Published in final edited form as:

Clin Endocrinol (Oxf). 2013 August ; 79(2): 199–203. doi:10.1111/cen.12028.

Impact of metformin monotherapy versus metformin with oestrogen-progesterone on lipids in adolescent girls with polycystic ovarian syndrome

Miriam A. Bredella*, Shilpa McManus†, and Madhusmita Misra†,‡

*Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

†Pediatric Endocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

‡Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Summary

Objective—Hyperinsulinaemia is an important determinant of the polycystic ovarian syndrome (PCOS). In addition to lifestyle measures, therapeutic strategies include the use of oestrogen–progesterone combination pills (EP), and insulin sensitizers such as metformin, either alone or in combination. Data are limited regarding the impact of metformin alone vs metformin with EP on cardiometabolic risk in overweight adolescents with PCOS. We hypothesized that metformin alone would lead to an improvement in HbA1C and lipid levels in overweight adolescent girls with PCOS compared with metformin with EP.

Study design—Retrospective clinic-based therapy.

Patients and measurements—We examined the effects of therapy with metformin alone ($n = 14$) vs metformin with EP ($n = 13$) on HbA1C and lipid parameters over 10–14 months in 27 overweight girls, drawn from a clinic population of adolescents with PCOS.

Results—The groups did not differ for age, body mass index (BMI), HbA1C or baseline lipids. After at least 10 months, the metformin only group compared with the metformin and EP group had a decrease in total cholesterol (-0.605 ± 0.100 vs 0.170 ± 0.348 mm, $P = 0.02$, nonparametric test) and triglycerides (-0.342 ± 0.184 vs 0.262 ± 0.133 mm, $P = 0.02$), despite similar changes in BMI (-1.6 ± 0.7 vs 0.6 ± 2.1 kg/m², $P = 0.25$) and HbA1C (0.03 ± 0.06 vs $0.03 \pm 0.13\%$, $P = 0.99$). Differences between groups remained significant after controlling for baseline parameters and for changes in BMI.

Correspondence: Madhusmita Misra, BUL 457, Neuroendocrine Unit, Massachusetts General Hospital, Boston, MA 02114, USA. Tel.: 617 726 3870; Fax: 617 726 5072; mmisra@partners.org.

Conflict of interests

The authors have no conflicts to disclose.

Conclusion—Metformin alone more effectively improves lipid parameters than metformin with EP in adolescent PCOS, as indicated by a decrease in total cholesterol and triglycerides. This effect is not related to BMI changes.

Introduction

The current clinical paradigm for treating polycystic ovarian syndrome (PCOS) in adolescents is primarily based on lifestyle intervention and oral oestrogen–progesterone (EP) combination pills. However, lifestyle modification is difficult to sustain and recidivism is common. Additionally, the use of oral EP decreases free androgen levels and treats symptoms of PCOS without addressing the underlying pathophysiology, namely higher insulin resistance (IR) and hyperinsulinaemia, which also increase cardiovascular (CV) risk. EP pills may also adversely affect lipid levels. Metformin, an insulin sensitizer, reduces IR, hyperinsulinaemia and androgen levels in PCOS, but is not as effective as EP at restoring menstrual cyclicity. Metformin is increasingly being used in combination with EP in adolescents with PCOS, although data regarding the efficacy of this strategy are limited in an adolescent population, as highlighted in a review by Geller *et al.*¹

One study of 15 obese adolescents with PCOS reported that metformin monotherapy led to a decrease in body fat associated with a decrease in insulin over a 3-month period, but the study did not assess CV risk.² Another study compared metformin *vs* oral EP *vs* lifestyle *vs* placebo in obese adolescents with PCOS and reported a decrease in triglycerides and fasting glucose in the six subjects in the metformin group. C-reactive protein (CRP) showed a nonsignificant decrease with metformin compared with an increase in 10 girls on EP.³ Therefore, although oral EP effectively reduces androgen levels, there are potentially deleterious effects of oestrogen on markers of CV risk. Studies have not compared metformin alone *vs* metformin with EP in obese adolescents with PCOS. If metformin monotherapy is more effective than metformin with EP in reducing CV risk in PCOS, this may be a better strategy to treat PCOS than the combination regime.

We conducted a retrospective chart review of overweight and obese adolescents with PCOS to determine the impact of metformin alone *vs* metformin with EP in reducing HbA1C and lipid levels. We hypothesized that the use of metformin alone would be associated with improved HbA1C and lipid levels compared with use of metformin and EP in combination.

