Role of metformin in the management of polycystic ovary syndrome

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***Abstract*:** Polycystic ovary syndrome is the most common endocrinological disorder affecting 4–12% of women and also the most controversial. Metformin was logically introduced to establish the extent to which hyperinsulinaemia influences the pathogenesis of the condition. Early studies were very encouraging. Randomized controlled studies and several meta-analyses have changed the picture and put the drug that was once heralded as magic in a much contracted place. More work is needed to establish its right place in particular with regards to the prevention of many gestational and long-term complications.

***Keywords*:** gestational diabetes, insulin-sensitizing drugs, metformin, polycystic ovary syndrome (PCOS)

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Background

Polycystic ovary syndrome (PCOS) is the most common endocrinological disorder affecting 4–12% of women [Diamanti-Kandarakis *et al.* 1999; Farah *et al.* 1999; Knochenhauer *et al.* 1998]. It has also been the most controversial medical condition and every aspect has received a lot of attention from the nomenclature to the management. Several descriptions of similar conditions took place in the 20th century and it was named Stein–Leventhal Syndrome in 1935 after the authors who described polycystic ovarian morphology in patients suffering from hirsutism, amenorrhoea and infertility [Leventhal, 1958; Stein and Leventhal, 1935]. PCOS was also called polycystic 'ovarian' syndrome implying that the primary pathology lies in or triggered by the ovary. Others have called it polycystic ovary disease (PCOD), which is the least used term for obvious reasons.

Currently, PCOS refers to a disorder with a combination of reproductive and metabolic characteristics. This has evolved over time with controversy over the definition culminating in the latest consensus [ESHRE/ASRM, 2004] which instead of solving the issue created more controversy [Azziz *et al.* 2006]. In the European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine (ESHRE/ASRM) consensus, at least two of the following features are needed to make the diagnosis; oligo/anovulation, hyperandrogenism, and polycystic features on ultrasound scan [ESHRE/ASRM, 2004]. The Androgen Excess Society, however, recommended that androgen excess should remain a constant feature of PCOS irrespective of the ovulatory status and morphological features of the ovaries [Azziz *et al.* 2006]. For almost three decades, PCOS has been regarded as a life course disease which besides its reproductive features has a long-term impact on the risk of type 2 diabetes mellitus (T2DM) and metabolic syndrome [Apridonidze *et al.* 2005] as well as any concomitant cardiovascular disease (CVD) risks [Grundy, 2002].

Polycystic ovary syndrome and insulin resistance

Failure of the target cells to respond to normal or ordinary levels of insulin is regarded as insulin resistance (IR) [Le Roith and Zick, 2001]. This definition may not be universally agreeable but it gives a simplified understanding of the condition for the purpose of this review. Other definitions have been offered by the World Health Organization (WHO) [Alberti *et al.* 1998]. The presence of IR, however, leads to a compensatory increased production of insulin by the pancreatic beta cells to control the hyperglycaemia which ultimately fails leading to T2DM. In PCOS, hyperinsulinaemia has been thought to increase hyperandrogenaemia via a central role [Barbieri *et al.* 1986] or by decreasing the circulating levels

of sex hormone binding globulin [Nestler *et al.* 1991].

IR is not considered a diagnostic criterion in PCOS [ESHRE/ASRM, 2004]. However, it is recognized by many as a common feature in PCOS independent of obesity [Dunaif *et al.* 1987; Chang *et al.* 1983; Burghen *et al.* 1980]. An estimated prevalence of IR among PCOS patients of 60–70% has been reported [DeUgarte *et al.* 2005]. However, being overweight or obese is common among PCOS women, affecting up to 88% of these women [Holte *et al.* 1995; Pasquali and Casimirri, 1993; Kiddy *et al.* 1992], therefore casting doubt on the role IR plays in the pathogenesis of PCOS. Further, clinical quantification of IR is not accurate enough [Legro *et al.* 2004; Gennarelli *et al.* 2000] to enable a better understanding of the role of IR in PCOS pathogenesis or to incorporate it into the work up programme of PCOS patients. However, it is generally acceptable that IR plays a significant role in PCOS either directly or through obesity and represents a clinical concern to physicians and patients.

