Polycystic ovary syndrome (PCOS) is associated with about 75% of all cases of anovulatory infertility. PCOS is a very heterogeneous syndrome both in its clinical presentation and laboratory manifestations. Hyperinsulinemia is the commonest contributor to the state of anovulation and its reduction, by weight loss or insulin sensitizing agents such as metformin will alone often restore ovulation or will improve results when used in combination with other agents. Insulin is of prime importance in the pathophysiology of PCOS. Women with PCOS exhibit a decrease in insulin sensitivity between 30% and 40%, a deficit similar to that seen in subjects with type 2 diabetes mellitus (1), which means that a very large proportion of cases of anovulation and infertility is associated with hyper-insulinemia and that the lowering of insulin concentration provides a new therapeutic pathway. The indications for the administration of metformin to anovulatory women with PCOS in anovulation induction program have widened, as it seems to be difficult to predict which individuals will respond well with this medication (2). Metformin, a biguanide, an oral hypoglycemic that does not cause hypoglycemia in normoglycemic patients, is a non-steroidal compound that appears to influence ovarian function both directly and indirectly. It is metformin that has been extensively used in the management of insulin-resistant states and that has been most thoroughly investigated for the management of PCOS. The sum of total of its action is a decrease in insulin levels and, as a consequence, a lowering of circulating total and free androgen levels with a resulting improvement of the clinical sequelae of hyperandrogenism. There is evidence that metformin also has a direct effect on androstenedione and testosterone production by theca cells in vitro by inhibiting the expression of steriodogenic acute regulatory (StAR) protein and 17-alpha-hydroxylase (CYP17) (3). In the last few years a number of mostly uncontrolled short-term studies have assessed the effects of metformin on insulin sensitivity and endocrine profile in women with PCOS. Velazquez et al demonstrated that an improvement in insulin sensitivity induced by 1500 mg of metformin a day for 8 weeks, leads to a favorable change in serum concentrations of androgens, SHBG and gonadotrophins. Metformin resulted in rapid fall insulin and the insulin to glucose ratio, with a concurrent significant decrease in serum concentrations of testosterone (T), free T, DHEAS and androstenedione. As far as gonadotrophin concentrations were concerned, there was a significant decrease in LH concentrations, an increase in FSH and a normalization of the LH: FSH ratio (4). Not all the data, however, have been so encouraging. Two trials with essentially identical recruitment criteria and using slightly higher doses of metformin (850 mg twice and three times a day) over similar lengths of time, showed little or no benefit with respect to insulin metabolism, hormone concentrations or lipid variables (5,6). The reasons for these
disagreements are unclear, but could be due to different methods used to assess insulin action and large BMI differences (29 versus 39 kg/m²) between study groups. In fact, it has been claimed that the ability of metformin to alter insulin sensitivity in individuals with major obesity (≥ 40 kg/m²) is limited. The largest prospective placebo-controlled double-blind study to date, recruited 143 women with clomiphene-resistant anovulatory PCOS and a BMI of >30 kg/m² (7). As regards significant weight loss and improved menstrual cyclicity, there was no difference either in the degree of weight loss or the degree of cycle improvement between those treated with metformin or placebo. It is likely that a higher dose of metformin is required for very obese women with PCOS, although data are lacking on predictive factors for response and appropriate dosages. The evidence so far is encouraging concerning the efficiency and safety of metformin as a single agent or in combination with clomiphene or gonadotrophins for women with hyperinsulinemic PCOS. A recent Cochrane review has confirmed a beneficial effect of metformin in improving rates of ovulation when compared with placebo, and also in improving both rates of ovulation and pregnancy when used with clomiphene citrate compared with clomiphene citrate alone (8). The data indicate that serum concentrations of insulin and androgens improve, although, contrary to popular belief, body weight does not fall. When women with clomiphene-resistant PCOS were administered FSH with or without pre-treatment with metformin for one month in an RCT, those receiving metformin developed fewer large follicles, produced less estradiol and had fewer cycles cancelled due to excessive follicular development (9).

