

W Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome

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Use of metformin in polycystic ovary syndrome (PCOS) is becoming increasingly accepted and widespread, but clinical practice is ahead of the evidence. Although a wide range of benefits in metabolic, reproductive, and clinical measures have been reported from non-randomised trials with metformin, close inspection of results from the adequately controlled studies shows that the benefits are modest. Our aim in this descriptive review is not to define practice guidelines but to improve clinicians' knowledge of the available published clinical evidence, concentrating on the few randomised controlled trials. We also highlight other issues, including hirsutism, acne, pregnancy, and neonatal outcome, that require more attention before clinical recommendations for the use of metformin in PCOS can be formalised. The potentially greater benefits achievable by lifestyle changes alone are also emphasised. We hope that the review will lead to more judicious use of metformin in PCOS and a more structured approach to research.

Polycystic ovary syndrome (PCOS) is a common disorder of chronically abnormal ovarian function and hyperandrogenism, which affects 5–10% of women of reproductive age.¹ The primary aetiology remains unclear, and historically there was no consensus on absolute defining features of the phenotype. At the US National Institutes of Health Conference in 1990, three key features of PCOS were generally agreed; oligomenorrhoea, hyperandrogenism (clinical or laboratory evidence), and the absence of other endocrine disorders (congenital adrenal hyperplasia, hyperprolactinaemia, thyroid dysfunction, and androgen-secreting tumours).² The presence of polycystic ovaries, as shown by ultrasonography, was not included in the definition but this feature is mandatory in many centres. Patients with PCOS tend to present with complaints of infertility, menstrual disturbance, or hirsutism, with or without acne. They are therefore seen by gynaecologists, primary-care physicians, endocrinologists, and dermatologists.

A link between disturbed insulin action and PCOS was first highlighted in 1980.³ Subsequent studies have convincingly shown that insulin resistance is an integral feature of PCOS, particularly in obese women.^{4,5} Current evidence indicates insulin resistance in both adipose tissue and skeletal muscle in PCOS.² The associated hyperinsulinaemia may directly promote ovarian androgen secretion and abnormal follicular development, which ultimately leads to dysfunctional ovarian and menstrual activity.⁶

Androgens are carried in the circulation bound with high affinity to sex-hormone-binding globulin (SHBG). Conditions of high androgen and insulin concentrations⁷ are associated with lower than normal circulating amounts of SHBG, which results in high free androgen activity.

Thus, clinical manifestations of androgen activity (hirsutism, acne, and alopecia) depend on SHBG activity as well as the total circulating androgen concentrations.

Other metabolic abnormalities commonly linked to insulin resistance are evident in patients with PCOS; these include dyslipidaemia,⁸ increased concentrations of tissue plasminogen activator,⁹ and low-grade chronic inflammation.¹⁰ In line with these metabolic features is emerging evidence that patients with a history of PCOS, or its surrogate marker oligomenorrhoea, are at increased risk of diabetes and cardiovascular disease later in life.^{6,8,11,12}

Until now, the use of insulin-sensitising agents has been targeted towards symptoms and signs of PCOS: ovulation induction for infertility and antiandrogen therapy for hirsutism. In clinical terms, the most important consequence of recognising the role of insulin resistance in PCOS is the possibility of therapeutic intervention at a more fundamental level (figure). Many trials of insulin-sensitising agents in PCOS have been reported since 1994. Reports of non-randomised trials with metformin have enthusiastically recorded a wide range of benefits in metabolic, reproductive, and clinical measures. The aims of this descriptive review are to provide a framework for pragmatic clinical use and to highlight a range of relevant factors that require greater attention in future investigations.

