Metformin in the Treatment of Polycystic Ovary Syndrome

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Abstract: Polycystic ovary syndrome (PCOS) is one of the most frequent diseases that affects women in their reproductive age. The heterogeneity of PCOS makes not only the diagnosis but also the choice of an adequate treatment difficult. The biguanide, N, N´ dimethyl-biguanide : Metformin is an antidiabetic drug that increases glucose utilization in insulin-sensitive tissues and is useful in the reduction of both insulin resistance and circulating androgens as well as restoring ovulation. However, metformin is being clinically used without a complete understanding of the mechanism involved. The present review explores some of the actions and efficacy of metformin in the treatment of PCOS during different reproductive periods.

Key Words: Polycystic ovary syndrome (PCOS), metformin, diabetes, adolescents, pregnancy, ovulation, cardiovascular.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a diagnosis of exclusion, with other androgen excess and ovulatory dysfunction disorders to be ruled out. There are 3 principal features of the syndrome, including hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. These features have been included in slightly different permutations in the 3 criteria currently available to diagnose PCOS, including that of the National Institutes of Health (NIH) 1990, Rotterdam 2003, and the Androgen Excess Society 2006 [1]. The diagnosis of the PCOS requires the finding of "pearl line" in ultrasonography, occurrence of early follicular phase (2-5 th day of menstrual cycle), biochemical abnormalities including: high level of luteinizing hormone (LH) (> 10 IU/l), LH/FSH (LH/ follicle-stimulating hormone) ratio > 2, testosterone level above 2.5 mmol/l, androstenedione > 10 mmol/l and free androgen index > 4 [1]. The exclusion of other endocrine diseases such as congenital adrenal hyperplasia, hormone-producing adrenal or ovary tumors, Cushing syndrome or disease, prolactinoma and disorders of the thyroid gland is also essential [1]. Despite being heterogeneous in nature, the hallmarks of the disease are constant and involve hyperandrogenemism, hirsutism, oligo- or amenorrhoea and anovulation, infertility, increased first trimester miscarriage rate, dyslipidemia and insulin resistance [2, 3]. The management of PCOS depends on the time in the reproductive period of the patient; it includes lifestyle modification combined with dietary-induced weight loss in the case of obese women. If the patient is an adolescent with PCOS consulting by side effects of PCOS such as hirsutism, acne, altered lipid metabolism or irregular menstrual cycles (2-3 years after menarche), she could be treated with oral contraceptives. However, if this patient shows insulin resistance (evaluated by the homeostasis model assessment: HOMA), the treatment with oral contraceptives is not recommended and the use of insulin sensitizing agents (as biguanides) or lowering drugs are recommended. On the other hand, if the PCOS patient is consulting by infertility caused by anovulation, the first pharmacological approach to induction of ovulation is the administration of clomiphene citrate. However, a subgroup of patients is "clomiphene resistant" and these women are generally obese and more markedly insulin resistant than "responders". In this case, insulin sensitizing agents as biguanides are recommended. Gestational diabetes and the first trimester miscarriages (in part due to the no compensated insulin resistance generated during pregnancy) are complications generally present in pregnant PCOS women. In these cases the treatment with metformin is also recommended. This review aims to discuss the efficacy of metformin in the treatment of PCOS during different stages of reproductive period.

METFORMIN TREATMENT IN THE INDUCTION OF OVULATION

The first pharmacological approach to induction of ovulation in infertile women with PCOS is the administration of clomiphene citrate. The daily dose of clomiphene citrate is gradually titrated from 50 mg to 150 mg per day. If no improvement is present, this group of patients is considered as "clomiphene resistant". The pronounced degree of hyperinsulinemia in obese women with PCOS is believed to be the cause of their low responsiveness to clomiphene citrate [4]. In the treatment schedule, metformin is administered only if clomiphene citrate at a dose of 150 mg per day is ineffective. In addition, the results of the latest studies have revealed the benefits of metformin or the combined treatment clomiphene citrate plus metformin in the treatment of anovulatory women with PCOS (Table **1**). In contrast, Legro *et al.* [9] in a study that included 626 patients from 13 centers, reported that clomiphene (50 mg daily for six cycles or 30 weeks) is superior to metformin (500 mg twice daily for six cycles or

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Table 1. Comparative Effects between Metformin and Clomiphene Citrate Treatment

