

Review

The use of insulin sensitising agents in ovulation induction in women with Polycystic Ovary Syndrome

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ABSTRACT

Insulin resistance is an important ‘upstream’ driver for reproductive and metabolic abnormalities in women with Polycystic Ovary Syndrome (PCOS). This theoretical background is now supported by substantial evidence for treating women with PCOS with insulin sensitising agents such as metformin or the thiazolidinediones. Although the available data are based upon studies comprised of relatively small numbers of patients, powerful evidence of potential benefit is emerging. Data from controlled studies, which are usually short-term and of limited magnitude, indicate modest effects of insulin sensitizers on ovulation when applied as the only drug. However, potentially important benefits are achieved when such treatment is combined with other methods. These benefits include both increased fertility and decreased risks for ovarian hyperstimulation syndrome (OHSS). Furthermore, there may also be benefits in terms of alleviation of pregnancy complications. The available evidence supports consideration of the use of metformin from the earliest stages of treatment in women with PCOS.

Key words: Insulin sensitising agents, Insulin sensitivity, Metformin, Ovulation, PCOS

INTRODUCTION

Patients with PCOS present at clinics complaining of infertility, menstrual disturbances or hirsutism, with or without acne, and are therefore seen by gynaecologists, primary care physicians, endocrinologists and dermatologists. Correspondingly, there appear to be substantial variations in the features of the disorder, depending upon the background of

the patients studied, including primary complaint, ethnic origins and degree of obesity. It is noteworthy that, although it has been accepted for some years that abnormal insulin metabolism is a major feature of PCOS, no aspect of it is included in the most recent consensus definition [Rotterdam Consensus, 2005].¹ It is therefore even more surprising that one of the most common therapeutic approaches is via oral antihyperglycaemic medication in the form of metformin. Metformin is used in women with PCOS for many indications: infertility, pregnancy outcome, hirsutism or cycle regulation, as well as for long-term prevention of undiagnosed and theoretical morbidities. In none of these indications is metformin licensed, and the prospect of any change

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in this situation is remote.

This review will discuss the role of insulin resistance in PCOS and the real and potential role of insulin sensitizers (particularly metformin) in promoting fertility. The evidence base addressing many of these important themes, though not extensive is growing, and several interesting issues are emerging.

INSULIN RESISTANCE IN PCOS AND ITS ROLES

The link between perturbed insulin action and PCOS was first highlighted in 1980² and, though peripheral insulin resistance is most evident in obese patients, it has been proposed that obesity and PCOS have separate and synergistic relationships with insulin resistance.³ In reality, lean women with PCOS rarely demonstrate frank insulin resistance, although they do show insulin hypersecretion.^{4,5}

The mechanism(s) underlying insulin resistance and reproductive abnormalities in women with PCOS are unclear. There are several factors potentially implicated including:

- Genetic contributions to both reproductive and metabolic features, with the possibility that the same genetic factor(s) are simultaneously responsible for both;³
- Defects in adipose tissue lipolytic cascades;⁶
- Inflammation mediators leading to insulin resistance;⁷
- Fetal programming effects;^{8,9}
- Primary ovarian hypersensitivity to insulin, and/or androgens, at least in some functional aspects, leading firstly to altered hormonal milieu and over time to alterations in body fat distribution (central > peripheral) with positive feedback towards greater insulin resistance.

Research to clarify potential mechanisms in general requires larger studies than those published so far. The heterogeneity of PCOS also allows the possibility that differing factors underlie the various phenotypes in PCOS women. Furthermore, differences in ethnicity combined with disparities in environmental and clinical perspectives (gynaecologists/endocrinologists/vascular biologists) across the world render it a phenomenon whose comple-

xity will take much effort to resolve.

Despite insulin resistance in adipose tissue and skeletal muscle, the ovary (and adrenals) may remain relatively sensitive to insulin for at least some of insulin's actions, and both insulin and insulin-like growth factor 1 (IGF-1) have stimulatory effects enhancing thecal and stromal androgen production within the ovary. Androgens are carried in the circulation bound to sex hormone binding globulin (SHBG) with high affinity. Thus, clinical manifestations of androgen activity (hirsutism, acne and alopecia) depend upon the SHBG activity as well as the total circulating androgen concentrations, and insulin resistance (and/or hyperandrogenism) is associated with reduced circulating SHBG.¹⁰

INFLAMMATION

Inflammation is intimately linked to insulin resistance and its role as a causal factor in the atherogenic process is currently a major topic. Surrogate markers of inflammation, such as C-Reactive Protein (CRP), predict the risk of Coronary Heart Disease (CHD) events in both men and women, independently of classical risk factors. Women with PCOS have been shown to have increased concentrations of circulating CRP,^{11,12} possibly independent of Body Mass Index (BMI). Thus, low-grade chronic inflammation might be another mechanism contributing to increased risk of CHD and type 2 diabetes in women with PCOS. However, it is equally possible that these factors may also contribute to subfertility in women with PCOS, since vascularisation is a critical component in both follicular development and implantation. There is evidence, cited below, suggesting that oocytes subject to 'inflammatory stress' may demonstrate sub-optimal developmental potential.

