Abdominal fat excess, endothelial dysfunction and impaired insulin sensitivity have each been related to the circulating levels of adiponectin and other adipocytokines, as well as to inflammatory markers such as interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), C-reactive protein (CRP) and the neutrophil count; hence, a prolonged state of low-grade inflammation and body adiposity is thought to contribute to the early appearance of cardiovascular disease in women with PCOS (Fernández-Real et al., 1998; Kelly et al., 2001; Morin-Papunen et al., 2003a; Rexrode et al., 2003; Boulman et al., 2004; Goldstein and Scalia, 2004; Ibáñez et al., 2004a, 2005c; Orio et al., 2004, 2005; Tarkun et al., 2004; Gonzalez et al., 2005; Ibáñez and de Zegher, 2005; Sjöholm and Nyström, 2005; Vural et al., 2005).

At present, there is no approved therapy for PCOS in adolescents or women. A first step in the classic treatment approach is to give an oral contraceptive (OC), even to young teenagers; although OCs reduce the hyperandrogenemia, they do not correct the low-grade inflammation, the adipose body composition and most other endocrine-metabolic anomalies (Baumann and Rosenfield,
2002; Mastorakos et al., 2002; Diamanti-Kandarakis et al., 2003; Ibáñez and de Zegher, 2003a; Morin-Papunen et al., 2003b; Ibáñez et al., 2004a; Rautio et al., 2005; Vrbikova and Cibula, 2005).

About 20 years ago, Dunaif recognized the importance of hyperinsulinemic insulin resistance in PCOS (Dunaif et al., 1985). This finding prompted the exploration of insulin-sensitization with metformin (Met) (Velazquez et al., 1994), an approach that is now broadly applied (reviewed by Lord et al., 2003; Cheang and Nestler, 2004; Kashyap et al., 2004; Checa et al., 2005; La Marca et al., 2005). In monotherapy, however, high doses of Met (∼2 g/day) may be needed (Nestler, 2001), and efficacy may still be suboptimal, even in non-obese adolescents (Ibáñez et al., 2000b).

About 10 years ago, the therapeutic view on PCOS was further broadened by testing the potential of anti-androgens, flutamide (Flu) being a prime choice (Cusan et al., 1994; Diamanti-Kandarakis et al., 1995, 1998). Flu is a non-steroidal androgen-receptor blocker with pure anti-androgenic effects that are superior to those of spironolactone or cyproterone-acetate (Poyet and Labrie, 1985; Luthy et al., 1988; Cusan et al., 1994) and with a reassuring safety profile if given in a low dose (Diamanti-Kandarakis et al., 1998; Muderris et al., 2000; see in Low-dose Flu: hepatic safety section). In monotherapy, Flu has cosmetic benefits, attenuates the hyperandrogenemia and lowers serum low-density lipoprotein (LDL)-cholesterol, but it fails to improve insulin sensitivity or to raise high-density lipoprotein (HDL)-cholesterol (Diamanti-Kandarakis et al., 1995, 1998; Sahin et al., 2004), even in non-obese adolescents (Ibáñez et al., 2000a).

Combination therapies are nowadays under accelerated investigation. For example, the addition of Met to an OC like ethinyestradiol-cyproterone-acetate proved to result in a consistent benefit on insulin resistance and on androgen excess; however, the extra-benefit on dyslipidemia or abdominal adiposity was less robust (Elter et al., 2002; Cibula et al., 2005; Mitkov et al., 2005).

Recently, independent teams found that major endocrine-metabolic benefits can be achieved by combining androgen-receptor blockade and insulin-sensitization in both non-obese (Ibáñez et al., 2002) and obese women with PCOS (Gambineri et al., 2004). Each of these teams combined the same generics: Flu and Met (Flu-Met). Here we provide an update (≥2004) on Flu-Met therapy, which seems to maintain its efficacy when further combined with an oral or a transdermal contraceptive (TC) in non-obese adolescents and young women with PCOS (Table I; Ibáñez et al., 2002, 2003, 2004a, 2005a,b,c; Ibáñez and de Zegher, 2003a,b, 2004a,b, 2005). The present update will highlight Flu-Met’s effects on the pro-inflammatory state and on

