PCOS and metformin: from pharmacology to clinical use for women’s health

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Abstract
Metformin is an old compound optimal for treatment of type 2 diabetes. Since when PCOS patients have been reported to have insulin resistance, metformin has been demonstrated to modulate several aspects of PCOS and to improve the most common cause of menstrual irregularity, anesthetisms and infertility. Metformin induces a better control of glucose uptake inducing a lower synthesis/secretion of insulin. Such effect permits to reduce insulin resistance which is the cause of the compensatory hyperinsulinemia typical in most but not all of PCOS patients. The positive control of metabolism has many positive effects on the hormonal patterns such as the restoration of menstrual cyclicity, ovulatory cycles and fertility since abnormal insulin levels affect the hypothalamus-pituitary-ovarian function as well as peripheral tissues use of glucose. The combination of an improved life-style with metformin treatment improves the impairments typically observed in hyperinsulinemic PCOS patients, reducing the possible evolution towards the metabolic syndrome and type 2 diabetes; and when pregnancy occurs, it consistently reduces the risk of gestational diabetes, eclampsia and hypertension. Though it might seem that metformin is the “optimal treatment” for PCOS patients, only hyperinsulinemic PCOS patients are those with higher chances to get the best results from metformin administration, mainly if diet and life-style are attentively combined.

Key words: PCOS, metformin, hyperinsulinemia, chronic anovulation, obesity, BMI, insulin resistance

Introduction
Metformin is quite an old compound introduced into clinical use in 1957. From the chemical point of view is 1,1-dimethylbiguanide hydrochloride, a biguanide currently used as an oral antihyperglycemic agent for diabetes mellitus. In these last 20 years, growing evidences occurred to demonstrate that a large percentage of PCOS patients with or without obesity, show insulin resistance and a reactive compensatory hyperinsulinemia and that the use of metformin is optimal not only in the presence of diabetes mellitus Type 2, but also in patients with PCOS and hyperinsulinemia, resolving several issues such as menstrual cyclicity, fertility, hormonal levels and metabolic syndrome (MS) [1].

PCOS characteristics
Polycystic ovary syndrome occurs in as many as 8-10% of women of reproductive age [2], with onset manifesting as early as puberty [3]. From the very beginning, diagnostic criteria proposed by the NIH for PCOS were the presence of hyperandrogenism and chronic anovulation with clear exclusion of related ovulatory or other androgen excess disorders (i.e., hyperprolactinemia, thyroid diseases, androgen-secreting tumors and adrenal dysfunction/ hyperplasia) [4]. These criteria did not include the presence of polycystic ovaries at ultrasound examination because it was observed that polycystic ovaries could also be present in healthy eumenorrheic women [5]. A few years later, during the European Society of Human reproduction and Embryology (ESHRE)/American Society for reproductive Medicine (ASRM) conference, the diagnostic criteria were expanded and PCOS was considered as present when at least two of three features were diagnosed: oligo or anovulation, clinical/ biochemical hyperandrogenism and polycystic ovaries as assessed by ultrasound examination [5]. This evolution was relevant because it permitted the inclusion of women with PCOS who were excluded by previous NIH criteria [4]: those with polycystic ovaries affected by hyperandrogenism and ovulatory cycles, or chronic anovulation and normal androgen levels.

More recently, the Androgen Excess and PCOS Society indicated that PCOS should always be considered an androgen excess disorder and concluded that PCOS was, above all, a disorder of androgen biosynthesis, utilization and/or metabolism in women [6].
Despite the diagnostic criteria, PCOS is still an unclear disease in terms of pathogenesis, and although the main clinical features related to the syndrome are menstrual irregularities, anovulation and clinical/biochemical signs of hyperandrogenism, PCOS patients frequently show other physiopathological characteristics. Recently it has been made clear that both genetic and environmental factors may contribute to the onset of PCOS features [7, 8]. On such genetic predisposition, environmental factors may play a key role, such as peculiar lifestyle, types of food, living conditions and also the impact during the intrauterine growth [8]. In fact, if intrauterine growth is characterized by an exposure to exaggerated androgen levels, this peculiar situation may lead to the development of hyperandrogenism and ovarian dysfunction later in life [8].