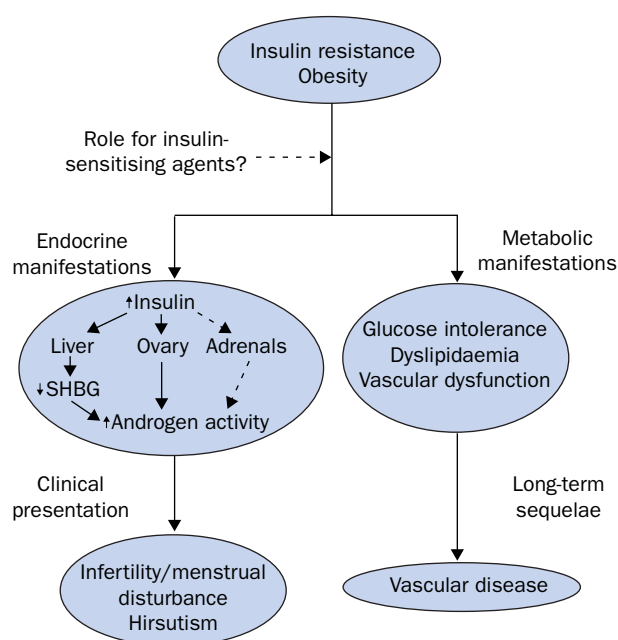
Search strategy and selection criteria

Many of the publications on this topic were already familiar to us, but we searched for all relevant articles in PubMed and Medline (1980–2002) using specific search terms: “PCOS” or “oligomenorrhoea” and “metformin” or “insulin”. We have extracted results from all the studies we found of insulin-sensitising agents in PCOS that included control elements quantifiably similar to the experimental cohort. We also restricted our analysis to studies with a systematic longitudinal examination of ovulatory function and metabolic measurements. When no randomised controlled trials that met selection criteria were identified for other specific topics, non-randomised controlled or non-controlled trials were reviewed. This descriptive review summarises data from the most robust trials. A systematic review is not possible at this time.

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Postulated role for insulin-sensitising agents in the scheme describing the range of consequences linked to insulin resistance in women with PCOS

Insulin-sensitising agents

These agents, which increase tissue sensitivity to insulin action *in vivo*, have been used in type 2 diabetes for many years. The agent used most commonly in clinical practice is metformin, a biguanide antihyperglycaemic drug that can be taken orally, which has been used for many years in Europe and is now also widely used worldwide. Newer agents include the thiazolidinedione group of drugs, of which the most widely used lately is troglitazone.

Hepatotoxicity of this drug has led to its withdrawal, but newer agents are now available, including rosiglitazone (GlaxoSmithKline, Uxbridge, UK) and pioglitazone (Takeda, High Wycombe, UK). D-chiro-inositol has been used with some success as an insulin sensitiser in women with PCOS,¹³ but extensive clinical data are lacking.

Metformin

Metformin is thought to have primary effects on increasing peripheral glucose uptake in response to insulin, perhaps at the postreceptor level, with some reduction in basal hepatic glucose production.¹⁴ However, it also lowers adipose-tissue lipolysis and improves insulin sensitivity in muscle.¹⁵ Recent findings suggest a unifying role of AMP-activated protein kinase in all the mechanisms of metformin action.¹⁶ The drug does not provoke hyperinsulinaemia and therefore does not cause hypoglycaemia. It is now recommended as first-line therapy in overweight patients with diabetes by most leading clinical associations. It is also inexpensive.

Non-randomised trials of metformin in PCOS

Early trials of insulin-sensitising agents in PCOS, between 1994 and 1997, were mainly with metformin.¹⁷ Most had cohort designs and showed an improvement in insulin metabolism and a reduction in circulating androgen concentrations.^{18–28} In most cases, small reductions were seen in body-mass index, waist/hip ratio, or both, and improvements in menstrual cyclicity (presumed ovulation) were also found. Only one of these trials²⁶ examined the effect of metformin on hirsutism, and there was no reported evidence on acne. In general, the results were encouraging, but all trials involved small numbers of patients, and most were of short duration and limited in design by not having a control or placebo group.^{18–28} More importantly, in none of these trials was ovulation incidence assessed directly by use of frequent hormonal measurements.