Metformin

Metformin is the only remaining member of the biguanide family that has been used for the treatment of diabetes for a long time. It is the most commonly used drug in T2DM. Metformin works by improving the sensitivity of peripheral tissues to insulin [Bailey and Turner, 1996; Bailey, 1992], which results in a reduction of circulating insulin levels. Metformin inhibits hepatic gluconeogenesis and it also increases the glucose uptake by peripheral tissues and reduces fatty acid oxidation [Kirpichnikov *et al.* 2002]. Metformin has a positive effect on the endothelium and adipose tissue independent of its action on insulin and glucose levels [Diamanti-Kandarakis *et al.* 2010].

The main side effects associated with metformin treatment are the gastrointestinal symptoms of nausea, diarrhoea, flatulence, bloating, anorexia, metallic taste and abdominal pain. These symptoms occur with variable degrees in patients and in most cases resolve spontaneously. The severity of side effects can be reduced by gradual administration of metformin and titrating the dose increase guided by the severity of symptoms. A start dose of 500 mg daily during the main meal of the day for 1–2 weeks can lessen the side effects and allow tolerance to develop. A weekly or biweekly increase by 500 mg a day can then be pursued as required until a maximum dose of 2500–2550 mg/day is reached depending on the clinical benefit and side effects. If the dose increase results in worsening of the side effects, the current dose can be maintained for 2–4 weeks until tolerance is developed [Nestler, 2008]. Slow release metformin can be associated with fewer side effects. Metformin can also lead to vitamin B12 malabsorption in the distal ileum in approximately 10–30% of patients which is an effect dependent on age, dose and duration of treatment [Ting *et al.* 2006]. Rarely, lactic acidosis can occur, mainly in diabetic patients, which is a serious condition that can potentially be fatal. However, unless there is a contraindication to taking metformin such as renal disease the risk of lactic acidosis is negligible [Salpeter *et al.* 2003a, 2003b].

Metformin in PCOS

Metformin was the first insulin sensitising drug (ISD) to be used in PCOS to investigate the role of insulin resistance in the pathogenesis of the syndrome [Velazquez *et al.* 1994]. Velazquez and colleagues reported in an observational study a significant improvement in menstrual regularity and reduction in circulating androgen levels [Velazquez *et al.* 1994] as well as a significant reduction in body weight which confounded their findings. A few years later another ISD (troglitazone, which is no longer available) was used in a similar study and reported improvement in cycle regularity and serum androgen levels despite the lack of change in body weight [Dunaif *et al.* 1996].

Since then several studies have reported conflicting evidence regarding the role of metformin in PCOS. Several meta-analyses that incorporated all of the accessible evidence have also been published with conflicting results [Nieuwenhuis-Ruifrok *et al.* 2009; Costello *et al.* 2006; Lord *et al.* 2003].

In principle, ISD works in PCOS by reducing the circulating insulin levels. There is, however, some conflicting evidence as to whether metformin can directly affect ovarian steroidogenesis [Mansfield *et al.* 2003; Arlt *et al.* 2001]. Several effects have been reported as related to metformin in PCOS patients including restoring ovulation, reducing weight, reducing circulating androgen levels, reducing the risk of miscarriage and reducing

the risk of gestational diabetes mellitus (GDM). Other studies have reported that the addition of metformin to the ovarian stimulation regime in *in vitro* fertilization (IVF) improves the pregnancy outcome. These effects will be addressed individually.