**Endocrine profile of PCOS patients**

Polycystic ovary syndrome is characterized by increased ovarian and adrenal androgens, increased luteinizing hormone (LH) levels, high estrogen levels (especially estrone) due to extraglandular conversion from androgens, lower levels of sex hormone-binding globulin (SHBG) and higher levels of insulin, the latter often in presence of overweight or obesity.

Hyperandrogenism is a key feature of the syndrome, although it is not constant [9]. It is mainly of ovarian origin with an adrenal contribution, since a certain percentage of PCOS patients might show a mild steroidogenic defect in adrenal glands (such as for 21-hydroxylase) or just a higher adrenal hyperactivation due to stress [10]. Androstenedione and testosterone are the best markers of ovarian androgen secretion, while dehydroepiandrosterone sulfate (DHEAS) is the best marker of adrenal secretion. Most testosterone is derived from peripheral conversion of androstenedione and from direct ovarian production. Dysregulation of cytochrome p450c17, the androgen-forming enzyme in both the adrenal glands and the ovaries, is the central pathogenic mechanism underlying hyperandrogenism in PCOS [11, 12]. In the presence of 5a-reductase, testosterone is converted within the cell to the more potent androgen dihydrotestosterone. Excess or normal 5a-reductase activity in the skin determines the presence or absence of hirsutism [13]. Additionally, estrone plasma levels, a weak estrogen with biological activity 100-times less than estradiol, are increased as a result of peripheral conversion of androstenedione by aromatase activity – more active in PCOS than in healthy controls – while estradiol levels are normal or low because of the frequent anovulatory cycles. All this results in a chronic hyperestrogenic state with the reversal of the estrone:estradiol ratio that might predispose to endometrial proliferation and to a possible increased risk for endometrial cancer [12, 14].

Normally, less than 3% of testosterone circulates as unbound in the serum. In fact, most circulating androgens are bound to SHBG, thus being biologically inactive. Any condition that decreases the levels of SHBG or other binding proteins can lead to a relative excess of free circulating androgens. In PCOS, hirsutism usually occurs with decreased SHBG levels and obesity [13, 15].

A great percentage of PCOS patients show overweight up to severe obesity, and typically any excess of weight can induce a reduction of peripheral tissues sensitivity to insulin, thus inducing the compensatory hyperinsulinism.

It is relevant to say that hyperinsulinemia may be central to the pathogenesis of the syndrome in many cases, because it can induce higher ovarian androgen production and anovulation [16, 17], sustained also by the abnormal LH secretion, with a higher frequency of menstrual abnormalities than in normoinsulinemic women with PCOS [18, 19]. Insulin resistance and compensatory hyperinsulinemia are metabolic disturbances easily observable in at least 45-65% of PCOS patients, and frequently appear to be related to excessive serine phosphorylation of the insulin receptor [11, 20].

**Metabolism & PCOS**

In PCOS patients, there is an increased risk of developing Type 2 diabetes and coronary heart disease (CHD) [21-23]. Such risk has also been demonstrated to be higher in postmenopausal women, previously demonstrated to be PCOS during fertile life [24, 25]. PCOS has been reported to have an increased risk of MS, which refers to a clustering within the same individual of hyperinsulinemia, mild-to-severe glucose intolerance, dyslipidemia and hypertension, and an increased risk for cardiovascular disease (CVD) and diabetes [26-28].