THE OVARY AND FERTILITY

Fertility abnormalities in PCOS are mostly due to reduced ovulation frequency, possibly secondary to the fundamental observation of an increased density of primary follicles in relation to the primordial follicle pool.¹³⁻¹⁵ After a long growth phase to antral stage, an excess of small follicles leads to a reduced

incidence of follicular maturation and ovulation as well as to definitive and diagnostic hyperandrogenaemia.¹⁶

It should always be borne in mind that ovarian follicles, when allowed or induced to undergo maturation, do not appear to be compromised in women with PCOS, as high fecundity rates can be achieved in this patient group by simple stimulation with low doses of exogenous Follicle Stimulating Hormone (FSH).¹⁷ Furthermore, this may occur without modification of body mass or other factors related to hyperinsulinaemia.

In addition to the ovarian sequelae, there is also a possible increase in the incidence of early pregnancy loss and an increased frequency of pregnancy complications. These are diverse phenomena which are not clearly related except by an unidentified concept linking energy metabolism, follicular growth factors, steroid metabolism and developmental factors. The incidence and degrees of all these phenomena appear to be promoted by obesity, which may be independent of insulin resistance *per se*.

MEANS OF REDUCING INSULIN RESISTANCE IN WOMEN WITH PCOS

Classical approaches to reducing insulin resistance and its effects are generally applied in cohorts of older individuals rather than in infertile woman with PCOS. There is no study examining effects of lifestyle or insulin sensitizing agents on the incidence of diabetes or CHD in women with PCOS. The evidence base is also sparse concerning the effects of intervention on surrogate vascular end-points, such as endothelial function measures or carotid Maximum Intimal Thickness (MIT).

There are now many short-term (and generally small) studies on changes in insulin measures and related reproductive hormonal changes, in particular with metformin. Since the detailed measures of ovulation frequency remain under-reported and few robust studies have addressed changes in CHD risk factors with interventions, further data are required. There are also studies using the potentially more potent thiazolidinediones in women with PCOS, but they are few, and these products have intrinsic the-

oretical risks in women wishing to conceive, as they are designated category C risk in pregnancy, due to evidence of retarded fetal development in rats.

Lifestyle modification

Good evidence exists demonstrating substantial metabolic and reproductive benefits attainable by lifestyle improvements in PCOS, as in the general population. In women with PCOS, a reduction in BMI of around 5-10% by dint of dietary therapy leads to improvements in ovarian function and some metabolic risk factors.^{18,19} The most exciting evidence in support of lifestyle modification derives from a non-PCOS population showing that intensive intervention incorporating a 7% weight loss and at least 150 minutes of physical activity per week can substantially reduce (by 58%) the development of diabetes in subjects at risk.²⁰ This work should promote more vigorous dietary and exercise intervention studies in women with PCOS. It could be mentioned that due to their greater accumulation of risk factors for similar weight gain, women with PCOS will reap greater benefits from increasing physical activity levels than their non-PCOS counterparts.

Critically, since many women with PCOS wish to improve fertility, lifestyle measures will be physiologically far better for subsequent pregnancy outcomes than approaches requiring medication alone.

METFORMIN: OVARIAN FUNCTION AND METABOLISM

Metformin, the oral biguanide antihyperglycaemic drug used for many years in Europe, is now also extensively employed worldwide in both PCOS and type 2 diabetes. It has primary effects on increasing peripheral glucose uptake in response to insulin, with some reduction in basal hepatic glucose production. It also lowers adipose tissue lipolysis and improves insulin sensitivity in muscle. It does not provoke hypoglycaemia and is now first line therapy in overweight patients with diabetes.

The first placebo controlled randomised study on the use of metformin treatment alone in women with PCOS²¹ showed both a shorter delay between initiation of treatment and the first ovulation as well as a higher ovulation rate during the 4 months of

treatment, compared with the placebo treated group. However, only 1/3 of the patients treated achieved normal menstrual rhythm, indicating that the ovarian elements were not completely resolved by this treatment. It also showed that the high levels of circulating Luteinizing Hormone (LH) remained elevated in those patients not achieving normal menstrual rhythm and normalized only in those undergoing ovulation on a regular basis. This observation suggests that abnormal LH secretion is a product of anovulation rather than a causative element of the ovarian disorder.

