HORMONES 2013, 12(2):192-200

Review

The guidelines issued by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine regarding the induction of ovulation with metformin in patients with the polycystic ovary syndrome potentially require reconsideration

Dimitrios Panidis,[1] Konstantinos Tziomalos,[2] Efstathios Papadakis,[1]
Eleni A. Kandaraki,[1] Ilias Katsikis[1]

[1]Division of Endocrinology and Human Reproduction, Second Department of Obstetrics and Gynecology, Hippokration Hospital, [2]First Propedeutic Department of Internal Medicine, AHEPA Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

ABSTRACT

In 2007, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) issued guidelines in Thessaloniki regarding the use of metformin and clomiphene for the induction of ovulation in patients with anovulatory polycystic ovary syndrome (PCOS). According to these guidelines, the use of metformin should be limited to patients with impaired glucose tolerance and should be interrupted well before the administration of clomiphene, thus restricting the use of metformin to a minority of patients with PCOS. More recent data suggest that these guidelines potentially require reconsideration. Indeed, metformin appears to be useful in patients with PCOS who have a body mass index within the normal range and present with infertility due to anovulation. Moreover, the combination of metformin with clomiphene appears to be the best treatment choice in patients with PCOS who are resistant to clomiphene, i.e. it should precede the administration of gonadotropins. In addition, the administration of metformin reduces the incidence and severity of ovarian hyperstimulation syndrome when given to patients with PCOS who undergo multiple ovulation induction for in vitro fertilization and have a high risk for this syndrome. However, it should be emphasized that more studies are needed to support the above arguments and, more importantly, to determine the factors that predict the success of ovulation induction.

Key words: Anovulation, Clomiphene citrate, Metformin, Polycystic ovary syndrome, Thessaloniki ESHRE/ASRM-sponsored PCOS Consensus Workshop Group

Address for correspondence:
Konstantinos Tziomalos, MD, PhD, First Propedeutic Department of Internal Medicine, AHEPA Hospital, 1 Stilponos Kyriakidi Str., 546 36, Thessaloniki, Greece, Tel.: +30 2310994621, Fax: + 30 2310274434, e-mail: ktziomalos@yahoo.com

Received 06-09-2013, Accepted 14-02-2013

INTRODUCTION

The polycystic ovary syndrome (PCOS) is a heterogeneous disorder that affects 6-10% of all women of reproductive age.[1] Indeed, PCOS is now regarded as the commonest endocrine disorder affecting women in this age bracket. The major manifestations of PCOS include menstrual cycle irregularities due to anovulation and signs of androgen excess, including hirsutism, oily skin, acne and androgenic alopecia.[2,3]

A central characteristic of PCOS is insulin resistance (IR). Another important component of the syndrome is obesity. Indeed, IR and obesity are present in 50-70% and 50-60% of patients with PCOS, respectively.[3] The majority of patients with PCOS, independently of their body weight, present with a type of IR which is characteristic of the syndrome and of unclear pathogenesis. Obese patients with PCOS additionally have IR due to obesity.[2,4,5]

PCOS is the most frequent cause of anovulatory infertility in developed countries. The aim of the present paper is to review the current data on the role of metformin in the induction of ovulation in anovulatory patients with PCOS.

METFORMIN

Metformin is a hypoglycemic agent that is administered orally and is a synthetic compound of biguanides. Even though this agent has been used in the management of type 2 diabetes mellitus (T2DM) for more than 30 years, its mechanism of action is not entirely clear.[6]

Metformin exerts its action post-insulin receptor. Recent data suggest that in all the mechanisms of action of this agent a protein kinase is implicated, which is activated by adenosine monophosphate (AMP). The mechanism of action of metformin differs from that of other antidiabetic agents. Metformin does not induce hyperinsulinemia and therefore does not cause hypoglycemia (i.e. has no action on the pancreatic β-cells).