	Study characteristics				Change in key study variables			
	Number of women	Design and duration of treatment	Dose	Mean baseline body-mass index (kg/m ²)	Adiposity measures	Insulin-resistance measures	Testosterone or SHBG	Lipids
Reference								
38	35 metformin, 26 placebo	RPCT (35 days)	500 mg three times daily initially, then + clomiphene	32.0 (metformin), 33.0 (placebo)	Yes	Yes	Yes	..
39	23	RPCT-DB (6 months)	500 mg three times daily	27.0 (metformin), 33.0 (placebo)	No	Yes	Yes	↑HDL-cholesterol
40	32	RCT vs Diane Nova (6 months)	500 mg twice daily then 1 g twice daily	32.5	Yes	Yes	No	↓FFA
41	20	RPCT-DB (6 months)	850 mg twice daily	39.8	Yes	Yes	Yes	..
42	40	RPCT-DB (3 months)	500 mg three times daily	24.1 (metformin), 23.8 (placebo)	Yes	No	Yes	No change
43	94	RPCT-DB (4 months)	850 mg twice daily	35.3	Yes	No	No	↑HDL-cholesterol; trend ↓LDL-cholesterol
44	56	RPCT-DB 2 cycles	850 mg twice daily in first cycle; clomiphene added in second cycle	31.9 (metformin) 30.8 (placebo)	Yes	Yes	Yes	..

RPCT=randomised placebo-controlled trial; DB=double-blind; RCT=randomised controlled trial; FFA=free fatty acids.

Table 1: Summary of findings from trials of metformin in PCOS that included a randomised component

		Body-mass index (kg/m ²)				Insulin (IU/mL)				SHBG (nmol/L)				Androgen measures*			
		Metformin		Placebo		Metformin		Placebo		Metformin		Placebo		Metformin		Placebo	
		Baseline	% change	Baseline	% change	Baseline	% change	Baseline	% change	Baseline	% change	Baseline	% change	Baseline	% change	Baseline	% change
Reference																	
38	32.3	NA		32.2	NA	19.0	NA	22.0	NA	2.0†	35	2.7†	33	1.0†	-20	0.8	-20
39	27.1	-4.0		32.6	-2.1	15.2	-33	20.1	4	35.6	25	33.5	3	11.6†	-16	10.7	-3
40‡	32.5	-3.6		NA	NA	99.0§	-26	NA	NA	32.0	-17	NA	NA	11.5	-15	NA	NA
41	39.8	-8.5		39.6	-4.0	43.0	-49	33.5	-43	18.7	-11	16.0	-14	0.68	-28	0.51	-8
42	24.1	-3.7		22.7	1.8	10.8	-25	12.1	-40	28.7	-7	36.6	-10	1.8	-33	1.5	13
43	35.2	-2.0		35.3	0.9	16.8	-2	18.4	-5	29.2	4	28.1	9	10.3	-5	13.7	4
44	31.9	-4.4		30.8	1.0	28.1	-24	21.3	5	NA	NA	NA	NA	1.5	-29	1.3	0
Average		-4.4	..	-0.5	..	-27	..	-16	..	5	..	4	..	-21	..	-2	

NA=not available. *For testosterone measures, free testosterone in studies 38 and 39, free androgen index in studies 40 and 43, and total testosterone in studies 41, 42, and 44; see individual papers for units. †Units=μg/dL. ‡Control-group data are omitted because the group was assigned treatment with Diane Nova, not placebo. §Units=pmol/L.

Table 2: Changes in insulin and SHBG concentrations and body-mass index in controlled PCOS metformin studies

More recent uncontrolled studies have confirmed the observations that metformin treatment effectively lowers insulin and androgen concentrations but have provided more specific evidence to support an improvement in menstrual cyclicity with metformin.²⁹⁻³⁷ The range of perceived benefits in uncontrolled studies is wide, with normal menstrual frequency being achieved in 16% (four of 24 cases) of women with PCOS in one trial²⁶ and over 90% (39 of 43 cases) in another.³⁰

Results from controlled studies

There have been seven published studies on metformin that included some form of randomisation (ie, control group with or without placebo), of which five were double-blind in design (table 1).³⁸⁻⁴⁴ Attention should be focused on these studies owing to the potential for bias in uncontrolled investigations. Measures of obesity (eg, body-mass index, waist/hip ratio) decreased with active treatment in six of the seven studies, and insulin action and the SHBG and androgen axis improved in five studies. Table 2 shows the baseline data and changes in body-mass index, fasting insulin concentration, SHBG, and androgen measures in the main studies.³⁸⁻⁴⁴ The studies examined a wide range of patients in terms of pretreatment fasting insulin concentrations and body-mass index. The most consistent findings were decreases in body-mass index of around 4% and in androgen measures of around 20% compared with placebo. The data on improvements in insulin concentrations and, in particular, SHBG are less convincing when considered together with placebo data. These observations show the potential for confounding effects during any prospective studies and re-emphasise the importance of control in study design.