Patients and methods

We conducted a retrospective chart review of overweight and obese adolescents with PCOS [body mass index (BMI) 85th percentile for age] seen in a tertiary care outpatient centre between 2001 and 2011. Two hundred and seventy five patients were initially identified based on the International Classification of Disease, ninth edition, code for PCOS. We next narrowed our search to patients diagnosed with PCOS by NIH criteria, who were treated with metformin monotherapy or metformin with EP. This process allowed us to identify 27 patients with PCOS (14 consecutive patients in the metformin monotherapy group and 13 in the metformin plus EP group).

Metformin was begun at a dose of 500 mg daily and increased as tolerated to a maximum of 2000 mg daily (mean metformin dose 1579 ± 114 mg/day in the metformin monotherapy group vs 1512 ± 141 mg/day in the metformin with EP group, $P = 0.71$). All but two patients received at least 1000 mg metformin daily. The EP combination pills contained 20–30 mcg of ethinyl estradiol (three patients were on 20 mcg ethinyl estradiol, and the rest on the higher dose).

The following information was collected at baseline (before starting medication) and follow-up (after 10–14 months of starting medication): age, BMI, triglycerides, total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol and HbA1C. BMI standard deviation scores (SDS) were calculated using CDC tables (<http://www.cdc.gov/growthcharts/2000growth-chart-us.pdf>). Total testosterone was measured at baseline, and the free androgen index calculated as testosterone level (nm) divided by the SHBG level (nm). We also report total testosterone in multiples of the upper limit of normal (ULN) based on laboratory reference ranges.⁴ We collected information regarding patients' race and ethnicity. The study was approved by the Partners HealthCare Institutional Review Board (IRB). Because of the retrospective nature of the study and with permission from our IRB, informed consent was not obtained from the patients.

Data analysis was completed using JMP[®] statistical software (SAS Institute, Cary, NC, USA). A paired *t*-test using initial and final measures of BMI, HbA1C and lipid levels was employed within each treatment group to determine whether treatment with metformin monotherapy or with metformin plus EP was associated with significant changes in these parameters. Between group differences (across treatment groups) were assessed using the Student's *t*-test when data were normally distributed, or the Wilcoxon rank sum test when data had a skewed distribution. We examined associations of maximum metformin dose, baseline BMI and changes in BMI over the treatment duration with changes in HbA1C and changes in lipid levels using Pearson's correlation when data were normally distributed, or Spearman's correlation analysis when data were not normally distributed. We also used multivariate analysis to determine whether treatment group remained a significant predictor of changes in HbA1C and lipid levels after controlling for change in BMI. Data are reported as means $\pm$ SE unless otherwise indicated. A *P* value of <0.05 was considered significant.

Results

Clinical characteristics

Table 1 shows the clinical characteristics at baseline for the two treatment groups. The groups (metformin alone vs metformin with EP) did not differ for age, BMI, BMI SDS, HbA1C or baseline lipids (Table 1). The majority of study patients had normal lipid levels, and the proportion of patients with high lipids did not differ across groups ($P > 0.05$). Total cholesterol levels were above 4.4 mM in five and three patients in the metformin monotherapy vs metformin plus EP groups respectively. LDL cholesterol was above 2.6 mM in four and five patients in the metformin monotherapy vs metformin plus EP groups. Triglycerides were above 1.7 mM in two and three patients in the metformin monotherapy vs metformin and EP groups. HDL levels were below 1.0 mM in five and four patients in the metformin monotherapy vs metformin plus EP groups. For race, 16 patients self-identified as White,

three as Black, six as mixed, and race for four patients was not known. For ethnicity, eight self-identified as Hispanic, 16 as Nonhispanic and three did not indicate their ethnicity. The two treatment groups did not differ for distribution of race and ethnicity ($P = 0.59$ and 0.47 , respectively) (data not shown).

Changes in lipids and HbA1C within treatment groups

On a paired t -test, within the metformin monotherapy group, there was a significant decrease in BMI (mean difference $\pm$ SEM: -1.6 ± 0.7 kg/m², $P = 0.04$), total and LDL cholesterol (mean difference $\pm$ SEM: -0.605 ± 0.100 mM, $P = 0.0005$ and -0.531 ± 0.112 mM, $P = 0.002$) over at least 10 months of therapy. The change in HbA1C ($0.03 \pm 0.06\%$, $P = 0.65$), HDL cholesterol (0.110 ± 0.076 mM, $P = 0.10$) and triglycerides (-0.342 ± 0.184 mM, $P = 0.10$) within the group was not significant. Using the paired t -test within the metformin plus EP group, there was no significant change in BMI (0.6 ± 2.1 kg/m², $P = 0.78$), HbA1C ($0.03 \pm 0.13\%$, $P = 0.83$), total and LDL cholesterol (0.170 ± 0.348 mM and -0.167 ± 0.310 mM, $P = 0.64$ and 0.60 respectively), and a trend towards an increase in triglycerides (0.262 ± 0.133 mM, $P = 0.08$) over the treatment duration. However, HDL cholesterol showed a significant increase in girls who received metformin with EP (mean difference $\pm$ SEM: 0.166 ± 0.067 mM, $P = 0.04$).