Metformin reduces hepatic production and intestinal absorption of glucose and improves insulin sensitivity through an increase in peripheral uptake and use of glucose by the muscles and liver. In addition, it reduces insulin levels and does not affect glucose levels when they are within the normal levels.[6,7] Moreover, metformin potentially increases uterine vascularization and blood perfusion through a decrease in serum endothelin-1 levels (i.e. the most potent endogenous vasoconstrictive agent), increases serum glycodelin levels, reduces androgen and luteinizing hormone (LH) levels and causes weight loss in some patients.[8-12] Advantages of metformin include the absence of hyperinsulinemia, and thus avoidance of hypoglycemia, and its low cost.

CAUSES OF INFERTILITY IN PATIENTS WITH PCOS

Anovulation is the cause of infertility in approximately one third of women in couples with reduced fertility. Among anovulatory women, 80-90% have PCOS.[13]

Infertility in patients with PCOS is due to oligo- or anovulation. PCOS is actually a cause of oligoovulation rather than anovulation. From time to time, and for unknown reasons, an ovarian follicle becomes dominant and can escape from the inhibitory intrafollicular effect and progress to ovulation and formation of corpus luteum. Due to these random episodes of ovulation, the proportion of fertility among patients with PCOS who are not undergoing any treatment is not zero, even though it is lower than in normally ovulating women. Moreover, some patients with PCOS have regular ovulation and normal fertility despite the presence of biochemical hyperandrogenemia or clinical manifestations of hyperandrogenemia.[14]

Five theories have been proposed for the pathogenesis of anovulation in PCOS: a) the theory of an autoinhibitory effect on the pool of recruitable ovarian follicles, due to their excessive number,[15] b) the theory of the premature effect of LH on the granulosa cells of the recruitable follicles,[16] c) the theory of follicular arrest due to IR and compensatory hyperinsulinemia,[17] d) the theory of increased activity of catechol-O-methyltransferase in the granulosa cells of the follicles,[18] and, e) the theory of oocyte abnormalities.[19]

In addition to oligo- or anovulation, infertility in patients with PCOS is due to other factors. It is

well known that during the induction of ovulation in the course of in vitro fertilization (IVF), a large number of oocytes are retrieved from patients with PCOS. However, these oocytes are of poor quality leading to low rates of fertilization, cleavage and implantation and higher rates of abortion. The former are not associated with higher rates of aneuploidy. Other factors, non-chromosomal, are implicated in the increased risk for abortion among patients with PCOS. Impaired follicular maturation and impaired fetal development in patients with PCOS are probably related to abnormal endocrine and paracrine mediators, metabolic disorders and alterations in the intrafollicular microenvironment during folliculogenesis and follicular maturation. Therefore, we need a better understanding of the relationship between PCOS and the abnormal intra- and extrafollicular mediators and of the effects of these mediators on the crosstalk between granulosa cells and oocyte, on follicular maturation and on the potential for fetal development. This improved understanding will ameliorate clinical stimulation and fertilization, increasing favorable pregnancy outcome rates in patients with PCOS who undergo IVF.[20]

A high proportion of patients with PCOS are obese[21] or have the metabolic syndrome.[22] Both obesity and the metabolic syndrome considerably impair the functionality of the reproductive system. The pathogenetic mechanism underlying the adverse effects of obesity on the reproductive system is unclear. However, both animal and clinical studies suggest that obesity exerts detrimental effects at all levels of the hypothalamus-pituitary-ovaries axis. Indeed, obesity appears to impair ovulation, oocyte maturation, endometrial growth, uterine receptiveness and zygote implantation. Accordingly, weight loss represents first-line treatment for obese women who seek management of fertility problems.[23,24]

The use of metformin in reproductive medicine has increased since clinical studies showed that metabolic treatments improve the reproductive disorders of patients with PCOS.[25] Metformin soon evolved into a major therapeutic tool for the restoration of ovulation,[26] the management of infertility,[27] the prevention of abortion[28] and the reduction of the incidence of pregnancy complications, including gestational diabetes mellitus, preeclampsia and preterm delivery, which are associated with IR and systemic subclinical inflammation that characterize PCOS.[29] Metformin reduces circulating insulin and androgen levels, which are elevated in patients with PCOS, leading to the restoration of ovulation in these patients.[2,26]