Ovulation

For ovulation, the most important observations were that the interval from start of treatment to first ovulation was significantly shorter with metformin than with placebo, that menstrual or ovulation cyclicity was increased with metformin, and that these improvements were variable and modest. Table 3 shows a compilation of comparable ovulation data from five of the seven controlled studies; the original data were all presented in different ways. However, on average, one additional ovulation was attained in every 5-month interval with metformin treatment. Specifically, the increase is from one ovulation to two ovulations per 5-month interval. These results relate to short-term observations (up to 6 months), and protracted treatment combined with weight loss might result in a higher frequency of normal ovarian function. This speculation requires further detailed examination.

Timescale of responses and ovulation

Spontaneous ovulation can occur rapidly and normal menstrual rhythm can be achieved within 3 months of the start of therapy.^{38,41} In several studies, the ovulation rate increased with no change in weight, which suggests that the effect is independent of weight loss.^{29,31,34,38,39}

Metformin in infertility

Intensive monitoring is not necessary during metformin treatment, and available evidence and logic indicate a negligible risk of ovarian hyperstimulation and multiple gestation when the drug is used alone.⁴³ It thus has potential merit as the first-line treatment for ovulation induction.⁴⁵

Infertile women seek rapid resolution of their problems. If ovulation has not occurred within 12 weeks, the antioestrogen clomiphene citrate can be added to treatment. When clomiphene citrate was used after metformin pretreatment,^{38,44} ovulation rates were higher by 82% and 64%, respectively, than those achieved with placebo and clomiphene citrate (table 4). Thus,

Reference	Change in ovulation measures	Cycles per 100 patient-months		
		Placebo	Metformin	Difference
38	Ovulation 34% M, 4% P; with clomiphene 90% M, 8% P	4	34	30
39	Increase of 0.35 cycles/month; increased cycles in 50% of women M, no change P	22	59	37
40	Time between periods decreased from 98 to 69 days M, from 88 to 28 D	32*	44	12
41	Increased cycle frequency, M>P	29	39	10
42	Median ovulation rates 0% in both groups	NA	NA	NA
43	Normalised cycles M 30%, P 18%; days to ovulation M 23, P 42	18	30	12
44	Ovulations over two cycles: M 78%, P 14%	NA	NA	NA
Average		21	41	20

M=metformin; P=placebo; D=Diane Nova; NA=not available because either effect of metformin use alone⁴⁴ or mean ovulation rates⁴² were not reported. For a normally menstruating woman, the cycles per 100 patient-months value would be 100. *Compared with baseline pretreatment value since there was no placebo group.

Table 3: Ovulation/cyclicity data in metformin studies including, where possible, extraction of cycles per 100 patient-months during placebo and metformin phases

Category	Strength of evidence	Magnitude of benefit
Spontaneous ovulation	+	Non-randomised trials up to 90% improvement Randomised trials 0–35%
Ovulation with clomiphene	+	Ovulation rate 82% and 64% higher after metformin
With FSH and before IVF	+	Compared with FSH alone: decrease in dominant follicles; decrease in peak oestradiol; lower cycle cancellation rate (0 vs 32%)
With IVF	+	More mature oocytes; higher fertilisation rate (64% vs 43%); higher clinical pregnancy rate (70% vs 30%)
Pregnancy loss	+/-	73% before treatment vs 10% with metformin; 42% control group vs 13% with metformin; 35% spontaneous abortion rate in series of PCOS women given metformin up to 12 weeks of gestation

IVF=in-vitro fertilisation.