Treatments	Subjects	Results
Metformin treatment: 500 mg three times daily for 7 weeks Sills *et al.* 2000 [4]	Anovulatory women with PCOS and clomiphene resistant	Metformin increases ovulation and pregnancy rate
Metformin treatment: 500 mg three times daily for 35 weeks Clomiphene citrate treatment: 50 mg daily daily for 35 weeks Nestler *et al.* 1998 [5]	Anovulatory women with PCOS	In the group of women metformin-treated: 89 % of spontaneous ovulation or ovulation in response to clomiphene citrate In the group of women clomiphene citrate-treated: 8 % of ovulation rate In the group of women placebo-treated: 4 % of ovulation rate Reversion of insulin resistance syndrome
Comparison between metformin and clomiphene citrate. Review and meta-analysis Lord *et al.* 2003 [6]	Anovulatory women with PCOS	In the group of women metformin-treated: 46 % of ovulation rate In the group of women placebo-treated: 24 % of ovulation rate In the group of women clomiphene citrate plus metformin-treated: 76 % of ovulation rate
Metformin treatment: 500 mg three times daily on 5-9 th of the cycle Clomiphene citrate treatment: 50 mg daily daily on 5-9 th of the cycle Neveu *et al.* 2007 [7]	Anovulatory women with PCOS	In the group of women metformin-treated: 75.4 % of ovulation rate In the group of women clomiphene citrate-treated: 50% of ovulation rate In the group of women clomiphene citrate plus metformin-treated:63.4 % of ovulation rate
Metformin treatment: 1700 mg daily for 6 months Clomiphene citrate treatment: 50 mg daily for 6 months Palomba *et al.* 2007 [8]	Anovulatory women with PCOS	In the group of women metformin-treated: 55.4 % of ovulation rate and 10.8% of pregnancies In the group of women clomiphene citrate-treated: 59.8% of ovulation rate and 11.2% of pregnancies

PCOS: Polycystic Ovary Syndrome.

30 weeks) in achieving live birth in infertile women with PCOS (the live birth rate was 22.5 % in the clomiphene citrate group; 7.2 % in the metformin group and 26.8 % in the combination-therapy group). However, the rate of ovulation was significantly higher in the combination group than in either or the single-agent groups (the ovulation rate was 29% in the metformin group, 49% in the clomiphene citrate group and 60% in the metformin + clomiphene citrate group) and among pregnancies, the rate of multiple pregnancy was 6.0 % in the clomiphene citrate group, 0 % in the metformin group, and 3.1 % in the combination-therapy group. In agreement with their previous findings, the authors found that the groups receiving metformin (both the metformin group and the combination-therapy group) had improved insulin sensitivity (including effects on BMI, pro-insulin, and insulin levels, and insulin resistance as determined by homeostasis model assessment: HOMA). According with these findings, Moll *et al.* [10] with an another large, multicenter, randomized trial have reported that among 228 subjects with PCOS who were randomly assigned to receive either clomiphene alone or combination of metformin and clomiphene for up to six ovulatory cyles, there were no significant differences in ovulation rates or pregnancy rates between the combination-therapy (clomiphene citrate plus metformin) group and the group that received clomiphene alone. These results are inconsistent with data from several other studies reporting benefits of metformin, especially in combination with clomiphene citrate in stimulating ovulation in women with PCOS [4-8]. However, Legro *et al.* [9] have not address the effects of continuing metformin throughout pregnancy. In addition, subjects in this study received extended-release metformin and this form of the drug has increased tolerability but less efficacious in women with PCOS than is immediate-release metformin [11]. Regarding the large, multicenter and randomized trials consider in these two studies [9, 10], the use of clomiphene citrate alone as first-line therapy for infertility in women with PCOS must be considered whereas the use of metformin should be limited to clomiphene resistant patients.

METFORMIN TREATMENT DURING PREGNANCY

Despite the lack of randomized, double blind clinical studies, the comparison of miscarriage rate in women before and after metformin therapy indicates that metformin (belonging to pregnancy group B) is a safe, effective and non-teratogenic agent [12, 13]. Pregnancy rate growth is attributed to the restoration of insulin sensitivity, normalization of insulin level, stimulation of the follicle growth, the improvement of oocyte quality, the induction of ovulation and normalization of plasminogen activator inhibitor 1 (PAI-1) concentration [14, 15].

Pregnancy increases requirements for insulin secretion while increasing insulin resistance, and increasing demands

on pancreatic beta cells [16] and promoting development of gestational diabetes [17, 21]. Women with gestational diabetes have 67% impairment in pancreatic beta cell compensation for insulin resistance as compared with normal women [22]. The physiological increase in insulin resistance during pregnancy promotes shifting metabolic fuel supplies from mother to fetus [23- 25]. Since 46 % of women with PCOS develop gestational diabetes [26], they have higher insulin resistance than normal women when they become pregnant [26- 32]. Recent years have shown that metformin administered during pregnancy decreased the risk of gestational diabetes [33]. Another favorable effect of metformin in pregnant patients with PCOS is a reduction of an increased miscarriage rate found in these subjects [13, 34]. Metformin administration during pregnancy was found to be associated with a five-fold lower probably of early pregnancy loss (8.8 %) when compared to untreated women (41.9 %) [13, 35]. These reports differ from those in which metformin was not efficient in achieving live birth in infertile women with PCOS because its have suspended metformin treatment during pregnancy [9, 10]. Among the potential mechanisms responsible for this effect, an important role seems to be played by the stimulation of insulin growth factor binding protein (IGF-BP) and glycodelin production. The concentration of both of them in plasma of PCOS patients is reduced [36]. IGF-BP plays an important role in fetus implantation, whereas glycodelin is suggested to take part in rising tolerance of the endometrium to the developing fetus [37]. Moreover, metformin decreases PAI-1 concentration, which is considered as an independent risk factor of miscarriage in PCOS [35, 38], and increases the blood flow through the spiral arteries of the uterus [36]. In addition, a direct effect of metformin has been recently reported on uterine tissue [39, 40].