Figure 1. Changes (0–9 months) in lean body mass, body fat and abdominal fat mass in two polycystic ovary syndrome (PCOS) populations. Upper panels, teenage girls (age ∼15 years; n = 32) randomized to receive either ethinylestradiol (EE)-drospirenone or flutamide-metformin (Flu-Met). Lower panels, young women (age ∼19 years; n = 22), starting all on EE-drospirenone at time 0 and randomized to receive this either in monotherapy or together with Flu-Met. Subgroups receiving Flu-Met present more gain in lean mass and more reduction in fat mass, including in abdominal fat mass (**P < 0.0001).
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Table I. The development (2001–2005) of flutamide-metformin (Flu-Met) as a therapy for hyperinsulinemic hyperandrogenism in non-obese women (I) and adolescents (II)

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| Hyperandrogenemia      | x                    | x                             | x                    | x                           | x                           | x                           | x                    | x                    | x                    |
| Hyperinsulinemia       | x                    | x                             | x                    | x                           | x                           | x                           | x                    | x                    | x                    |
| Dyslipidemia           | x                    | x                             | x                    | x                           | x                           | x                           | x                    | x                    | x                    |
| Anovulation            | x                    | x                             | x                    | x                           | x                           | x                           | x                    | x                    | x                    |
| Adiposity (by absorptiometry) |             | x                             | x                    | x                           | x                           | x                           | x                    | x                    | x                    |
| Interleukin-6 and adiponecin |             | x                             | x                    | x                           | x                           | x                           | x                    | x                    | x                    |
| TNF-α and CRP          | x                    | x                             | x                    | x                           | x                           | x                           | x                    | x                    | x                    |
| Ovarian vascular resistance |             | x                             | x                    | x                           | x                           | x                           | x                    | x                    | x                    |
| Hepatic safety (Ibáñez et al., 2005a) | x | x                           | x                    | x                           | x                           | x                           | x                    | x                    | x                    |
| Leukocytosis (Ibáñez et al., 2005b,c) |             | x                             | x                    | x                           | x                           | x                           | x                    | x                    | x                    |

a, baseline treatment; b, focus of randomization; CRP, C-reactive protein; TNF-α, tumour necrosis factor-α; x, main outcome markers.
Doses of Flu and Met are listed, together with the type of oral contraceptive (OC).
body adiposity, both of which are thought to be sensitive markers of the pathophysiology underpinning PCOS.

**Flu-Met and OC: opposite effects on adipocytokines and body adiposity**

The effects of two treatments—ethinylestradiol-drospirenone and Flu-Met—and of their combination were studied on adipocytokininemia and body adiposity in non-obese adolescents and women with hyperinsulinemic hyperandrogenism, a variant of PCOS (Ibáñez and de Zegher, 2004a).

Adolescents with PCOS \([n = 32; \text{age } \sim 15 \text{ years}; \text{BMI } \sim 22 \text{ kg/m}^2]\) were randomly assigned to receive the OC ethinylestradiol-drospirenone or the low-dose duo of Flu (62.5 mg/day) plus Met (850 mg/day).

Young women with PCOS \([n = 22; \sim 19 \text{ years}; \text{BMI } \sim 22 \text{ kg/m}^2]\) were randomized to receive the same OC, either alone or with Flu-Met. Fasting blood glucose, serum insulin, lipids, androgens, IL-6, adiponectin and body composition (by dual X-ray absorptiometry) were assessed at start, after 3 and/or 9 months.

At start, serum concentrations of the pro-inflammatory IL-6 were high, and those of the anti-inflammatory adiponectin were low; body composition was adipose in each subgroup. Dysadipocytokinemia, hypertriglyceridemia and adiposity diverged further from the norm in adolescents on OC; in contrast, girls on Flu-Met reverted all study indices towards normal, lost part of their fat excess and reduced their lean mass deficit: in comparison to the girls on OC, those on Flu-Met lost a mean \(-4 \text{ kg of fat and gained } -4 \text{ kg of lean mass. Similarly, dysadipocytokinemia and adiposity aggravated in women on OC alone and improved in women on OC plus Flu-Met; within 9 months, the latter subgroup lost a mean } -3 \text{ kg of fat and gained } -3 \text{ kg of lean mass, in comparison to women on OC alone (Figure 1).}

In this study, young and non-obese PCOS patients were found to be in a low-grade, chronic inflammation state and to have a body adiposity that evolves according to the balance of circulating adipocytokines and lipids, rather than to androgen excess or fasting hyperinsulinemia. Monotherapy with ethinylestradiol-drospirenone may not be a prime choice for PCOS, given its inefficacy to attenuate dysadipocytokinemia and body adiposity; ethinylestradiol-drospirenone plus Flu-Met, however, is a first OC combination that was found capable of reverting both the adipocytokine balance and the body composition towards normal and that may therefore improve the long-term cardiovascular perspectives of women with PCOS.

