

Review Article

The Effect of Metformin on Clinical Symptoms of Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age. Pathophysiological mechanisms include insulin resistance, which contributes to the development of hyperandrogenemia. Modification of insulin resistance by insulin sensitizers (eg metformin) is one of the therapeutic options for treating PCOS. Metformin improves menstrual cycle, induces fertility, reduces abortions and improves insulin sensitivity and androgen and lipid metabolism. Although metformin is an interesting treatment modality in PCOS women before and during pregnancy, according to the U.S. Food and Drug Administration, it is classified in Class B. Despite the lack of randomized and double-blind clinical trials, treatment is recommended to be safe, effective and non-pathological based on a comparison of the incidence of abortion before and after treatment with metformin.

Keywords

- Polycystic ovary syndrome
- Insulin resistance
- Metformin
- Infertility
- Pregnancy

ABBREVIATIONS

PCOS: Polycystic Ovary Syndrome; CYP17: Cytochrome P450 17 α -Hydroxylase/17,20-Lyase; PI3K: Phosphatidylinositol 3-Kinase; LH: Luteotropic Hormone; Star: Steroidogenic Acute Regulatory; HSD3-B: 3-B-Hydroxysteroid Dehydrogenase/ Δ -5-4; CYP11A1: Cytochrome P450 Family 11 Subfamily A Member 1; FSH: Follicle-Stimulating Hormone; ESHRE/ASRM: European Society for Human Reproduction and Embryology American Society for Reproductive Medicine; GDM: Gestational Diabetes Mellitus; BMI: Body Mass Index; STK11: Serine Threonine Kinase; OCT1: Organic Cation Transporter

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in premenopausal women. The definition of PCOS is based on the presence of hyperandrogenism (clinical or biochemical), chronic an ovulation and ultrasonographic evidence of polycystic ovary after excluding other causes of hyperandrogenism. Its prevalence varies depending on the used diagnostic criteria ranging from 15-20%. The etiology of PCOS is not clearly elucidated. It's association with metabolic diseases including type 2 diabetes mellitus has been known only in the last decades. Insulin resistance and associated hyperinsulinemia are important pathogenetic factors in the development of hyperandrogenemia in most women with PCOS, particularly obese, although it may occur in slim women too. Hyperinsulinemia plays a key role in the development of ovarian overproduction of androgens and the development of metabolic consequences (diabetes mellitus, hyperlipoproteinemia, cardiovascular diseases). The treatment of PCOS depends on the clinical

situation, the phenotype, the degree of hyperandrogenism, age, present infertility, the desire to become pregnant, the presence of obesity and the spectrum of metabolic abnormalities.

The first data on the beneficial effects of metformin (biguanide used in diabetes type 2 treatment) on reproductive disorders originated in 1994. Since then, a number of clinical studies have observed the effect of metformin on infertility, menstrual cycle, anovulation, pregnancy and endometrial function in women with PCOS [1]. According to the FDA (Food and Drug Administration), metformin is not approved for the treatment of ovulation. However, studies have confirmed that treatment with metformin leads to the menstrual cycle improvement, induction of ovulation, reduction of abortions, and treatment of hyperandrogenemia and dyslipidemia in PCOS women [2].

METFORMIN AND OVARY

Metformin affects ovarian function by a dual mechanism - indirectly (insulin-dependently) by reducing the effect of insulin excess and directly (insulin-nondependently) by effect on the ovary function [1,3,4].

Insulin-dependent effect of metformin on the ovary

Metformin affects ovarian function indirectly by inhibiting the effect of hyperinsulinemia on steroidogenesis and follicular growth. In theca cells it inhibits CYP17 (cytochrome P450 17 α -hydroxylase/17,20-lyase) activity by decrease in hyperinsulinemia with subsequent suppression of insulin-induced PI3K (phosphatidylinositol 3-kinase) activity. In granulosa cells the decrease in insulin levels may inhibit LH (luteotropic hormone) receptor expression as well as the activity

of the enzymes StAR (steroidogenic acute regulatory), HSD3- β (3- β -hydroxysteroid dehydrogenase/5-4 isomerase) and CYP11A1 (cytochrome P450 family 11 subfamily A member 1) [1].