The ovulation rate summaries for placebo and metformin arms from the major reviews are shown in Table 1. One important point to recognise in all these studies is the short-term nature of the observation period. Insulin is known to promote the actions of LH leading to increased androgen production from ovarian tissue, and metformin treatment leads to a rapid, if modest, reduction in circulating androgen concentrations in most studies.

It was noted above that one of the prime features of PCOS is abnormal primordial-to-primary follicle development, and so far little attention has been paid to these events with any clinical intervention in PCOS. However, there is evidence from two studies of protracted metformin treatment,^{22,23} suggesting that the number of follicles recruited to grow at this earliest stage may indeed be attenuated by such treatment, which may be related to reduced insulin and/or androgen drive at the earliest stages of development. This in turn suggests that in order to explore a role for metformin in correcting the over-production of follicles by women with PCOS, the investigations should start only after 6 months treatment or more, not during the first 6 months.

Table 1. Summary of evidence on ovulation rates with metformin from recent reviews

Reviews	Ovulation rates (%)		
	No of studies included (n)	Placebo	Metformin
Harborne et al, ³⁹	7	21%	41%
Lord et al, ²⁵	7	24%	46%
Costello et al, ²⁶	9	35%	56%

Ovulation rates and patients who benefit most

Restricted to short-term observations as we are, the first three reviews²⁴⁻²⁶ suggest that metformin doubles ovulation rates from low basal levels. On average, one additional ovulation is attained every 5 months with metformin treatment, which is a modest benefit in a clinical setting, while it has rarely been shown to increase pregnancy rates.

One recent randomised study demonstrated that metformin treatment conferred no benefit over and above that of lifestyle modification.²⁷ However, more encouraging results, in a relatively lean cohort, were obtained by comparison with the effect of laparoscopic ovarian diathermy, showing that metformin was at least as effective in terms of achieving pregnancy within 6 months.²⁸

Sub-group analysis²¹ and direct investigation²⁹ indicate that metformin may be more effective in lean women, with least metabolic disturbance, suggesting that the therapy is insufficient to correct the metabolic disturbance induced by obesity in the short-term, at least at current doses. This observation supports the hypothesis that obesity and insulin resistance may have independent roles in PCOS.³

Metformin as first line fertility treatment?

In standard fertility treatment, metformin has been shown to increase the response rate to clomiphene citrate (the erstwhile first line therapy), leading to an increased pregnancy rate in this first line approach.³⁰ However, a recent large prospective randomised, multicentre trial in Holland³¹ comparing clomiphene citrate alone or combined with metformin, has produced strong evidence contradicting the original observations.³⁰ It may be anticipated that this will lead to a re-consideration of the general practice, and possible explorations of sub-groups in which the combined therapy may be deemed beneficial.

As metformin alone may lead to spontaneous ovulation, particularly in the leaner patient with PCOS, and given that any pregnancy is more likely to be a singleton (in contrast to clomiphene citrate, where we can expect a >10% twinning rate), there is a valid case supporting the use of metformin as first line therapy in women with PCOS. There is no

direct evidence to corroborate this concept, but it should be tested prospectively.

METFORMIN IN ASSISTED CONCEPTION (IVF/ICSI)

Standard assisted conception treatment involves stimulation of multiple follicular development with exogenous gonadotrophins, and because metformin appears to improve some aspects of follicular growth, its potential role has been explored in some interesting trials. Though many of the trials lack acceptable levels of control, useful evidence is emerging.

The main observations in two randomised control studies^{32,33} indicate that relatively short-term metformin treatment does not influence total follicular responses to exogenous FSH, evidenced by numbers of follicles, duration and dose of FSH and numbers of oocytes. This is an important observation, leading us to conclude that short-term modulation of the insulin and androgen environment does not affect either the stockpile of follicles awaiting FSH stimulation or the sensitivity of those individual follicles to FSH stimulation in terms of growth rate and amount of FSH required to achieve maturation.