Table 4: Summary of benefits of metformin use in ovulation induction and early pregnancy

metformin as pretreatment and cotreatment with clomiphene citrate seems successful, perhaps by sensitising follicles to follicle-stimulating hormone (FSH). Therefore, metformin alone and later in combination with clomiphene citrate has been proposed as a sequential treatment programme before the use of gonadotropin therapy for ovulation induction in infertile women with PCOS.^{45,46}

Metformin also improved responses to ovulation induction with exogenous FSH stimulation. De Leo and colleagues⁴⁷ randomly assigned 20 women with clomiphene-resistant PCOS either FSH alone or FSH after 1 month's pretreatment with metformin 500 mg three times daily. Compared with FSH alone, FSH plus metformin resulted in fewer dominant follicles (2.5 vs 4.5, $p<0.01$), a lower peak oestradiol concentration, and a lower cycle cancellation rate (zero vs 32%, $p<0.05$). Similarly, metformin treatment of patients with PCOS undergoing in-vitro fertilisation improved outcome. 46 women with clomiphene-resistant PCOS received daily metformin (1000–1500 mg) in half of 60 cycles before gonadotropin treatment. The total number of follicles on the day of treatment with human chorionic gonadotropin was lower in the women given metformin than in those who did not receive it, but there were more mature oocytes and both the fertilisation rate and the clinical pregnancy rate were significantly higher (table 4).³⁶

Panel 1: Issues for which more prospective data are required

Dose studies and effects on ovulation
Effects on stimulated ovarian function
Lean women with PCOS
Ethnic variability of response
Compliance issues
Acne and hirsutism
Early pregnancy loss
Pregnancy outcome
Neonatal outcome
Effects on surrogate risk factors for coronary heart disease
Longer-term risk of diabetes and coronary heart disease
Effects of long-term treatment
New insulin-sensitising agents
Identification of baseline factors predicting benefit from insulin-sensitising agents

Although there are questions over gonadotropin dose and variable sensitivity in these observations, metformin pretreatment may allow more orderly follicular growth in response to exogenous gonadotropins (table 4). The evidence currently supporting this proposal is encouraging but has significant limitations. Thus, prospective definitive studies should be undertaken (panel 1).

Metformin treatment continued into pregnancy

Consistent with improved ovulation rates is an improvement in the rate of spontaneous pregnancy in several trials.^{31,34,36} With respect to pregnancy, metformin is a category B agent—ie, there is no evidence of animal or human fetal toxicity or teratogenicity.^{45,48} Current conservative practice would be to stop treatment once pregnancy has been established. Two retrospective analyses^{49,50} of metformin treatment continued through the first trimester suggested reduced rates of pregnancy loss, but data from a more recent prospective study did not support this effect.⁵¹ This issue requires much more investigation before any recommendations can be made.

Whether the apparent beneficial effect of metformin treatment is due to improved developmental potential of the oocyte or embryo or to improved implantation is not known. If the effect is on implantation, continuation of therapy into pregnancy would be advised; however, an effect on the developmental potential of the embryo would support the advice to withdraw treatment at establishment of pregnancy. These issues demand formal prospective clarification, as do several clinical issues associated with metformin and pregnancy, including the well-being of the mother through pregnancy, and also the neonate (panel 2). Metformin has been used to treat diabetes in the second and third trimesters of pregnancy (after the main teratogenic period) and no increased perinatal morbidity was recorded, although an increase in the frequency of neonatal jaundice was noted.⁵² A recent report of 118 pregnancies in women with diabetes who had received an oral hypoglycaemic agent⁵³ suggested an association of metformin treatment in the third trimester with significantly higher perinatal mortality and a higher frequency of pre-eclampsia. However, compared with the reference group of women treated with insulin or a sulphonylurea, women given metformin were older and had significantly higher body-mass index before pregnancy (31.2 kg/m² metformin group, 24.8 kg/m² insulin group, and 22.8 kg/m² sulphonylurea group). This difference in baseline characteristics, rather than metformin itself, might account for the study findings.

Panel 2: Summary of evidence for benefit on key endpoints

Ovulation

Metformin treatment achieves only a small improvement in ovulation rate, on average increasing from a baseline of one ovulation in every 5 months to two

Ovulation induction

Metformin improves ovarian function when used in conjunction with clomiphene, but more data are needed

Weight and androgens

Metformin achieves small reductions in body mass and androgenicity

Pregnancy

More precise controlled data are required on pregnancy and neonatal outcome; in particular, caution may be needed with ovulation induction in obese women with PCOS

Acne and hirsutism

There is insufficient evidence to warrant metformin for first-line treatment of these disorders