Metformin and ovulation induction

Several of the early studies on metformin in PCOS were compiled in a meta-analysis by Lord and colleagues [Lord *et al.* 2003]. They concluded accordingly that metformin was an effective treatment to induce ovulation in PCOS patients and that it was justifiable to use it as a first-line treatment. However, they emphasized that it should be used in conjunction with a change in lifestyle. They included 7 studies comprising a total of 156 PCOS patients who received metformin of whom 72 (46%) ovulated *versus* 1154 who received either placebo or no treatment of whom 37 (24%) ovulated. They also reported that the combination of metformin and clomiphene citrate (CC) resulted in more ovulation than CC alone. However, this was based on relatively smaller number of patients included in two and three studies.

In a later meta-analysis by Palomba and colleagues, the authors concluded that the combination of metformin with CC is not superior to CC alone [Palomba *et al.* 2009] with regards to ovulation, pregnancy, or live birth rates. They also found no difference in the miscarriage rates between the two treatment modalities. With regards to metformin in combination with CC, that was more effective than metformin alone in ovulation and pregnancy rates. They based their conclusion on combinations between four randomised controlled trials (RCTs) that were published after the meta-analysis by Lord and colleagues [Zain *et al.* 2009; Legro *et al.* 2007; Moll *et al.* 2006; Palomba *et al.* 2005]. They also commented on the heterogeneity of body mass index (BMI) among the populations of the four studies and that the patients in the study by Palomba and colleagues were not representative of the PCOS population [Palomba *et al.* 2005], i.e. they were relatively slimmer. Others used menstrual regularity as evidence of resumption of ovulation and reported in a RCT that included obese PCOS women that weight loss alone through lifestyle modification was more effective in restoring regular menses [Tang *et al.* 2006].

It is important in analysing the outcome of all such studies and meta-analyses to realize that the duration of treatment also plays a role in the outcome. Metformin is likely to take longer to exert an effect in comparison to CC, therefore CC should be considered the first line of treatment in ovulation induction among PCOS patients and that life-style change leading to a sustainable weight loss is an important adjuvant to all types of medications in such patients.

The use of gonadotrophins for ovulation induction in conjunction with metformin also received attention and was the subject of a meta-analysis [Costello *et al.* 2006]. However, due to the small number of studies included and small sample size in each study along with the difficulty disentangling potential confounding variables a conclusion could not be reached on the efficacy of metformin as a coadjuvant to gonadotrophins for ovulation induction in PCOS women. It seems, however, that the length of ovarian stimulation was shorter among those receiving a combination of gonadotrophins and metformin [Costello *et al.* 2006].

Metformin and IVF

There is a dearth of studies reporting on the use of metformin in conjunction with gonadotrophin for ovarian stimulation for the purpose of IVF treatment. A recent Cochrane review has concluded that adding metformin to the ovarian stimulation protocol in PCOS undergoing IVF treatment had no impact on pregnancy or live birth rates. However, it reduced the risk of ovarian hyperstimulation syndrome (OHSS) [Tso *et al.* 2009]. In a small study, it was reported that the addition of metformin to an antagonist protocol improved the oocyte quality in PCOS patients undergoing IVF [Doldi *et al.* 2006]. Others have also reported that the addition of metformin to their regular stimulation protocol had a positive effect on the quality of the oocytes and embryos [Qublan *et al.* 2009]. The evidence regarding this issue is scarce and therefore difficult to consolidate. The benefits of metformin on pregnancy, which will be discussed later, should be taken into account when addressing this issue. Further, considering the recent evidence as to the safety of metformin in pregnancy [Glueck *et al.* 2008], it would seem wise to add metformin to the stimulation regimes in PCOS patients in order that the risk of OHSS can be reduced.