Changes in lipids and HbA1C across treatment groups

Table 2 shows comparisons across treatment groups for change in BMI, HbA1C and lipid levels after at least 10 months of therapy. After at least 10 months, the metformin only group compared with the metformin plus EP group had a decrease in total cholesterol ($P = 0.02$, nonparametric test) and triglycerides ($P = 0.02$), despite similar changes in BMI and HbA1C. No differences were seen between groups for changes in LDL or HDL cholesterol. Of importance, these differences persisted after controlling for baseline levels of the respective lipids.

Determinants of changes in lipid levels

Baseline BMI and BMI SDS and changes in BMI over the treatment duration did not predict changes in lipid levels on simple correlation analysis. Additionally, in a multivariate model, with change in BMI and treatment group entered into the model, treatment group remained a significant predictor of change in total cholesterol ($P = 0.02$) and change in triglycerides ($P = 0.03$). Interestingly, in this multivariate model, change in BMI was inversely associated with change in total cholesterol ($P = 0.03$) and change in LDL cholesterol ($P = 0.03$).

Metformin dose did not predict changes in lipid levels, although we did see an inverse association between metformin dose and change in HbA1C ($r = -0.48$, $P = 0.05$) for the group as a whole, which remained significant ($P = 0.03$) after controlling for change in BMI.

Discussion

We show for the first time that in a clinic-based population of overweight and obese adolescent girls with PCOS, metformin monotherapy is associated with significant decreases in BMI, total and LDL cholesterol, whereas metformin with EP is associated with significant

increases in HDL and a trend for an increase in triglycerides. In addition, when compared with metformin with EP, the use of metformin alone is associated with greater decreases in total cholesterol and triglycerides, and these differences persist after controlling for baseline levels of these lipids. Differences between the groups also persist after controlling for changes in BMI over the study duration.

In obese adolescents with PCOS, EP combination pills are the standard of care when lifestyle modification is not effective. EP pills treat hyperandrogenism by increasing SHBG thereby decreasing free testosterone. In addition, EP reduce LH and FSH secretion and decrease ovarian stimulation and androgen production. Progesterone induces menstrual cyclicity and prevents endometrial hyperplasia.¹ However, EP pills do not treat IR or components of the metabolic syndrome⁵ and are instead associated with glucose intolerance, decreased insulin sensitivity, abnormal lipid profiles and CV disease.^{6,7} Two meta-analyses associated low-dose EPs with more than a doubling of the risk of myocardial infarction in healthy adult women.^{8,9} Although this risk remains low in adolescents,^{10,11} concerns have led to consideration of other approaches for adolescents with PCOS, including treatment that targets IR. Metformin reduces insulin and increases insulin sensitivity by reducing gluconeogenesis, by inhibiting hepatic lactate and alanine uptake, by increasing conversion of pyruvate to alanine, and by inhibiting hepatic glucose output. Metformin also increases peripheral glucose uptake, and decreases fatty acid oxidation and gut glucose absorption. Reductions in insulin cause increases in SHBG and decreases in androgens,^{5,12} with induction of ovulatory cycles in 50–60% of adults with PCOS.^{13–18} The contribution of IR to increased CV risk has led to growing use of metformin in adults with PCOS to decrease this risk.^{18–21} However, studies of metformin in adolescents with PCOS are limited.^{2,19,22,23} In uncontrolled studies, metformin causes resumption of menstrual cyclicity in 75–90% of adolescents with PCOS.^{24,25}

Studies of metformin administered with EP in PCOS have yielded variable results regarding cardiometabolic risk. Overall, IR and androgen levels decrease, however, the beneficial impact of metformin on body composition and lipids is blunted, as reported in one study of adolescents with PCOS randomized for 6 months to EP and metformin or to EP and placebo.³ In this study, total cholesterol increased in both groups, but insulin and glucose did not change.³ The data thus suggest only modest metabolic benefits of adding metformin to EP.