Caveat: metformin and pregnancy in obese women

Many patients with PCOS are obese, and pregnancy complications are linked to maternal obesity. Therefore, pregnancies achieved in women with PCOS by use of metformin may lead to a greater proportion of adverse obesity-related pregnancy complications. If metformin is to be used before and during pregnancy, carefully designed prospective randomised trials of metformin in pregnancy are required to assess pregnancy outcomes in mothers and neonates (panel 1). There is also an ethical issue of assisting grossly obese women to achieve pregnancy when the mother and baby are at increased risk under normal circumstances.⁵⁴

Metformin and ovulation: prediction of who will benefit

There is little published evidence on this important issue. Metformin should theoretically have best results on ovulation rates in infertile women who are most insulin resistant (provided the dose schedule is satisfactory). However, the picture is not entirely clear. Moghetti and colleagues³⁹ found that higher body-mass index and plasma insulin concentration, lower serum androstenedione concentration, and less severe menstrual abnormalities were baseline predictors of clinical efficacy measured by improved menstrual cyclicity. By contrast, subgroup analysis in the large randomised study by Fleming and co-workers⁴¹ revealed that body-mass index and insulin measures did not predict the ability to establish normal ovarian function, but high SHBG concentrations and lower free-androgen index did. At present, therefore, we conclude that there are insufficient data to limit a trial of metformin treatment to a specific subgroup of women with PCOS. One of the factors to be resolved at this stage is the relation between dose and body mass. Neither can we assume that lean women with PCOS will not respond to metformin treatment. Nestler and Jakubowicz⁷ have shown significant reductions with metformin 500 mg three times daily in insulin response to glucose load and androgen concentrations in lean women with PCOS (mean body-mass index 21.7 kg/m²) despite no change in body-mass index, but waist/hip ratio was reduced in the active-treatment group alone.

Metformin use for women seeking cycle regulation but not pregnancy

As discussed above, metformin alone will not restore normal menstrual cyclicity in every woman with PCOS, at least in the short term. In fact, achievement of normal ovarian function occurs in less than 50% of women prescribed metformin at current doses. Thus, in women not wishing to become pregnant, oral contraceptives may be a better way to regulate cycles. However, women with PCOS tend to show insulin resistance, a state exacerbated by oral contraceptives,⁵⁵ although the clinical relevance of such effects requires clarification. The use of combined oral contraceptives is cautioned in obese women (body-mass index more than 30 kg/m²) and contraindicated in morbidly obese women (body-mass index more than 39 kg/m²). These rules should be taken into account when addressing this issue.

Metformin and hirsutism

Six trials^{26,29,32,39,41,56} have examined the treatment of hirsutism with metformin (1.5–1.7 g daily). In only one of these⁵⁶ was hirsutism the primary endpoint. Three of the studies showed no change,^{26,29,39} and three showed small but significant reductions in the Ferriman-Gallwey score after metformin treatment. Most of the trials were of only 3–6 months' duration, and included small numbers of

women. In addition, no breakdown of anatomical site was included. Because of the duration of the average hair-growth cycle, a response to any treatment is generally not seen within 6 months. At least 12 months should be allowed to optimise potential effects on hair growth, so future trials need to be more focused and of longer duration. The mean Ferriman-Gallwey scores before treatment in the studies published so far represented only moderate hirsutism (between 8 and 17). A larger effect may be seen in patients with a greater degree of hirsutism before treatment. Future studies (panel 1) should also compare metformin with the established therapies in a randomised manner, and objective methods of hair growth (eg, hair diameter or growth rates or mass) should be used.

Currently, there is no evidence to support a clinically significant effect of metformin on hirsutism, and this drug should not be considered as first line treatment for hirsutism until more definitive evidence is available.

Metformin and acne

To date there has been only one published trial addressing acne as a specific endpoint. Kolodziejczyk and colleagues³² found a significant decrease in acne score from 1.45 to 1.14 ($p < 0.001$). However, the trial was not placebo controlled, and the clinical significance of the decrease is uncertain. More data are required (panel 2).

Metformin in adolescents

A recent small ($n=11$) non-randomised study⁵⁷ suggested that metformin (1.50–2.55 g/day) can achieve normal menstrual frequency in adolescent girls in association with weight loss and reductions in testosterone concentration. The data are consistent with results in adult women with PCOS, but more rigorous, randomised studies are required.