In 2006, the International Diabetes Federation defined the features of the MS, and defined central obesity as present when the waist circumference is above 80 cm; in European women, this was considered as a necessary prerequisite risk factor for the diagnosis of MS [29]. However, it is of great relevance to point out that although the MS has been identified for more than 80 years, only in these last years has controversy about its definition emerged [26].
The risk factors for MS are:

- Waist circumference is over 80 cm,
- Elevated triglycerides (≥ 1.7 mmol/l),
- Reduced HDL (< 1.29 mmol/l in women),
- Specific treatment for lipid abnormalities,
- Elevated blood pressure (systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg),
- Specific treatment or precedent diagnosis of hypertension,
- Fasting plasma glucose at least 5.6 mmol/l,
- Previous diagnosis of Type 2 diabetes mellitus.

The prevalence of MS in polycystic women is approximately 40-45% [30], and the main predictor factors are the elevated free serum testosterone and reduced serum SHBG level [31]. The association of MS with PCOS appears to be particularly strong in those PCOS women who are young (< 30 years) and overweight or obese (BMI > 27 kg/m²) [32].

Women with PCOS have lower HDL levels, higher LDL:HDL ratios and higher triglyceride levels than healthy eumenorrheic women [22]. All these are inducers of subclinical atherosclerosis as demonstrated by the increased thickness of the carotid intima media and by the higher endothelial dysfunction observed in PCOS patients [33, 34], probably related to the insulin resistance and/or to the higher free testosterone plasma level [35, 36].

Indeed, several studies reported an increased risk factor profile for cardiovascular disease in women with PCOS [37]. It is of great relevance the fact that women with PCOS have an increased risk for impaired glucose tolerance and Type 2 diabetes mellitus [38, 39], with a tendency to an early development of glucose intolerance state [40, 41]. In fact, the decrease of insulin sensitivity in PCOS women appears to be quite similar to that observed in patients with Type 2 diabetes mellitus and to be relatively independent from obesity, fat distribution and lean body mass [42]. On the other hand, there is strong evidence that obesity, particularly the abdominal phenotype, represents an important independent risk factor for glucose intolerance in PCOS women [39].

**Rationale of metformin use in PCOS women**

The logic for the use of insulin sensitizer drugs, such as metformin, to treat patients with PCOS is the fact that a large percentage of PCOS patients have been demonstrated to have insulin resistance and a compensatory hyperinsulinemia that negatively affect ovarian function in terms of steroid biosynthesis and follicular recruitment and maturation [7, 43, 44]. 45-65% of PCOS patients show insulin resistance and the compensatory hyperinsulinemia [7, 45], and this percentage is significantly higher than age- and BMI-matched healthy controls [46]. Obviously, when insulin resistance is present independently from obesity, whatever the weight gain that might occur, it certainly exaggerates insulin resistance and more severely alters the glucose metabolism and, later on, the hormonal profile.

It is important to remember that several studies reported that insulin modulates LH secretion from pituitary cells in vitro [40] and in vivo, and that the reduction of hyperinsulinemia induces the significant decrease of LH plasma levels [38, 47, 48], although it is not clear whether decreased LH levels are due to the reduced insulin levels or secondary to the recovery of ovarian function (i.e., estrogen production) induced by decreased insulin plasma levels [48].

Excess insulin increases androgen concentrations blocking follicular maturation and increasing cytochrome P450c17a activity, a key enzyme in the synthesis of both ovarian and adrenal androgens [7, 40]. This situation typically increases 17-hydroxyprogesterone (17OHP), androstenedione and testosterone plasma levels. The excess of intraovarian androgens negatively modulates follicular function and ovarian activity, thus inducing the typical stromal hypertrophy and maintaining ovarian atresia and anovulation [7, 49].

When abnormal insulin sensitivity is diagnosed, the use of metformin might be suggested [7, 50]. Metformin reduces hepatic glucose production from 9 to 30% and on peripheral tissues, such as muscle cells and adipocytes, metformin acts by increasing glucose uptake through the glucose transport system.