Our study is the first to compare the impact of metformin alone vs metformin and EP on serum lipids and HbA1c in adolescents with PCOS. We found that metformin monotherapy is associated with significant decreases in BMI and total and LDL cholesterol, and when compared with metformin with EP, metformin alone causes a greater decrease in total cholesterol and triglycerides. These data suggest that monotherapy with metformin may be a better strategy to treat cardiometabolic morbidity associated with PCOS than metformin and EP. Of importance, only a minority of our patients had elevated lipids at baseline, which may have confounded our analyses. However, differences between the groups persisted after controlling for baseline levels of lipids.

Our study has several limitations. First are limitations inherent to a retrospective chart review. The study was not randomized, although baseline characteristics, such as age and BMI, did not differ across the groups. Another limitation is the relatively small sample size. However, this is the only study comparing metformin vs metformin and EP, and even with these numbers, we observed significant differences between the groups for changes in lipid levels over time.

In conclusion, we present the first study on metformin monotherapy vs metformin with oestrogen–progesterone in overweight and obese adolescents with polycystic ovarian syndrome and show that metformin monotherapy is associated with significant decreases in body mass index, total and low-density lipoprotein cholesterol and greater decreases in total cholesterol and triglycerides than metformin with oestrogen–progesterone. This suggests that metformin monotherapy is more effective in reducing cardiovascular risk in overweight and obese adolescents with polycystic ovarian syndrome than the combination with oestrogen–progesterone.

References

1. Geller DH, Pacaud D, Gordon CM, et al. State of the art review: emerging therapies: the use of insulin sensitizers in the treatment of adolescents with polycystic ovary syndrome (PCOS). *International Journal of Pediatric Endocrinology*. 2011; 2011:9. [PubMed: 21899727]
2. Arslanian SA, Lewy V, Danadian K, et al. Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. *Journal of Clinical Endocrinology and Metabolism*. 2002; 87:1555–1559. [PubMed: 11932281]
3. Hoeger K, Davidson K, Kochman L, et al. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. *Journal of Clinical Endocrinology and Metabolism*. 2008; 93:4299–4306. [PubMed: 18728175]
4. Bekx MT, Connor EC, Allen DB. Characteristics of adolescents presenting to a multidisciplinary clinic for polycystic ovarian syndrome. *Journal of Pediatric and Adolescent Gynecology*. 2010; 23:7–10. [PubMed: 19648034]
5. Givens JR, Andersen RN, Wiser WL, et al. Dynamics of suppression and recovery of plasma FSH, LH, androstenedione and testosterone in polycystic ovarian disease using an oral contraceptive. *Journal of Clinical Endocrinology and Metabolism*. 1974; 38:727–735. [PubMed: 4823918]
6. Mastorakos G, Koliopoulos C, Creatsas G. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. *Fertility and Sterility*. 2002; 77:919–927. [PubMed: 12009344]
7. Mastorakos G, Koliopoulos C, Deligeoroglou E, et al. Effects of two forms of combined oral contraceptives on carbohydrate metabolism in adolescents with polycystic ovary syndrome. *Fertility and Sterility*. 2006; 85:420–427. [PubMed: 16595221]
8. Baillargeon JP, McClish DK, Essah PA, et al. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *Journal of Clinical Endocrinology and Metabolism*. 2005; 90:3863–3870. [PubMed: 15814774]
9. Khader YS, Rice J, John L, et al. Oral contraceptives use and the risk of myocardial infarction: a meta-analysis. *Contraception*. 2003; 68:11–17. [PubMed: 12878281]
10. Burkman RT. Hormone replacement therapy. Current controversies. *Minerva Ginecologica*. 2003; 55:107–116. [PubMed: 12711997]
11. Keeling D. Combined oral contraceptives and the risk of myocardial infarction. *Annals of Medicine*. 2003; 35:413–418. [PubMed: 14572165]