Metformin and weight loss

The first observational study on metformin in PCOS reported weight loss during metformin therapy [Velazquez *et al.* 1994]. In their meta-analysis of all of the earlier small studies, Lord and colleagues reported that metformin had no significant effect on body weight or waist:hip ratio [Lord *et al.* 2003]. In a RCT designed specifically to investigate the effect of metformin on body weight, Harborne and colleagues reported a significant decrease in BMI in obese and morbidly obese women independent of lifestyle modification [Harborne *et al.* 2005]. Others reported no effect of metformin on body weight over and above that induced by lifestyle modification alone [Tang *et al.* 2006]. However, it was reported independently by two other groups that the combination of low-calorie diet and metformin led to a significant reduction in visceral fat [Gambineri *et al.* 2006, 2004; Pasquali *et al.* 2000]. In a recent meta-analysis, it was reported that metformin treatment was associated with a significant decrease in BMI compared with placebo. They also reported an effect related to both the dose and duration of treatment [Nieuwenhuis-Ruifrok *et al.* 2009]. However, due to the limited power caused by the small sample size, the authors could not be categorical about their findings and cautiously advised structured lifestyle modification as an imperative adjuvant to metformin therapy. Based on my own experience I tend not only to agree with their emphasis on lifestyle modification to aid weight loss but also corroborate that unless there is evidence of IR, prescribing metformin is unnecessary.

Metformin and steroidogenesis

The effect of metformin on androgen production has been controversial [Arlt *et al.* 2001; Bailey and Puah, 1986]. It may be argued that the metformin effect on circulating androgen is a byproduct of ovulation resumption. However, *in vitro* experiments demonstrated that metformin significantly inhibited both androstenedione and testosterone production by the theca cells [Attia *et al.* 2001]. Further, it has been suggested that metformin reduces hyperandrogenism through its effect on both the ovary and adrenal gland suppressing their androgen production, reducing pituitary luteinizing hormone and increases the production of sex hormone binding globulin by the liver [Bailey and Turner, 1996]. Harborne and colleagues, on the other hand, reported no significant changes in androgen or sex hormone binding globulin levels in hirsute patients treated with metformin [Harborne *et al.* 2003] and assigned the improvement in symptoms to the reduction of circulating insulin levels. Others reported that reducing fasting insulin and insulin-stimulated glucose levels leads to a reduction in ovarian cytochrome P450c17α activity in obese [Nestler and Jakubowicz, 1996] and lean PCOS patients [Nestler and Jakubowicz, 1997]. A meta-analysis of three RCTs comparing metformin with combined oral contraceptives (COC) on hirsutism gave a no difference verdict [Pasquali *et al.* 2000]. However, that meta-analysis suffered from heterogeneity caused by the variation in PCOS diagnostic criteria as well as the obvious problems of participants' diversity and hirsutism assessment.

Metformin and pregnancy

Early small observational studies suggested that the administration of metformin in pregnancy had a positive effect on the miscarriage and gestational diabetes rates.

Miscarriage. PCOS women have a much higher risk of miscarriage compared with non-PCOS women. The risk has been estimated at 30–50% [Regan *et al.* 1989]. Among PCOS sufferers, high rates of miscarriage reaching threefold that of healthy women have been reported [Jakubowicz *et al.* 2004]. Many assign such an increase in risk to the high prevalence of obesity among PCOS patients [Legro *et al.* 2007; Wang *et al.* 2000; Norman and Clark, 1998]. The exact mechanism is not known and to what extent IR may contribute to such problem remains unclear. Metformin was thought to improve the ovarian artery impedance and perifollicular vascularization which theoretically can bring ovarian follicular development in line with normal women [Palomba *et al.* 2006]. Further, improvements in uterine artery blood flow along with several other implantation markers have also been reported in PCOS patients receiving metformin [Palomba *et al.* 2006]. Observational studies have suggested that metformin administration reduced the risk of miscarriage among PCOS sufferers [Thatcher and Jackson, 2006; Glueck *et al.* 2002; Jakubowicz *et al.* 2002]. In two RCTs, no reduction in miscarriage rates was associated with the use of metformin, nonetheless none of the studies was designed to investigate the effect of metformin on miscarriage rates as a primary outcome measure [Legro *et al.* 2007; Moll *et al.* 2006]. In a meta-analysis, Palomba and colleagues reported that metformin had no

beneficial effect on the miscarriage rate [Palomba *et al.* 2009].