Insulin-nondependent effect of metformin on the ovary

Potential direct effects of metformin are attributed to its ability to reduce the androgen production in theca cells [1,2,5]. In granulosa cells, metformin reduced basal and FSH (follicle-stimulating hormone) stimulated production of progesterone and estradiol. In addition, FSH decreased the stimulated expression of 3 β -HSD, StAR, CYP11A1 and CYP19A1 by inhibiting the proliferation of granulosa cells [3,6,7]. These mechanisms can contribute to the inhibition of overproduction of sex hormones and premature luteinization and consequently to decrease the excess of androgens and to improve ovulation [1].

The effect of metformin on infertility, menstrual cycle disturbances and anovulation

In PCOS women metformin improves ovulation in different ways [8,9]. Metformin-induced improvement of ovulation lasts about 26 months [9]. The results of many studies confirm that the interval between treatment initiation and first ovulation is significantly shorter with metformin than with placebo. In the short-term (6 months) administration of metformin monotherapy, one or two ovulations were induced within 5 months. Long-term administration may lead to weight loss and may increase the ovulation rate. Spontaneous ovulation may occur within 3 months of starting treatment with metformin [10]. Metformin treatment during gonadotropin induction of ovulation or IVF (in vitro fertilization) in PCOS women increased the pregnancy rate and reduced the risk of OHSS (ovarian hyperstimulation syndrome) [1,3].

Dosing of metformin

There are several dosing regimens [8]. Due to the gastrointestinal side effects, treatment usually begins with a dose of 500-850 mg with a gradual increase to 2550 mg daily [8,9,11]. In most studies of PCOS women, efficacy and the clinical effect of metformin are dose-independent [4].

Metformin versus clomiphene

The pharmacological effects of metformin and clomiphene (standard therapy) are different. Clomiphene directly induces ovulation by blocking negative feedback at the hypothalamus and pituitary gland, with multiple pregnancy occurring at 10%, and the onset of action is rapid. Metformin affects metabolism and indirectly affects ovulation induction by reducing hyperinsulinemia. The onset of this effect is slower. According to the ESHRE/ASRM (European Society for Human Reproduction and Embryology American Society for Reproductive Medicine) consensus, clomiphene remains the drug of first choice for induction of ovulation in anovulatory women with PCOS. According to Nestler the consensus does not include the type of infertile woman with PCOS as an important indicator in treatment decisions. Many infertile women with PCOS wish to get pregnant in the short term. Clomiphene would be suitable

for these women due to rapid onset of action. On the other hand, there are many young patients with PCOS who do not plan a baby in the near future. These women would be suitable for treatment with metformin with its gradual onset of action without potential risk of multiple pregnancy [12]. Essah et al., compared in a retrospective study the effect of short-term (3-6 months) and long-term (more than 6 months) metformin treatment in women with PCOS on the improvement of menstrual disturbances. Metformin effectively improved menstrual cycle, especially in long-term administration (77% vs. 55% for short-term treatment) [13]. Treatment with clomiphene is still possible after 6 or more months of unsuccessful metformin treatment [12].

Metformin and pregnancy

The beneficial effect of metformin persists from preconception to period during pregnancy [3]. Metformin administration during pregnancy reduces the increased risk of gestational diabetes mellitus (GDM) and spontaneous abortions in the first trimester [1,3,9,14]. No teratogenic effect, intrauterine death or slowing of fetal development have been reported when using metformin during pregnancy [9]. However, metformin is included in Category B for use in pregnancy, which means that reproductive studies in animals did not confirm the risk to the fetus but that adequate and adequately controlled studies in pregnant women are not available. Since there are currently no recommendations for its use in pregnancy, its continued use in pregnancy is dependent on the clinical experience of the physician and the individual approach [10,14]. In terms of reducing perinatal morbidity in women with PCOS and GDM diabetes mellitus, metformin is comparable to insulin [10].