**Flu-Met plus OC: switch from third- to fourth-generation OC reduces adiposity**

This study examined whether the lipolytic efficacy of Flu-Met in women with PCOS is enhanced by co-administering an OC that contains drospirenone, instead of gestodene (Ibáñez and de Zegher, 2004b).

Non-obese women with PCOS \([n = 29; \text{age } \sim 20 \text{ years}]\) who had been on a combination of Flu (62.5 mg/day), Met (850 mg/day) and ethinylestradiol-gestodene for 8–15 months were randomized for replacement of the gestodene-OC by a drospirenone-OC. Assessments of endocrine-metabolic state and body composition (by absorptiometry) were performed at randomization and after 6 months.

The switch to drospirenone-OC was accompanied by a reduction of total and abdominal fat (mean \(-0.8 \text{ kg and } -0.5 \text{ kg, respectively}\) and by an increment of lean body mass (+0.6 kg; all \(P < 0.01\)) so that body adiposity was reduced without changing weight (Figure 2).

These findings suggest that, in non-obese women with PCOS, low-dose Flu-Met reduces total and abdominal fat excess more effectively if contraceptive co-therapy contains drospirenone, instead of gestodene.

**Flu-Met plus drospirenone-OC: the key role of Flu**

This study questioned the need to give low-dose Flu together with an OC that contains drospirenone, a progestin claimed to have anti-androgen properties (Ibáñez et al., 2004a).

The additive effects of low-dose Flu (62.5 mg/day) were assessed over 3 months in young patients with hyperinsulinemic hyperandrogenism \((n = 40; \text{age } \sim 17 \text{ years}; \text{BMI } \sim 22 \text{ kg/m}^2)\); all participants started on Met (850 mg/day) and an OC (ethinylestradiol 30 mcg + drospirenone 3 mg, 21 days/months), and they were randomized to receive Flu in addition \((n = 20)\) or not \((n = 20)\). Fasting blood glucose, serum insulin, lipids, testosterone, adiponectin and

![Figure 2. Absolute changes (0–6 months) in the abdominal fat mass of young and non-obese women with polycystic ovary syndrome (PCOS) who were randomized (at 0 month) to remain on a gestodene-oral contraceptive (OC) (open dots; \(n = 14)\) or to switch from a gestodene-OC to a drospirenone-OC (closed dots; \(n = 15)\), whereas background therapy with low-dose flutamide-metformin (Flu-Met) remained unaltered in both subgroups. The switch from gestodene-OC to drospirenone-OC was accompanied by a loss of abdominal fat excess, as judged by absorptiometry.
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IL-6 were determined at start and after 3 months, together with body composition (by absorptiometry) and with Doppler assessment of ovarian artery resistance. At start, pulsatility and resistance indices of ovarian arteries were elevated.

By comparison of 3 month changes between subgroups, the addition of low-dose Flu was found to have consistently (more) normalizing effects on LDL-cholesterol, IL-6 and adiponectin, on body adiposity (Figure 3) and on arterial flow in the ovaries.

This study identified low-dose Flu as a pivotal component within a combination therapy that attenuates the hypoadiponectinemia, the ovarian vascular hyper-resistance, the lean mass deficit, and the central adiposity of young women with PCOS. These data also challenge any claim that drospirenone, as currently used in a contraceptive, is a clinically significant antiandrogen.

Flu-Met plus drospirenone-OC: the key role of Met

This study questioned the need (i) to add Met at start of Flu plus ethinylestradiol-drospirenone and (ii) to maintain Met after >1 year on full combination therapy. The additive effects of Met (850 mg/day for 3 months) were in studies (i) and (ii) assessed in patients with hyperinsulinemic hyperandrogenism, a variant of PCOS (Ibáñez and de Zegher, 2005).