Gestational diabetes mellitus. PCOS sufferers have a higher risk of developing GDM in pregnancy [Boomsma *et al.* 2006]. Further, it has been reported that the risk of PCOS is significantly high at 40% among women with a previous history of GDM. An early pilot study suggested that the continuation of metformin throughout pregnancy reduced the risk of GDM among PCOS women. This subsequently led to a wide discussion on whether the continuation of metformin in pregnancy is of benefit to women with PCOS [Norman *et al.* 2004]. GDM is associated with high perinatal mortality and morbidity for the foetus and both short- and long-term complications for the mother [The HAPO Study Cooperative Research Group, 2008; Pettitt *et al.* 1980]. Glueck and colleagues reported a prevalence of GDM of 7% among pregnant PCOS women who continued taking metformin throughout pregnancy compared with 30% among those who did not. Both groups were instructed on healthy dietary practices. This study included a relatively larger sample size compared with previous studies and was the culmination of previous small studies by the same group that reported similar results [Glueck *et al.* 2004, 2002]. Nonetheless, the study was not a RCT therefore their findings have to be considered carefully. Furthermore, it is not known whether the beneficial effect of metformin and weight loss prior to conception had contributed to the reduction of GDM risk. This question is of importance for the PCOS women who are seen for the first time during pregnancy; should they be given metformin or not? There are studies emerging on the benefits of administering metformin to all pregnant women at high risk of gestational diabetes and their results should clarify this issue.

As for the safety profile, a study by Rowan and colleagues reported that the use of metformin in the treatment of GDM had no increased risk of perinatal complications [Rowan *et al.* 2008], which settled a previous controversy regarding metformin safety in pregnancy.

Pregnancy-induced hypertension and pre-eclampsia. Women who suffer from PCOS are at increased risk of pregnancy-induced hypertension (PIH) and pre-eclampsia (PE) compared with non-PCOS pregnant women [Boomsma *et al.* 2006]. Although the underlying mechanism is not known, it has been argued that the pre-pregnancy increase in uterine artery resistance is a probable factor [Salvesen *et al.* 2007; Palomba *et al.* 2006]. The evidence regarding the benefits of metformin in reducing the risk of PIH and PE is at best sketchy and less clear [Glueck *et al.* 2004].

Long-term use and preventative value of metformin in PCOS women

Insulin resistance is believed by many to be pivotal in the pathogenesis of PCOS and that treatment strategies should revolve around reducing the IR and hyperinsulinaemia, hence the great attention metformin and other ISDs have received. Further, PCOS is not merely a reproductive disorder but a life course disease that has long-term consequences and complications receiving a great deal of attention in view of the associated high morbidity and mortality. T2DM, metabolic syndrome, CVD, hypertension and endometrial cancer are the potential long-term sequel of PCOS, all of which have been attributed to obesity and IR which are not part of the syndrome's diagnostic criteria. It is not evident so far, however, if the prophylactic use of metformin would reduce the long-term disease risk in those patients. However, this issue should be addressed.

Endometrial cancer. This is mainly caused by anovulation and endometrial stimulation by unopposed oestrogen over a lengthy duration. In a long-term follow-up study, Wild and colleagues reported that PCOS women are more likely to develop endometrial cancer with an odds ratio of 5.3 (95% CI = 1.55–18.6) [Wild *et al.* 2000]. In another study, it was reported that androstenedione levels were significantly associated with increased risk of endometrial cancer in premenopausal and postmenopausal women [Potischman *et al.* 1996]. However, this was in a case–control study and the evidence from other reports has been conflicting [Niwa *et al.* 2000]. Owing to the discrepancy between the high prevalence of PCOS and the relatively low incidence of endometrial cancer it is difficult to link the two directly. There has been recent evidence linking IR [Nagamani *et al.* 1991] and glycaemic index [Mulholland *et al.* 2008] to endometrial cancer. It may therefore appear logical that the prevention of endometrial cancer is feasible by dietary restriction and metformin. Despite the recent evidence suggesting that

metformin may reduce the risk of cancer [Ben Sahra *et al.* 2008], and the logical yet theoretical benefits of metformin in preventing endometrial cancer, it is difficult to justify its prophylactic use in PCOS patients without firm evidence addressing efficacy and cost implications.