Studies on the effect of metformin during pregnancy

Data on the beneficial effects of metformin during pregnancy are supported by small studies limited by retrospective design and lack of prospectively studied control groups. Available data are still insufficient to confirm the benefit and safety of this treatment during pregnancy [1]. Randomized controlled trials are needed to confirm safety [3]. Studies that observed metformin use during the first trimester of pregnancy confirmed the decrease in spontaneous abortions to 17% (in 30-50% of pregnancies in pregnant women with PCOS without metformin therapy). In the metformin-treated group GDM was present at 3% while in the non-treated group at 31%. Metformin used in the 2nd and 3rd trimesters did not lead to an increase in perinatal morbidity, did not affect the birth weight, length or motor and social development of the child in the 3rd and 6th month of life [15]. Gilbert et al., in the meta-analysis of studies of diabetic women not selected by PCOS and non-diabetic women with PCOS confirmed the safety of metformin use in the first trimester. The incidence of malformation in the control group was 7.2%, which was significantly higher than in the metformin group (1.7%) [16]. Bolton et al., in a retrospective study of 66 pregnant women with PCOS receiving metformin did not observe a difference in birth weight compared to non-metformin women. In the metformin group, there was a lower incidence of abortions, neonatal growth deficits, congenital malformations and hypoglycemia. Since metformin clearance is increased during pregnancy due to increased renal elimination, the dose of metformin should

be adjusted mainly in late pregnancy by approximately 20% to maintain the therapeutic effect of the drug [17]. Metformin passes through the placenta, with umbilical cord concentrations at the time of birth being approximately half the concentration in the mother's blood. Transfer to breast milk is minimal [18]. When metformin was administered from conception to birth, early abortion in the metformin group occurred in 8.8% versus 42% in the control group. There was no difference in the mean birth weight of newborns. Neonatal hypoglycemia was less common in the metformin group [19]. Also, Glueck et al. confirmed in 72 PCOS women with metformin treatment a significant reduction in spontaneous abortions compared to the anamnestic data of the same women who did not take metformin in the previous pregnancy (26% vs. 62%). Metformin did not have any adverse effect on the birth weight and length of newborns and their motor and social development in the 3rd and 6th months [20].

Based on the systematic review of studies from 2002-2012 on the use of metformin during pregnancy in women with type 2 diabetes mellitus, GDM or PCOS, no side effects of treatment or occurrence of congenital malformations have been reported. In women treating with metformin, there was a lower incidence of miscarriage compared to women without treatment. The mean birth weight of newborns in metformin treatment was comparable to placebo, with a lower incidence of neonatal hypoglycaemia than placebo in the metformin group. The incidence of premature births has also decreased. With the exception of one study, metformin reduced the prevalence of GDM compared to placebo [14].

Predictors for metformin response

The knowledge of metformin response predictors is critical because it can help with individualized treatment [1,2,21]. The main predictor of the response to metformin is BMI (body mass index). Higher BMI is associated with suboptimal therapeutic effects, while morbid obese women are often resistant to the effect of metformin on ovulation and pregnancy. Age and prolonged infertility have an adverse effect on the success of pregnancy in metformin therapy [1]. Another factor in the success of metformin therapy is the degree of androgen excess. Responders on metformin are less hyperandrogenic than non-responders [1,4]. The role of the genotype is also important. Serine threonine kinase (STK11) controls the levels of glucose in the liver. The STK11 gene polymorphism is associated with a significantly lower chance of ovulation in PCOS women treated with metformin, confirming that this gene may affect the efficacy of metformin [4]. The effect of metformin on hepatocytes is the result of the predominant expression of OCT1 (organic cation transporter), which is higher in the liver than in other tissues. OCT1 polymorphisms are associated with changes in metformin pharmacokinetics / pharmacodynamics [22].

DISCUSSION & CONCLUSION

None of the current therapeutic modalities is able to cope with the reproductive and metabolic consequences of PCOS. According to the ESHRE/ASRM consensus, clomiphene remains the drug of choice for induction of ovulation in anovulatory women with PCOS. Many infertile women with PCOS wish to get pregnant in the short term. Clomiphene would be suitable for

these women in terms of the onset of action. On the other hand, there are many young women with PCOS who do not plan to be pregnant in the near future. These women would be suitable for treatment with metformin with its gradual onset of action without potential risk of multiple pregnancy. Combination treatment of clomiphene citrate plus metformin resulted in a higher number of live-born children compared to other modalities. Metformin is one of the most commonly used off-label medications for PCOS. More than 30 meta-analyses of RCTs (randomized control trials) confirmed the role of metformin in PCOS management, including induction of ovulation, weight loss, menstrual control, premature birth, abortion and hirsutism. No teratogenic effect, intrauterine death, or delayed fetal developments have been reported with metformin during pregnancy. As there are currently no recommendations for its use in pregnancy, its continued use in pregnancy is individually determined by physicians based on their clinical experience and individual approach.

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