In study (i), all participants (n = 31; age ∼16 years; BMI ∼22 kg/m²) started on Flu (62.5 mg/day) and an OC (ethinylestradiol + drospirenone), and they were randomized to receive Met in addition or not. In study (ii), all participants (n = 42; ∼19 years; BMI ∼22 kg/m²) had been treated with Flu-Met plus the same contraceptive (for a mean duration of 17 months), and they were randomized for discontinuation of Met or not. Fasting blood glucose, serum insulin, testosterone, lipid profile, adiponectin and IL-6 were determined at start and after 3 months, together with body composition by absorptiometry.

The results of studies (i) and (ii) complemented each other; the addition of Met was found to have consistently (more) normalizing effects on IL-6 and adiponectin, on lean mass [mean Met benefit of +1.2 kg in study (i) and +0.6 kg in study (ii)] and, in particular, on abdominal fat excess [Met benefit of −0.7 kg (i) and −0.3 kg (ii)] (Figure 4).

This study identified Met as a pivotal component of a combination therapy that attenuates the dysadipocytokinemia, the lean mass deficit, and the central adiposity of young patients with hyperinsulinemic hyperandrogenism.

High neutrophil count: normalization with Flu-Met overcomes the aggravation by OC

One of the multiple facets of PCOS is a state of low-grade inflammation, as judged by moderate elevations of circulating markers such as CRP, IL-6 and leukocyte count; this chronic, low-grade inflammatory state has been linked to the degree of insulin resistance and

Figure 3. Changes over 3 months in lean mass, body fat mass and abdominal fat mass in 40 adolescents and young women with ovarian hyperandrogenism (age ∼17 years). All study participants started on metformin (Met) and on an oral contraceptive (OC) [ethinylestradiol (EE) + drospirenone], and they were randomized to receive Flu (62.5 mg/day), in addition [Flutamide (Flu), +; n = 20; ●] or not [Flu, −; n = 20; ○]. Addition of low-dose Flu was found to increase lean mass and to reduce total and abdominal fat excess, without changing total body weight.
to the early development of atherosclerosis. (Kelly et al., 2001; Morin-Papunen et al., 2003a; Boulman et al., 2004; Ibáñez and de Zegher, 2004a, 2005; Ibáñez et al., 2004a, 2005b; Orio et al., 2004, 2005; Tarkun et al., 2004; Gonzalez et al., 2005). Treatment effects on the leukocyte count are not available but, using CRP and IL-6 as markers, Met has been shown to attenuate the low-grade inflammatory state, whereas OC’s seem to aggravate it, even if they contain cyproterone-acetate or drospirenone as progestagen (Morin-Papunen et al., 2003a; Ibáñez and de Zegher, 2004a,b, 2005).

This study analysed whether the PCOS-associated rise in leukocyte count is already detectable at a young age and, if so, whether such elevation is lowered by treatment with Met, Flu-Met, OC or their combination (Ibáñez et al., 2005b).

In adolescents and young women with hyperinsulinemic hyperandrogenism (n = 220; mean age 16 years, BMI 22 kg/m²), the leukocyte count (×1000/mm³) was relatively high (7.5 ± 0.1 in patients versus 6.4 ± 0.1 in controls; P < 0.001) and this was attributable to a rise of the neutrophil count (4.2 ± 0.1 versus 3.0 ± 0.1; P < 0.001).

Randomized studies over 3 months at mean ages of 12.5 years (n = 24) and 15.2 years (n = 33) (Ibáñez et al., 2004b) evidenced normalizing effects of Met (850 mg/day; P < 0.001 versus untreated) and Met plus Flu (62.5 mg/day) on neutrophil counts (Figure 5); in young women (mean age 18.3 years; n = 41), the high neutrophil count rose further on OC in monotherapy (P = 0.003) but normalized on the same OC plus Flu-Met (P < 0.001 versus OC alone). The normal lymphocyte count remained stable on each of these treatments.

These data indicate that (i) a relatively high leukocyte count is already present in girls and adolescents with PCOS and is at this young age due to a high neutrophil count; (ii) this relative hyperneutrophilia is attenuated by Met or low-dose Flu-Met and is amplified by OC in monotherapy and (iii) if these treatments are combined, the normalizing effect of Flu-Met overcomes the OC-effect on neutrophil count.

These findings corroborate the anti-inflammatory benefit of adding low-dose Flu-Met to an OC in non-obese adolescents and young women with PCOS.