Cardiovascular risk factors

Women with PCOS have higher cardiovascular risk than weight-matched controls with normal ovarian function.⁸ The evidence is broadly consistent for abnormal lipids and greater glucose intolerance in women with PCOS. Evidence of hypertension is less consistent.⁸ There are also preliminary data now for altered haemostatic (tissue plasminogen activator antigen⁹) and inflammatory (C-reactive protein¹⁰) factors. In line with such data, invasive and non-invasive tests have reported greater atherosclerotic burden in PCOS, in various vascular beds.⁸ Moreover, a recent prospective study has linked menstrual irregularity, about 80% of which is due to PCOS, to increased risk of fatal coronary heart disease.¹¹

In clinical terms, all women with PCOS should have a fasting glucose test to screen for diabetes. However, measurement of lipid profiles will not alter management until the women reach their late 30s or early 40s, unless there are significant other risk factors.

Cardiovascular indices and metformin

Four of the studies discussed earlier^{39,40,42,43} examined circulating lipid profiles before and after 4–6 months of treatment, and in comparison with controls. Two showed an increase in HDL-cholesterol concentration of around 0.10 mmol/L with metformin, and a non-significant trend towards lower LDL-cholesterol concentrations was also noted in one. One study⁴⁰ reported a significant reduction in concentrations of free fatty acids. These changes are in keeping with improvements in insulin sensitivity and also reduced body mass. However, larger and more focused studies

are needed, examining established and novel risk factors for coronary heart disease in women with PCOS, such as inflammatory and clotting variables. The potential effect of metformin on factors associated with chronic inflammation would be particularly important to establish, since a proinflammatory phenotype has now been linked to risk of diabetes and coronary heart disease in men and women.^{58,59}

If women with PCOS are proven to be at excess risk of coronary heart disease and type 2 diabetes, there may be a case for long-term treatment with metformin. The UK Prospective Diabetes Study⁶⁰ showed that metformin treatment was more effective in reducing risk of coronary heart disease than either insulin or sulphonylurea. More recently, the Diabetes Prevention Program Research Group⁶¹ examined the effects of metformin, lifestyle modification, or placebo, during a 4-year prospective programme, on the frequency of newly diagnosed type 2 diabetes in non-diabetic individuals with high blood glucose concentrations. Metformin treatment resulted in a 31% reduction in the frequency of diabetes compared with placebo. However, intensive lifestyle intervention, involving at least a 7% weight loss and at least 150 min of physical activity per week, was associated with a much greater (58%) reduction in the frequency of diabetes. A similar reduction in body-mass index in women with PCOS can improve ovarian function and fertility;^{62,63} thus, there are strong reasons to emphasise the enormous benefits women with PCOS could achieve with lifestyle measures alone. In particular, the fact that such benefits can exceed effects of any pharmaceutical intervention should be strongly emphasised.

Side-effects

Nausea, vomiting, and diarrhoea may cause difficulties initially, leading to problems with compliance with metformin treatment.⁴³ Many physicians use a graduated dosing system, increasing the dose weekly to attempt to overcome this problem. A reduced frequency of dosing may be preferred when attempting to optimise compliance; some advocate switching from a regimen of 500 mg three times daily to 850 mg twice daily. However, the use of 850 mg doses in the study by Fleming and colleagues⁴³ was associated with a dropout rate three times higher in the metformin group than in the placebo group. This drawback has not been reported in other studies. Finally, a sustained release form of metformin (Glucophage XR, Merck Pharmaceuticals West Drayton, UK) is now available with a reported side-effect profile similar to placebo.

Contraindications to metformin treatment

Since metformin is contraindicated in patients with hepatic or renal impairment, caution is needed before starting this treatment. Testing of hepatic and renal function is necessary in advance of prescription, and thereafter yearly testing is indicated. Treatment is also contraindicated in conditions that predispose to lactic acidosis.

A large double-blind, multicentre randomised trial of metformin and clomiphene citrate in infertile women with PCOS is due to start in the USA. The primary efficacy endpoint is livebirth rate; secondary endpoints are singleton livebirth rate, abortion rate, time to pregnancy, and ovulation rate. Accordingly, this trial will help establish safety or otherwise of pregnancies facilitated by metformin use for both mother and child.