Patients with PCOS are insulin resistant and this condition typically decreases insulin’s ability to stimulate glucose disposal into peripheral cells and decreases the glucose response (i.e., glucose uptake by the cells) to insulin [7]. In addition, metformin positively acts on hormonal PCOS abnormalities through a direct and/or indirect action on steroidogenesis [7]. In fact, the recovery of normal ovulatory function is probably due to the direct modulation of metformin on the ovarian tissues and to the metformin-induced normalization of the ovarian steroidogenesis (lowering androgen production), thus determining the normal feedback on pituitary, lowering LH secretion and LH pulse characteristics [47, 48]. Metformin improves steroidogenesis not only at the ovarian, but also at the adrenal level, since insulin plays specific modulatory roles on these two distinct
endocrine glands that have the same enzymatic pathways [51, 52]. In fact, it has been demonstrated that metformin administration ameliorates adrenal enzyme activities in PCOS patients [53].

A recent meta-analysis of the published studies demonstrated that the use of insulin sensitizers do not reduce hyperandrogenism better than oral contraceptives [54], but as recently reported, the typology of PCOS to be treated is of great relevance, since only when insulin sensitivity is abnormal metformin shows a greater efficacy on all the PCOS features, including hyperandrogenism [48]. Obviously, it cannot be excluded that other metabolically active hormones (e.g., leptin, resistin, adiponectin and ghrelin) are positively activated by metformin administration and thus participate in the improvement of the reproductive function at the hypothalamic-pituitary-ovarian level [55]. However we have to remember that metformin effectiveness on reproductive and on metabolic parameters is mainly exerted in association with a reduction of circulating insulin levels, thus supporting the hypothesis that a high insulin level is one of the main effectors/modulators of the clinical and endocrine dysfunctions of PCOS [7, 56].

**Metformin therapeutic regimens**

The therapeutic dose of metformin cannot be standardized. Since its main indication is to treat diabetes, most of the dosages have been set according to the levels of glycemia achieved with the treatment, and the amount of metformin administered may vary from 500 to 1500 mg or more per day [7]. On the contrary, an extremely variable dosage has been used to treat PCOS, but up to now, no dose-finding study is available for PCOS, probably because there are various end points and goals for PCOS patients to reach, such as the recovery of menstrual cyclicity and of ovulation, loss of weight, reduction of hirsutism and skin defects. It is, however, important to point out that clinical studies clearly demonstrated that after long-term metformin treatment, drug suspension induces a quick reversal of the beneficial effects on peripheral insulin sensitivity [7, 57]. In addition, because recent data showed that better clinical results were obtained in insulin-resistant rather than in non-insulin-resistant PCOS patients [48], a clear adjustment of the dose of metformin must be performed according to the BMI and insulin resistance. The treatment must be started with a low dose, administered few minutes before lunch and dinner (10-15 min before), because an empty stomach minimizes the possible drug-related side effects [7], and only after 3-7 days can it be increased, slowly, up to the most effective dosage for the patient, as reported by Nestler [58, 59].

The known side-effects, although very limited in incidence, are abdominal discomfort, constipation, diarrhea, flatulence, heartburn, indigestion, nausea and vomiting [7, 60]. It is relevant the fact that the patient needs to help metformin modulation(s) on the metabolic side following all the advices concerning feeding and weight control. The experience suggests that metformin positively affects the metabolic problems of hyperinsulinemic, overweight/obese women together with a low caloric diet and a minimum of physical activity. Since metformin modulates insulin sensitivity, it works perfectly to restore insulin sensitivity within the normal ranges, and this usually happens when physical activity and loss of weight also induce the reduction of peripheral tissue insulin resistance together with metformin action [82]. However, it should be noted that previous data demonstrated that withdrawal of metformin treatment can be followed within 3 months by a reversal toward a pretreatment hyperinsulinemic state [57, 61, 62].