Discontinuous Flu-Met plus an OC or a TC: normalizing effects on CRP, TNF-α and neutrophil/lymphocyte ratio

This study (Ibáñez et al., 2005c) questioned (i) whether low-dose Flu-Met maintains efficacy when the dose is further reduced by switching to a discontinuous (21/28 day) regimen; (ii) how the efficacy of discontinuous Flu-Met plus a TC compares to Flu-Met plus a drospirenone-containing OC and (iii) whether the beneficial effects of Flu-Met (plus a contraceptive) include a lowering of the circulating CRP and TNF-α levels and of the high neutrophil/lymphocyte ratio.

Young patients with hyperinsulinemic hyperandrogenism (16.4 ± 0.3 years; range 13–21 years; BMI 22.1 ± 0.4 kg/m²; range 18.0–25.9 kg/m²; 2–8 years post-menarche; n = 31) were started on Flu (62.5 mg/day; 21/28 day) and Met (850 mg/day; 21/28 day) and were randomized to receive, in addition, either an OC (ethinylestradiol 30 mcg + drospirenone 3 mg; 21/28 day; n = 15) or a
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Low-dose Flu: hepatic safety

Flu is a pure non-steroidal anti-androgen (Singh et al., 2000). So far, Flu has been mainly used for the treatment of prostate cancer (Labrie et al., 1988). When Flu is given in a dose range of 750–1500 mg/day, hepatotoxicity is a rare but potentially fatal side effect, usually occurring within 3 months after initiation of Flu therapy for prostate cancer or hirsutism (Gomez et al., 1992; Wallace et al., 1993; Wysowski et al., 1993; Wysowski and Fourcroy, 1996; Andrade et al., 1999; Thole et al., 2004). Minor hepatotoxicity has been documented with doses in the 250–375 mg/day range (Venturoli et al., 2001; Thole et al., 2004). In an attempt to maintain Flu’s anti-androgen action, while avoiding its hepatotoxicity, doses as low as 62.5 mg/day have been explored in women with hirsutism (Muderris et al., 2000) and in adolescents and women with hyperinsulinemic hyperandrogenism or PCOS; there was no evidence of hepatotoxicity; however, treatment duration in those reports was limited to 3–9 months (Ibáñez and de Zegher, 2004a, 2005; Ibáñez et al., 2004a).

Long-term data on hepatotoxicity screening are now available (Ibáñez et al., 2005a). Circulating levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were assessed as markers of hepatotoxicity in a total of 190 hyperandrogenic girls and young women receiving Flu (mostly 62.5 mg/day) because of PCOS without obesity. Assessments were performed before start of Flu, after 3 months and subsequently at least twice yearly.

AST and ALT results were normal at baseline, and they remained so on Flu treatment, including between 3 months and the last assessment, which was after a mean duration of 19 months on Flu (range 3–54 months). None of the ALT or AST levels at any time during Flu treatment was 245 U/L.

These reassuring results represent a first step in a long process whereby the status of low-dose Flu may evolve from ‘absence of evidence on toxicity’ towards ‘evidence of absence of hepatic toxicity’.

Conclusion

Randomized studies have shown that a broad spectrum of the anomalies, that characterize PCOS, is normalized more by Flu-Met than by OC in adolescents and also more by (OC + Flu-Met) than by (OC alone) in young women. Table II lists the relative efficacies of these treatments for a series of PCOS features.

Within the pathophysiological cascade of PCOS, Flu-Met counters upstream anomalies of long-term relevance, thereby preventing or reversing downstream aberrations. In contrast, an OC merely masks downstream symptoms as hirsutism, acne or irregular menses, whereas the upstream anomalies remain unaltered or may even be worsened (Morin-Papunen et al., 2003a; Ibáñez et al., 2003, 2005c; Ibáñez and de Zegher, 2004a; Vrikoba and Cibula, 2005). Available experience with Flu-Met is still limited, but it indicates that Flu-Met is on a course to become part of PCOS therapy. We emphasize that Flu-Met may induce ovulation (Ibáñez et al., 2003) but is contra-indicated post-conception because of potential embryotoxicity; therefore, it seems wise to
combine Flu-Met therapy with an oral or a transdermal oestrogen-progestagen or with a non-endocrine method of contraception.

May this update prompt further research into Flu-Met’s therapeutic potential in patients with PCOS. Many of the abovementioned Flu-Met effects remain to be confirmed by other investigators and/or in other patient populations. In the meantime, Flu-Met should not yet be regarded as a therapy for widespread clinical practice.