12. Nestler JE, Jakubowicz DJ, de Vargas AF, et al. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. *Journal of Clinical Endocrinology and Metabolism*. 1998; 83:2001–2005. [PubMed: 9626131]
13. Checa MA, Requena A, Salvador C, et al. Insulin-sensitizing agents: use in pregnancy and as therapy in polycystic ovary syndrome. *Human Reproduction Update*. 2005; 11:375–390. [PubMed: 15878899]
14. Kashyap S, Wells GA, Rosenwaks Z. Insulin-sensitizing agents as primary therapy for patients with polycystic ovarian syndrome. *Human Reproduction*. 2004; 19:2474–2483. [PubMed: 15358717]
15. La Marca A, Artensio AC, Stabile G, et al. Metformin treatment of PCOS during adolescence and the reproductive period. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. 2005; 121:3–7.
16. la Marca A, Egbe TO, Morgante G, et al. Metformin treatment reduces ovarian cytochrome P-450c17alpha response to human chorionic gonadotrophin in women with insulin resistance-related polycystic ovary syndrome. *Human Reproduction*. 2000; 15:21–23. [PubMed: 10611182]
17. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ*. 2003; 327:951–953. [PubMed: 14576245]
18. Velazquez EM, Mendoza S, Hamer T, et al. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. *Metabolism*. 1994; 43:647–654. [PubMed: 8177055]
19. Ibanez L, Jaramillo AM, Ferrer A, et al. High neutrophil count in girls and women with hyperinsulinaemic hyperandrogenism: normalization with metformin and flutamide overcomes the aggravation by oral contraception. *Human Reproduction*. 2005; 20:2457–2462. [PubMed: 15905296]
20. Morin-Papunen L, Rautio K, Ruukonen A, et al. Metformin reduces serum C-reactive protein levels in women with polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism*. 2003; 88:4649–4654. [PubMed: 14557435]
21. Rasouli N, Raue U, Miles LM, et al. Pioglitazone improves insulin sensitivity through reduction in muscle lipid and redistribution of lipid into adipose tissue. *American Journal of Physiology. Endocrinology and Metabolism*. 2005; 288:E930–E934. [PubMed: 15632102]
22. Ibanez L, de Zegher F. Ethinylestradiol-drospirenone, flutamide-metformin, or both for adolescents and women with hyperinsulinemic hyperandrogenism: opposite effects on adipocytokines and body adiposity. *Journal of Clinical Endocrinology and Metabolism*. 2004; 89:1592–1597. [PubMed: 15070917]
23. Ibanez L, de Zegher F. Low-dose flutamide-metformin therapy for hyperinsulinemic hyperandrogenism in non-obese adolescents and women. *Human Reproduction Update*. 2006; 12:243–252. [PubMed: 16407452]
24. De Leo V, Musacchio MC, Morgante G, et al. Metformin treatment is effective in obese teenage girls with PCOS. *Human Reproduction*. 2006; 21:2252–2256. [PubMed: 16785260]
25. Glueck CJ, Morrison JA, Friedman LA, et al. Obesity, free testosterone, and cardiovascular risk factors in adolescents with polycystic ovary syndrome and regularly cycling adolescents. *Metabolism*. 2006; 55:508–514. [PubMed: 16546482]

Table 1

Baseline characteristics of patients receiving metformin monotherapy vs metformin with oestrogen and progesterone (EP)

	Metformin monotherapy <i>n</i> = 14	Metformin with EP <i>n</i> = 13	<i>P</i>
Age (years)	15.3 ± 0.48	15.4 ± 0.48	0.85
BMI (kg/m ²)	37.4 ± 1.7	33.9 ± 1.7	0.16
BMI SDS	4.5 ± 1.8	3.3 ± 1.7	0.09
Testosterone (nm)	2.69 ± 0.29	2.87 ± 0.67	0.79
Testosterone*ULN	1.03 ± 0.12	1.21 ± 0.39	0.63
Free androgen index	27.8 ± 9.5	21.1 ± 6.2	0.55
HbA1C (%)	5.4 ± 0.1	5.4 ± 0.1	0.69
Triglycerides (mm)	1.74 ± 0.26	1.53 ± 0.31	0.62
LDL cholesterol (mm)	2.52 ± 0.15	2.55 ± 0.19	0.92
HDL cholesterol (mm)	1.11 ± 0.08	1.05 ± 0.07	0.64
Total cholesterol (mm)	4.42 ± 0.20	4.30 ± 0.28	0.73

BMI, body mass index; SDS, standard deviation score; ULN, upper limit of normal; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Mean ± SE.

Table 2

Change in BMI, lipids and HbA1C in patients receiving metformin monotherapy vs metformin with oestrogen and progesterone (EP)

	Metformin monotherapy	Metformin with EP	<i>P</i>	<i>P</i> **
BMI (kg/m ²)	-1.6 ± 0.7	0.6 ± 2.1	0.25	0.83
HbA1C (%)	0.03 ± 0.06	0.03 ± 0.13	0.99	0.75
Triglycerides (mm)	-0.342 ± 0.184	0.262 ± 0.133	0.02	0.01
LDL (mm)*	-0.531 ± 0.112	-0.167 ± 0.310	0.18	0.17
HDL (mm)	0.110 ± 0.076	0.167 ± 0.067	0.58	0.59
Total cholesterol (mm)*	-0.605 ± 0.100	0.170 ± 0.348	0.02	0.03

BMI, body mass index; , change over time; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Mean ± SE.

* Wilcoxon Rank Sum test.

** *P* value after controlling for baseline values of the respective parameter.