CURRENT GUIDELINES FOR THE INDUCTION OF OVULATION IN PCOS ISSUED BY THE EUROPEAN SOCIETY FOR HUMAN REPRODUCTION AND EMBRYOLOGY (ESHRE) AND AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE (ASRM)

The ESHRE and the ASRM, at a meeting held in Thessaloniki, issued guidelines on the use of metformin and clomiphene for the induction of ovulation in anovulatory patients with PCOS.[30,31] According to these guidelines, metformin should be administered only in patients with impaired glucose tolerance, thus limiting the use of this agent to a minority of patients with PCOS. Indeed, the prevalence of impaired glucose tolerance in obese and non-obese patients with PCOS ranges between 31-45% and 6-17%, respectively.[32-35] This recommendation was based on a high-quality randomized controlled trial (RCT) that showed a substantial benefit from the use of clomiphene compared with metformin.[36] This study was considered as definitive evidence that clomiphene represents the treatment of choice for anovulatory PCOS and that metformin has no place in this context.[36] However, it should be mentioned that the ESHRE/ASRM consensus did not comment on another RCT from Italy, which reported that metformin is more effective than clomiphene in normal weight patients with anovulatory PCOS.[27]

The US multicenter RCT is the largest in the field and undoubtedly represents a powerful and robust study.[36] However, similarly to all studies, this RCT has some weak points. a) The mean body mass index (BMI) of the patients included in the study was >35 kg/m^2 and therefore its results cannot be generalized to all patients with PCOS.[13,29] In these patients, weight loss with diet and lifestyle changes is the treatment of choice and management of anovulation is the second step.[13,37] b) Even though the study included a large number of patients (n=626), this number appears

inadequate to assess the rates of live births in the group assigned combined clomiphene/metformin treatment (45%) compared with the metformin group (30%), whereas the lowest rate was observed in the clomiphene arm (20%). The recruitment of patients was discontinued prematurely because of the significant benefit of clomiphene over metformin, suggesting the possibility of type I error.[38] c) The use of extended-release metformin in the study of Legro et al[36] was potentially another reason for the poor results observed in the metformin arm.[38]

RECENT DATA SUGGESTING THAT METFORMIN PLAYS A BENEFICIAL ROLE IN THE INDUCTION OF OVULATION IN PATIENTS WITH PCOS

In a recent study, a decision analysis model was used to compare the efficacy of clomiphene citrate monotherapy, metformin monotherapy, clomiphene/metformin combination and placebo in achieving pregnancy and live births in patients with PCOS.[39] This model was applied to a theoretical population of 10,000 patients with PCOS. Live birth rates were estimated based on existing data. It was also assessed whether the results differed according to the variation in live birth rates in the different studies. This study showed that metformin/clomiphene combination treatment results in higher live birth rates than other treatments, followed by clomiphene monotherapy, metformin monotherapy and placebo. The authors concluded that metformin/clomiphene combination is the treatment of choice for achieving live births in patients with PCOS.[39]

A multicenter RCT conducted in Australia and New Zealand showed that metformin is equally effective with clomiphene in patients with PCOS and BMI <32 kg/m^2.[40,41] The main strength of this study was that patients were categorized according to BMI, whereas in the study by Legro et al. analyses according to BMI were post-hoc and not pre-specified and therefore should be interpreted with caution.[36,40] On the other hand, this study was considerably smaller than the study by Legro et al ($n=171$) and might have been too underpowered to detect differences between metformin and clomiphene.[36,40]

Given the discrepant findings of the former study, the study by Legro et al. and another RCT performed in Italy,[27,36,40] a meta-analysis that included these three studies, was recently performed and showed that there are no significant differences in the efficacy of metformin and clomiphene in the induction of ovulation in non-obese patients with anovulatory PCOS.[38] Accordingly, both metformin and clomiphene should be considered as first-line treatments. The strength of this meta-analysis is that it included all the studies that compared metformin and clomiphene in non-obese patients with PCOS. The major limitation is that it shares all the limitations of the studies included.