Other insulin-sensitising agents

Thiazolidinediones

The thiazolidinediones act by upregulating the orphan nuclear receptor, PPAR γ , sensitising tissue to insulin action. Troglitazone, which is no longer available owing to reports of hepatotoxicity, is the most researched agent in the context of PCOS. Initial trials with this agent^{18,19} showed improvements in insulin metabolism, concentrations of androgens, SHBG, luteinising hormone, and oestrogen, and an improvement in reproductive function in women with PCOS.

In a large multicentre, dose-determining study with troglitazone,⁶⁴ 410 women with PCOS were randomly assigned either placebo or one of three doses of troglitazone over a 44-week period. 305 (74.4%) patients completed the study. Ovulation rates were significantly higher for patients treated with 300 mg and 600 mg troglitazone daily than for those assigned placebo. 57% of the 600 mg troglitazone group ovulated over 50% of the time compared with 12% of placebo-group patients. Although not an entry criterion to this study,⁶⁴ about 50% of the patients had a Ferriman-Gallwey score of 6 or more before treatment, representing normal to moderate hirsutism. The mean baseline Ferriman-Gallwey scores were about 14 in each group. There was a dose-related decrease of 15% in the score by 20 weeks of therapy that was significant only with troglitazone 600 mg. This dose of troglitazone reduced circulating insulin concentrations by 53% and the insulin response to an oral glucose challenge by 45%. There was also a decrease in circulating free testosterone concentrations and a rise in SHBG.

These findings pave the way for studies with newer PPAR γ activators, such as rosiglitazone and pioglitazone, in women with PCOS. These agents appear not to cause the hepatic side-effects reported for troglitazone and are increasingly used in the management of patients with type 2 diabetes. They also seem to reduce surrogate risk factors for vascular disease, and large prospective multicentre trials are under way to find out whether they lower the risk of coronary heart disease and incidence of type 2 diabetes.

Caveats of thiazolidinedione treatment

There are two notes of caution for the use of these agents in PCOS. First, like troglitazone, they tend to increase body mass, and since many women with PCOS are already overweight this can be an unwelcome effect. Second, and more importantly, although pregnancy has been reported in a woman with PCOS after treatment with rosiglitazone,⁶⁵ these are class C drugs for pregnancy, which means that there is evidence of teratogenicity, including lethality, in animal studies. Fetal growth restriction has been noted and attributed to a reduction in the maternal high concentrations of insulin and insulin resistance that occur during pregnancy, thereby reducing the availability of metabolic substrates for fetal growth. Extreme caution must be taken with human studies.

Conclusion

We have reviewed the best available evidence on the use of metformin in women with PCOS (panel 2 presents a summary of findings). There was much variation in the patients examined and the methods of assessment used, but a consistent yet moderate improvement in ovarian function was established. On average, women treated with metformin have one more ovulatory event and

menstrual period in every 5 months, an increase from one ovulation per 5 months before treatment to two. Thus, ovulation frequency is by no means restored to normal in every woman with metformin use. The accumulated data also suggest that metformin reduces weight by around 4% in women with PCOS.

Several points remain unclear in relation to ovulation induction and infertility treatment: metformin dose and its relation to body mass, and the complications and outcomes of pregnancy in obese women. Evidence on effects on hirsutism and acne is limited at present, and no recommendations can be made. Clearly, a large multicentre trial of metformin use in women with PCOS would help clarify many remaining issues. One such trial is beginning in the USA, specifically addressing the issue of fertility and pregnancy outcome. Other features of PCOS, such as hirsutism, acne, and metabolic and cardiovascular risk factors, will not be addressed by this study.

Patients with symptoms related to PCOS are increasingly demanding treatment with metformin. They are receiving treatment for unlicensed indications, and often outside the research environment. There is no knowledge base supporting these actions, with the exception of ovulation induction.

To date, all studies reported have been investigator led, and existing evidence is not sufficiently valid for pharmaceutical companies to proceed to licensing procedures. Therefore, clinicians must counsel women appropriately before the initiation of metformin therapy.

Conflict of interest statement

LH has received a travel grant from Merck, one of the companies that markets metformin.

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