However, two end-points deserve further exploration. The Norwegian group³² observed that the lean sub-group showed a statistically increased pregnancy rate, and the study by Tang et al,³³ which included relatively lean patients in the whole study group, showed an unambiguous improvement in pregnancy rate. A large multi-centre study is now addressing this issue and we await the outcome with some anticipation

It would appear that the mechanism for any beneficial effect is unrelated to changes in FSH sensitivity and gross ovarian responses, as these were not influenced by metformin treatment in either study. One potential mechanism of benefit was proposed by Richardson et al,³⁴ who showed that the granulosa cells, which normally provide the oocyte with essential pyruvate, amino acids and growth factors, displayed altered metabolism in women with PCOS. The altered metabolism displayed reduced breakdown of glucose to pyruvate and increased lipolysis,

as in other tissues in the insulin resistant state. Consequently, the oocyte is exposed to reduced pyruvate (its main source of energy) and increased reactive oxygen species and inflammatory products, potentially reducing oocyte viability.

A second and possibly equally important observation is the clear benefit that metformin treatment affords in terms of ovarian hyperstimulation syndrome (OHSS). This observation is supported by another randomised trial.³⁵ Hence there is good clinical reason to use the drug in these circumstances, because women with PCOS are at increased risk of OHSS, which can be a serious side effect of IVF treatment. This is such a dramatic observation that it may also be instructive of the underlying ovarian abnormality in PCOS, and the role of insulin metabolism in vascular development of the ovary and follicles.

Metformin in pregnancy

Large observational studies³⁶ have suggested that metformin may confer a number of protective advantages through pregnancy in women with PCOS by reducing complications such as gestational diabetes and even early pregnancy loss. This effect was explored prospectively in a randomised programme³⁷ in which secondary end-point evaluations of late pregnancy problems were abundant in the placebo arm and virtually absent from the metformin arm. Since it has been shown that metformin crosses the placenta,³⁸ care must be exercised to avoid indiscriminate use and any benefits should be explored in a research environment.

Metformin in PCOS: weight loss

The high incidence of obesity amongst women with PCOS is an important consideration in management and approaches to treatment. The thiazolidinediones tend to increase weight by dint of their mode of action, which is a further argument militating against their use in potentially fertile women with PCOS. On the other hand, metformin is generally associated with weight reduction. In terms of metabolic and anthropometric effects, current evidence supports a reduction in BMI by around 4% over a few months compared to placebo (representing ~2-3 kg reduction) in women with PCOS.³⁹ In addition,

a role for different doses of metformin has been minimally explored, and where it has been, perhaps more consistent effects upon weight loss can be determined with a higher dose schedule.³⁹

SUMMARY

By and large, these studies suggest that women with PCOS in the fertility clinic may derive benefit and improved safety from treatment with metformin at all stages. Whilst it is critically important that these studies be confirmed in more extensive trials, it is also important to establish the mechanisms by which the drug confers these benefits. There may be an underlying issue of energy metabolism, but the connections with a number of the observations are tenuous and, in reproductive terms, the link with androgen metabolism may prove to be the critical element.

Overall, the metabolic and reproductive changes noted with metformin use in women with PCOS are consistent with its known effect in patients with type 2 diabetes. However, the effects are generally modest and larger trials of longer duration and more comprehensive controls are required.

It is important to note that metformin is not licensed for any of these indications in PCOS and, as shown in the evidence presented above, it is certainly not a 'cure' for all reproductive and metabolic derangements in women with PCOS. Despite this, once established on metformin treatment, women with a history of PCOS are reluctant to discontinue treatment.⁴⁰

In view of metformin's generally modest benefits in women with PCOS, the relative merits of metformin combined with lifestyle changes, in particular exercise, very definitely warrant further examination, and such studies are being developed. It is interesting that both exercise and metformin up-regulate AMP-activated protein kinase activity, a metabolic switch regulating efficient glucose and fatty acid metabolism. It should also be noted that lifestyle intervention was more successful than metformin alone in reducing risk of diabetes, once again emphasizing the critical role for lifestyle intervention.

Future research: reproduction in women with PCOS

In the fertility arena, there is a need for a coordinated programme of investigations using multi-centre prospective methods. The influence of obesity and metformin dose on ovarian function has yet to be explored to the degree that is needed to fully elucidate effects. As the life history of ovarian follicular development is so protracted and PCOS appears to be associated with abnormalities from the very beginning, examinations of the effects of treatment at this level are required. Other potential areas of benefit, including pregnancy complications, should be examined on a large, multi-centre scale.

There is evidence to support the use of metformin, in association with other approaches, from the very beginning of treatment of women with PCOS, and this issue should be explored in the research arena.

CONCLUSION

In the fertility arena, metformin may prove to be of considerable benefit, but mainly in association with other forms of treatment, and the results of recent studies are generally supportive of its extended use, perhaps from the very first stages of treatment.

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