Metformin improves the quality of oocytes in PCOS women, probably by local changes in insulin and IGF-1 concentration [33, 38]. These findings encouraged some investigators to conclude that metformin may be effective in women with PCOS who think about *in vitro* fertilization [41]. This effect seems to be related to the changes in follicle complex structure, increased IGF-1 and decreased IGF- BP level [41, 42].

METFORMIN MODULATES ENDOCRINE AND METABOLIC PARAMETERS

Metformin decreases fasting and post-oral glucose load plasma insulin levels [33]. Other endocrinological effects of metformin include lowering of spontaneous and gonadoliberin (GnRH) - induced LH secretion, reducing total and free testosterone level, increasing sex hormone binging globulin (SHBG) level [36, 43].

Interestingly, metformin which evidently reduced free and total androgen content, produced only slight impact on skin manifestations of hyperandrogenism [14, 35]. Although in the majority of patients acanthosis nigricans receded, hirsutism usually remained while acne subsided in only a small percentage of patients [35]. It should be stressed that all the studies examining the action of metformin on clinical manifestations of hyperandrogenism were short in duration and, therefore, can not given the answer to the question whether longer treatment is able to combat skin symptoms of hyperandrogenism more successfully or not [41]. Metformin therapy has many other positive effects. Most of the trials revealed that metformin administration led to the reduction in body mass, waist/hip ratio, and plasma levels of LDL cholesterol and triglycerides and elevated HDL cholesterol [44, 45].

An important finding is that metformin should not be restricted to PCOS patients with diabetes. According to the results of *Diabetes Prevention Study*, its taking (850 mg twice daily) by subjects with impaired glucose tolerance caused a 31 % reduction of the risk of diabetes development [34].

Adolescent girls have anovulatory menstrual periods during menarche and this period is considered physiological within the ontogeny of fertility [46, 47]. However, when young women show irregular menstrual cycles and /or anovulation within 2-3 years after menarche this is considered as a pathological condition. There are few reports about the use of metformin in adolescents; however, insulin sensitization with metformin is under exploration as an approach not only in preventing the postmenarcheal progression to PCOS but also in preventing early steps within this sequence. The literature shows a large range of metformin doses employed in the treatment of adolescents with hyperandrogenism and/or PCOS with a length of the treatments longer that 6 months (Table **2**).

The most frequent side-effects of metformin are gastrointestinal symptoms [42, 44]. To prevent or minimize the risk of their occurrence, the treatment should be started with a small dose (usually 500 mg per day) and then gradually titrated three times up to 500 mg 3 times a day or 850 mg twice daily [44]. To minimize the risk of the most serious adverse effect of metformin therapy, lactic acidosis, the drug is contraindicated in women with kidney failure, liver insufficiency, heart failure, serious pulmonary disorders or alcoholism [38, 54].

CONCLUSIONS

The complex pictures of PCOS and individual differences in the severity of complaints experienced by individual patients make the PCOS therapy difficult and thankless. The warranted therapy should be multidirectional and involve minimization of the symptoms of hyperandrogenism (such as hirsutism and acne), disappearance of anovulation (irregular menses, infertility) and prevention of late PCOS complications, especially type 2 diabetes mellitus and cardiovascular disorders. According to the data presented here, it appears that metformin is effective in controlling insulin resistance syndrome, hirsutism, and follicular development, in improving oocyte quality and in regulating endocrine balance of PCOS patients. In addition, metformin is able to prevent both apparition of type 2 diabetes mellitus and miscarriages during early pregnancy. However, recent reports have questioned the effectiveness of metformin in achieving live birth in infertile women with PCOS. Unfortunately, the relative paucity of randomized trials makes the question of the role and effectiveness of metformin treatment still open.

Table 2. The Use of Metformin During Adolescence

Authors	Treatment	Subjects	Results
Ibáñez *et al.* 2000 [48] Ibáñez *et al.* 2004 [49]	1275 mg daily metformin for 6-12 months	Adolescents with hyperandrogenism	Reduction of hirsutism
Ibáñez *et al.* 2001 [50]	1275 mg daily metformin for 6 months	Adolescents with irregular menstrual cycles	Normalization of menstrual cycles
Freemark et al. 2001 [51]	500 mg daily metformin for 6 months	Morbidity obese adolescents	Normalization of BMI, FBG, insulin levels
Ibáñez *et al.* 2006 [52]	850 mg daily metformin for 36 months	Low-weight-birth girls	Reversion of insulin resistance syndrome, increases IGF-1 levels and leptin levels and diminishes SHBG and IGFBP-1. Modulation of lipid profile
Ibáñez *et al.* 2004 [49] Ibáñez *et al.* 2006 [53]	425 mg daily metformin for 6 months	Girls with precocious pubarche	Prevention of early puberty onset

BMI: body mass index; FBG: fasting blood glucose; IGF-1: insulin growth factor 1; IGFBP-1: IGF-1 binding protein.

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