Type 2 diabetes mellitus. PCOS patients are at increased risk of developing impaired glucose tolerance and T2DM [Legro *et al.* 1999]. Despite the obvious association with IR, the presence of obesity confounds any presumed link between PCOS and T2DM. There is reliable evidence as to the use of metformin to reduce the risk of T2DM among high-risk general population [Knowler *et al.* 2002]. This study included three arms: lifestyle changes, metformin and troglitazone. However, the troglitazone arm had to be discontinued due to the hepatic risk associated with that type of ISD. During a mean follow-up period of 2.8 years, lifestyle changes reduced the incidence of newly developed T2DM cases by 58% while metformin reduced it by 31%. It is therefore obvious that lifestyle modification should be advocated to everyone at risk and metformin should be reserved for those unable to alter their lifestyle. In a follow on study, it was reported that after a washout period, 25% of the metformin benefits in preventing T2DM no longer existed [The Diabetes Prevention Program Research Group, 2003]. In a similar yet smaller study in PCOS women, Palomba and colleagues reported that the effect of metformin in such patients could not be maintained after 12 months of withdrawal of treatment [Palomba *et al.* 2007]. However, their study included normal weight non-IR PCOS population. In a large meta-analysis, Salpeter and colleagues reported no statistically significant difference between PCOS and non-PCOS or obese and nonobese patients with regard to the effect of metformin on their metabolic risk [Salpeter *et al.* 2008]. It is therefore clear that the use of metformin to prevent T2DM among PCOS should be considered carefully and on individual basis given the current evidence or lack of it.

Cardiovascular disease, dyslipidaemia and hypertension. Owing to several confounding variables such as obesity, IR, dyslipidaemia and hypertension rather than PCOS per se, it is believed that PCOS women are at increased risk of CVD [Guzick, 1996]. However, there is accumulating evidence indicating that hyperandrogenaemia is associated with an increased risk of CVD [Bernini *et al.* 1999; Phillips *et al.* 1997; Barrett-Connor and Goodman-Gruen, 1995].

Others have reported a correlation between hyperinsulinaemia in PCOS women and increased risk of CVD independent of obesity [Mather *et al.* 2000]. There are reports suggesting that PCOS and obesity are two independent factors affecting the endothelial function [Mancini *et al.* 2009].

PCOS women are reported to have abnormal lipid profiles in comparison to weight- and age-matched peers [Legro *et al.* 2001; Wild *et al.* 1985]. High triglycerides and low high-density lipoprotein cholesterol (HDL-C) are the most prominent abnormalities that are also strong predictors of CVD and myocardial infarction [Gaziano *et al.* 1997]. Metformin can theoretically influence dyslipidaemia either directly through its action on fatty acid metabolism [Tessari and Tiengo, 2008] in the liver or indirectly by improving hyperinsulinaemia. Several studies have reported that metformin had a favourable effect on dyslipidaemia in PCOS women [Fleming *et al.* 2002; Ng *et al.* 2001; Moghetti *et al.* 2000]. However, in their meta-analysis, Lord and colleagues reported no beneficial effect on total cholesterol, but there was a significant reduction in the low-density lipoprotein cholesterol (LDL-C) [Lord *et al.* 2003]. In another meta-analysis, no significant effect was found in total cholesterol levels between those receiving the COC pill or metformin [Costello *et al.* 2007]. It was also reported that discontinuation of metformin led to the worsening of the total LDL-C that quickly returned to the pretreatment levels [Palomba *et al.* 2007].

Metformin was also reported to improve dyslipidaemia in a non-PCOS, unselected population of obese and overweight patients [Salpeter *et al.* 2008]. It is evident therefore that metformin has potential benefits with regard to dyslipidaemia and IR which in turn can reduce the risk of CVD. However, its effect in a polymorphic population such as PCOS is yet to be confirmed.