**Perspectives**

**Towards earlier intervention**

Low-dose Flu-Met may become a treatment to prevent progression from the so called pre-PCOS—a condition in which girls already present the endocrine-metabolic abnormalities of PCOS but do not present hirsutism or menstrual disturbances yet—to overt PCOS. Prepubertal and early-postmenarcheal intervention with Met have proved useful to slow down or prevent such progression in girls at high risk for PCOS (Ibáñez et al., 2000b, 2003). However, these approaches seem to counter the fundamental drive to PCOS for as long as they are given, but they apparently fail to re-program the more fundamental settings. Given the rising evidence that such PCOS-prone settings may partly be programmed in early life (reviewed in Abbott et al., 2005), possibly through epigenetic mechanisms, it becomes plausible that the next generation of PCOS-prevention studies will aim at developing a re-programming intervention within a critical window of metabolic plasticity during early life.

**From high-dose monotherapy to low-dose polytherapy**

Given the complexity of PCOS’ pathophysiology, and given that drug combinations may allow to use lower doses with fewer side-effects, there is now a tendency to treat PCOS—as other complex disorders—with low-dose polytherapy rather than with high-dose monotherapy. The next addition to the PCOS-armamentarium is likely to be a member of a novel class of insulin-sensitizing agents, the thiazolidinediones. Pioneering experience suggests that these agents have beneficial effects on indices of hyperandrogenism, insulin resistance, anovulation and inflammation; however, some doubts about hepatotoxicity and peripheral lipogenesis remain to be cleared before these agents can be considered as alternatives or additives, for example, in adolescent girls (Seto-Young et al., 2005; Stout and Fugate, 2005; Tarkun et al., 2005). For the thiazolidinediones too, a low-dose in a polytherapy may prove to be a better choice than a high-dose in monotherapy. These two options are reminiscent of an old poem: two roads diverged in a wood, and I— I took the one less traveled by, and that has made all the difference (Robert Frost, *The Road Not Taken*, 1915).

**References**


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**Table II.** Comparison of the effects on endocrine-metabolic variables, body composition parameters and markers of inflammation of OC versus Flu-Met, and OC versus OC + Flu-Met in adolescents and young women with hyperinsulimemic hyperandrogenism

<table>
<thead>
<tr>
<th></th>
<th>OC versus (Flu-Met) in adolescents</th>
<th>OC versus (OC + Flu-Met) in young women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperandrogenemia</td>
<td>Comparable</td>
<td>Comparable</td>
</tr>
<tr>
<td>Reduced insulin sensitivity</td>
<td>Flu-Met</td>
<td>OC + Flu-Met</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Flu-Met</td>
<td>OC + Flu-Met</td>
</tr>
<tr>
<td>High LDL</td>
<td>Flu-Met</td>
<td>OC + Flu-Met</td>
</tr>
<tr>
<td>Low HDL</td>
<td>Flu-Met</td>
<td>OC + Flu-Met</td>
</tr>
<tr>
<td>High triglycerides</td>
<td>Flu-Met</td>
<td>OC + Flu-Met</td>
</tr>
<tr>
<td>Anovulation</td>
<td>(Flu-Met)</td>
<td></td>
</tr>
<tr>
<td>Body adiposity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low lean mass</td>
<td>Flu-Met</td>
<td>OC + Flu-Met</td>
</tr>
<tr>
<td>High fat mass</td>
<td>Flu-Met</td>
<td>OC + Flu-Met</td>
</tr>
<tr>
<td>Pro-inflammatory state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High IL-6, TNF-α and/or CRP</td>
<td>Flu-Met</td>
<td>OC + Flu-Met</td>
</tr>
<tr>
<td>Low adiponecin</td>
<td>Flu-Met</td>
<td>OC + Flu-Met</td>
</tr>
<tr>
<td>High neutrophil count</td>
<td>Flu-Met</td>
<td>OC + Flu-Met</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; IL-6, interleukin-6; LDL, low-density lipoprotein; OC, oral contraceptive; TNF-α, tumour necrosis factor-α.


Ibáñez L and de Zegher F (2003b) Low–dose combination of flutamide, metformin and an oral contraceptive for non–obese, young women with polycystic ovary syndrome. Hum Reprod 18,57–60.