A recent Cochrane review reported that metformin/clomiphene combination is more effective than clomiphene monotherapy in patients resistant to clomiphene citrate.[42]

A randomized, double-blind, placebo-controlled study conducted in Finland showed that metformin increases the rates of ovulation, pregnancy and live births in normal weight patients with PCOS.[13] However, this study did not include an arm that was treated with clomiphene and it is unclear whether clomiphene would be more, equally or less effective than metformin in this subgroup of patients.

The conflicting findings of RCTs might be attributed to differences in the studied populations, including differences in the included PCOS phenotypes, testosterone levels,[43] BMI levels and duration of infertility.[36] Indeed, patients with profound hyperandrogenemia, morbid obesity and longstanding infertility have more severe abnormalities in ovulation and implantation.[44] Overall, it is clear that both the study by Legro et al.[36] and the more recent studies that compared metformin with clomiphene for the induction of ovulation in non-obese patients with PCOS[39,40] have limitations. However, it appears that metformin might represent an alternative option in this subgroup of patients.

THE ESHRE/ASRM GUIDELINES REQUIRE RECONSIDERATION

The aforementioned data suggest that the ESHRE/ASRM guidelines should be reconsidered.[37,38,40,41] This poses the question: in which patients with anovulatory PCOS should metformin represent the first-line treatment?

1. ***Metformin appears to be useful in patients with BMI within the normal range who have infertility due to anovulatory PCOS.***[13,27,40,41] Even though traditionally metformin is recommended in patients with PCOS and high BMI and the UK National Institute of Clinical Excellence guidelines recommended that combination therapy with metformin should be offered to clomiphene-resistant women with BMI >25 kg/m^2,[45] more recent data suggest that the response to metformin is more favorable in patients with PCOS and lower BMI.[40,42] It is well known that metformin acts by improving insulin sensitivity. However, this agent is not considered a potent insulin-sensitizer. Obesity is associated with IR and it is possible that when two causes of IR coexist (i.e. obesity and PCOS), the efficacy of metformin is suboptimal, whereas when there is only one cause of IR (i.e. normal weight patients with PCOS), metformin is more effective.[41]

2. ***Metformin, in combination with clomiphene citrate, is the treatment of choice in clomiphene-resistant patients with anovulatory PCOS.***[45-47] Clomiphene resistance is defined as the inability to achieve ovulation after two cycles of clomiphene administration at a dose of 150 mg/day for 5 days (2nd-6th, 3rd-7th, 5th-9th).[42] Clomiphene resistance is associated with IR. It is well established that IR plays an important role in the pathogenesis of PCOS. Metformin/clomiphene combination treatment is three to four times more potent than clomiphene monotherapy in increasing pregnancy rates in these patients with PCOS.[40,48,49] The percentage of patients with PCOS and clomiphene resistance ranges in the different studies between 15-40%.[50,51] In these patients, metformin/clomiphene combination induces ovulation in 62.5-77.7% of cases.[52-56]

Several mechanisms contribute to the induction of ovulation when metformin is combined with clomiphene in clomiphene-resistant anovulatory patients with PCOS: a) changes in intrafollicular steroidogenesis resulting from the effect of metformin on granulosa cells through an increase in insulin-like growth factor 1,[53] b) inhibition of androgen synthesis by the direct action of metformin on the interna thecal cells,[57] c) metformin-induced decrease in adrenal responsiveness to adrenocorticotropic hormone resulting in reduced adrenal steroidogenesis,[58] and d) reduction in serum LH and prolactin levels resulting from the effects of metformin on the hypothalamus-pituitary axis.[59]