Hypertension in PCOS has been a controversial issue [Chen *et al.* 2007; Holte *et al.* 1996; Zimmermann *et al.* 1992]. In a Dutch PCOS population, Elting and colleagues reported a 2.5-fold increase in risk of developing hypertension among menopausal PCOS women

compared with age-matched controls [Elting *et al.* 2001]. However, they did not adjust for body weight. The mechanism of hypertension in PCOS women remains controversial with no specific evidence linking it to androgens or hyperinsulinaemia. Therefore, there has been very limited evidence as to the effect of metformin on hypertension in PCOS women. In a small RCT, it was found that metformin reduced ambulatory blood pressure among PCOS women [Luque-Ramirez *et al.* 2009]. In a non-PCOS population, there has been stronger evidence with regards to the effect of metformin on ambulatory blood pressure on an unselected obese and overweight population [Salpeter *et al.* 2008].

Summary and conclusions

PCOS is a reproductive endocrinological disorder with strong metabolic elements that are not part of the condition per se, i.e. not included in the definition or diagnostic criteria. Controversy has surrounded the syndrome, particularly with regards to the definition, leading to a great deal of heterogeneity in the literature on the prevalence and management. The elements included in the definition and other associated metabolic and hormonal elements have led to the emergence of several phenotypes of PCOS, some of which are closer than others. This heterogeneity has been the main cause of conflict in the response to treatment and has led some interested parties to reject the consensus that was reached in Rotterdam in 2003. Solving such a discrepancy will not be feasible without a clear understanding of the pathogenesis and establishing which is more influential, androgens or insulin, in the syndrome's pathophysiology. PCOS may well be an end result to different pathogenic pathways some of which are triggered mainly by hyperinsulinaemia and some by hyperandrogenaemia with similar clinical pictures and variable genetic predisposition.

Obesity is a major confounding factor in the management and understanding of PCOS that tends to complicate the findings in the current literature and is not always easy to adjust for, as it is dependent on the background population in any particular study.

Although PCOS is the commonest endocrinological disorder, it has proved difficult for any individual centre to achieve the right sample size for any study leading to controversy. Further, carrying out a reliable meta-analysis that does not suffer from significant heterogeneity is difficult due to the causes described earlier. Multicentre studies have not been forthcoming probably due to funding issues and perhaps the reluctance of funding bodies to commit in the absence of clear evidence.

The use of metformin in PCOS has received a lot of attention for obvious reasons. Once thought of as a wonder drug, the accumulating evidence on the efficacy of metformin has been disappointing. The lack of an emphatic or overwhelming efficacy is largely due to the patients' variability in phenotypes and their metabolic parameters. Some studies have tried to identify the patients that are most likely to benefit from metformin, yet again the results have not been forthcoming. Consequently the burden falls back on the clinician who should be familiar with the gist of the available evidence to be able to identify the right patient for the treatment in hand. Obtaining an evidence of IR is a good starting point prior to recommending its use.

Based on the available evidence, however, metformin does not replace the need for lifestyle modification among obese and overweight PCOS women. The evidence categorically does not encourage its use to help weight loss either although it may be useful in redistributing adiposity according to some evidence. It takes a longer time to help with ovulation induction hence it fared worse than clomiphene citrate in the head-to-head studies, however, as a long-term treatment, metformin supplemented with lifestyle changes may prove superior. Its benefit in IVF patients is only confirmed with regard to reduction of the incidence of OHSS which is important given its high risk among PCOS patients. As for its usefulness in pregnancy, the jury are still out regarding its role in reducing the risk of miscarriage; however, the available evidence regarding GDM prevention is encouraging.

The long-term use of metformin to prevent remote complications of PCOS is uncertain and a significant amount of work is needed before a decision can be made on this front. Stipulations from studies carried out on the general population is not the same and can be misleading given the diversity of PCOS patients with regard to their metabolic comorbidities.

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