The reduction of insulin concentrations induced by metformin seemed to favor a more orderly follicular growth in response to exogenous gonadotrophins for ovarian stimulation. Another published study on the effects of metformin on clomiphene-resistant patients undergoing IVF/ICSI, the results of cycles preceded by treatment with metformin were compared retrospectively to those in which metformin was not given.

Those receiving metformin had a decreased total number of follicles but no difference in the mean number of oocytes retrieved. There were more mature oocytes, embryos cleaved, increased fertilization and clinical pregnancy rates in the metformin group.

These latter two studies would seem to confirm that both obese and insulin-resistant PCOS women have a much greater tendency to a multi-follicular response and thus a relatively high cycle cancellation rate on low-dose FSH stimulation in order to avoid hyperstimulation (10). It remains to be seen whether metformin, which probably also has a direct androgen-lowering action on the ovary, will be of help to all women with PCOS wishing to conceive. Not only does metformin seem to be safe when continue throughout pregnancy, but preliminary data suggest that this strategy may decrease the high miscarriage rate usually associated with PCOS (11). It is hoped that the apparent lack of teratogenicity of metformin that has earned it a B classification and its beneficial effect on miscarriage rates if given throughout pregnancy will be confirmed by future studies.

The major concern with biguanides has been the risk of lactic acidosis. This is a very rare and serious metabolic complication of metformin therapy, occurring mainly in women with renal impairment, and does not appear to be a problem for otherwise fit women with PCOS who are not frankly diabetic and who have normal renal and liver function. The most commonly reported minor side-effects of metformin include bloating, nausea, vomiting, flatulence and diarrhea. These symptoms appear to be dose dependent and may be substantially minimized by taking the tablet with meals. It is likely that an incremental dosage protocol (500 mg up to 850 mg initially once and then twice daily) will be helpful to acclimatize patients and minimize undesirable gastrointestinal complaints. The use of troglitazone, the first oral thiazolidinedione approved for the treatment of type 2 diabetes, has a beneficial effect upon insulin resistance on PCOS (12). Unfortunately, troglitazone has been removed from the clinical practice because of its hepatotoxicity. Later generations of thiazolidinediones, such as rosiglitazone and pyoglitazone, may have a role in the future. Early indications suggest a positive effect for rosiglitazone when used alone and more so when combined with
clomiphene for ovulation induction, although there is natural reluctance to introduce them for the treatment of women of reproductive years because of the uncertainty regarding long term side-effects and teratogenicity (13).

CONCLUSION

At least in the short term, the deleterious effects of hyperinsulinemia in women with PCOS are reversible. This may be achieved by weight loss in the obese and with insulin-lowering medication (i.e. metformin). An additional bonus is that, in the long term, prevention of the metabolic syndrome in PCOS women by maintenance of a normal body weight and lifestyle changes seems to be an effective measure, although the use of insulin-lowering drugs for this purpose is still awaiting confirmation.

End Message: In spite of the extensive investigations on insulin sensitizers, mainly metformin, in the management of PCOS and miscarriage over the last decade, the pharmaceutical companies manufacturing metformin seem to be unaware by the progress in this field to the extent that they did not include PCOS in the indication list and did not change the firm recommendation stressing on the contraindication of its use during pregnancy. This will lead to better patient compliance and minimize their stress when using this medication.

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Metformin is an anti-diabetic drug from the biguanide class that has been used to help control blood glucose concentrations in people with type 2 diabetes, but does not cause hypoglycemia in non-diabetic patients. It is cheap, safe, with a few infrequent side effects such as gastrointestinal upset, diarrhea, cramps, nausea and vomiting, and the maximum safe dose is thought to be 850 mg three times daily (1).

Metformin is used in induction of ovulation in