The conventional method of ovulation induction in clomiphene-resistant patients with PCOS was administration of low doses of gonadotropins (starting daily dose of 37.5-75 IU and dose increase after 7 days if there was no follicle >10 mm). Ovulation rates with this method range between 85.2-90.9%. However, gonadotropins have a high cost and increase the risk for ovarian hyperstimulation syndrome and multiple gestation.[60-62]

3. ***The use of metformin in patients with PCOS who undergo multiple ovulation induction with gonadotropins in the course of IVF is a subject of controversy.***[63] It has been proposed that metformin/gonadotropin combination in patients with PCOS who are at high risk for ovarian hyperstimulation syndrome reduces the incidence and severity of the latter syndrome through an unclear mechanism.[64]

The duration of treatment with metformin for ovulation induction before the potential administration of clomiphene citrate is uncertain.[36,40,43,65] It has been reported that the reduction in serum androgen levels occurs soon, i.e. within a few weeks after the initiation of metformin treatment.[66] However, longer treatment is required for metformin treatment to reduce hyperinsulinemia and exert to a full extent its favorable metabolic actions and improve infertility. This interval ranges between three to six months.[2,13,27]

The role of androgens on follicular maturation is complex. Long-term (for several months) administration of dehydroepiandrosterone improves the recruitment of primordial follicles and the ovarian phenotype in patients with poor follicular reserve. The time period of exposure to the androgens appears to be important because androgens, acting synergistically with follicle-stimulating hormone, affect follicular maturation at the early stages of development, during which androgen receptors are present on the follicular granulosa cells.[67] Meanwhile in PCOS, the reduction in circulating androgens might also require some time to induce its effects since it must initially affect the small developing follicles that require weeks to months to reach ovulation.[13]

It is not entirely clear whether the favorable effects of metformin on fertility are due to the improvement in IR, to the reduction of circulating androgens or to both actions. Moreover, weight loss, which is observed

in some patients, might also partly contribute to the beneficial effect of metformin on fertility. However, it should be emphasized that the mechanism of action of metformin is not as yet entirely clear.[13]

The dose of metformin tested in different trials ranged between 1,000 and 2,500 mg/day (usual dose 1,700-2,000 mg/day).[2] It has been reported that weight loss in obese patients is achieved with higher doses. It should be mentioned that the dose of metformin should be higher in patients with BMI >25 kg/m^2.[68,69]

Metformin has certain advantages over clomiphene. Metformin does not affect endometrial thickness or the quality of cervical mucus.[70,71] In addition, regular follow-up is not required during treatment with metformin.[40,41] Moreover, metformin does not increase the risk for multiple gestation and reduces by three-fold the risk for preterm delivery,[72] which represents the leading cause of neonatal morbidity and mortality in developed countries.[73] Finally, metformin does not cause long-term side effects on the ovaries.[74,75]

The commonest adverse effects of metformin are mild and affect the gastrointestinal system.[13,40,41] These include abdominal pain, diarrhea, dyspepsia, flatulence and alterations in taste. However, it should be mentioned that metformin is well tolerated by the majority of patients and >90% adhere to treatment.[9,11]

CONCLUSIONS

In conclusion, it appears that the ESHRE/ASRM guidelines regarding the use of metformin for the induction of ovulation in patients with PCOS might have to be reconsidered.[76] Metformin appears to be useful in patients with PCOS and a normal BMI who present with infertility due to anovulation. Moreover, metformin/clomiphene combination is the treatment of choice in clomiphene-resistant patients with PCOS, i.e. it should precede the administration of gonadotropins. In addition, metformin reduces the incidence and severity of the ovarian hyperstimulation syndrome in patients with PCOS who undergo multiple ovulation induction in the context of IVF and have a high risk for this syndrome. However, it should be emphasized that more studies are needed to confirm the above recommendations and, more importantly, to determine the parameters that predict the efficacy of treatment with metformin.

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