Recent data suggest that metformin is more effective in insulin-resistant PCOS patients, with normal BMI, probably because some constitutional abnormality might be at the basis of the insulin resistance. Nevertheless, overweight (but not necessarily obesity) remains a feature that represents a strong indicator of good results when coupled with insulin resistance [53, 47], since a recent report showed equal response to metformin in those who were lean and obese [63]. However, it is interesting to point out that lifestyle changes have been demonstrated to be more effective in preventing diabetes risk and MS than treatment with metformin [64] and that metformin suspension induced a certain percentage of reversion of the beneficial effects on insulin sensitivity and on hyperandrogenism, and is probably related to the simultaneous worsening of both the ovarian function and the menstrual cyclicity [7].

In our opinion, the positive effects induced by metformin administration can be maintained when treatment is prolonged over the time (up to 12 months or more) and it is combined with a controlled diet and with moderate physical activity to aid metabolism and weight loss, especially when overweight or obesity is present [1, 65].

**When is metformin usefull?**

Metformin shows beneficial effects according to the clinical characteristics of the patient, and the more of these features present at the same time, the higher the chance of metformin treatment being effective [86].
**BMI**

Body weight, evaluated as BMI, is a fundamental characteristic. The higher the BMI is the higher the amount of fat is present triggering a compensatory hyperinsulinism. Unfortunately, this is not a general rule; it is valid for overweight or obese patients only. In fact, several studies reported that a certain percentage of PCOS patients as well as a certain percentage of the normal population have constitutional insulin resistance concomitantly with a lean body mass [7, 66, 67], and when patients were treated independently from the BMI, all of them demonstrated a beneficial effect in insulin plasma levels, insulin sensitivity and in AUC for insulin under the OGTT [66]. Our data demonstrated a great efficacy of metformin administration in non-obese PCOS patients, mainly in those with abnormal insulin response to OGTT and/or fasting hyperinsulinism [48]. These data let us infer that the ability to be sensitive to insulin is probably a real constitutional aspect; every patient has their own and it is worsened when BMI increases.

**Insulin sensitivity/resistance**

This is the most important feature. Metformin has more indications for PCOS patients with high basal insulin levels and/or with abnormal response to the OGTT [48], independently from BMI. Only insulin-resistant individuals may benefit from metformin administration in terms of both insulin sensitivity and of insulin-induced metabolic and hormonal functions [7, 48].

**Androgen excess**

In general, hyperandrogenism is a common feature of PCOS patients and cannot be considered a predictor of metformin efficacy. However, since hyperinsulinism might be a relevant trigger of anovulation and oligomenorrhea, it can be argued that the combination of menstrual irregularities, hyperandrogenism and anovulation can be positively affected by metformin administration.

**Waist-to-hip ratio**

The presence of overweight or obesity is certainly a risk factor for CVD in PCOS patients, and it is of great importance to state that a high waist-to-hip ratio (> 0.8) specifically indicates a greater amount of fat at the abdominal level, which is the typical android distribution [68].

**Genetic factors**

For sure, environmental factors (such as lifestyle and feeding) deeply condition the occurrence of overweight or obesity as well as of compensatory hyperinsulinemia. However, this cannot be extended to all PCOS patients. Recent data clearly reported that there are several kinds of genetic situations that are the genetic causal triggers or might just be the starting triggers if combined with predisponent environmental factors [7, 8]. It is important to observe that ethnic background is probably relevant as these genetic factors, since PCOS and/or mild-to-severe hyperandrogenism are more frequent in some populations than in others, as well as the incidence of metabolic diseases (i.e., diabetes Type 2), quite often mirroring a greater use of carbohydrates in the diet [68].

**What metformin can ameliorate**

From the clinical point of view it cannot be stated that metformin is the treatment for PCOS patients, but it is rather important to underline that metformin can be of great relevance when two or more of the aforementioned possible predictors are present [7]. Let’s see what metformin can improve.

**Effects on menstruation**

80% of PCOS have oligomenorrhea or amenorrhea and oligoovulation or anovulation [69, 70]. Metformin administration was reported to restore normal menstrual cyclicity in a high percentage of the patients affected by oligomenorrhea or amenorrhea [53, 71, 72], but was less effective than oral contraceptives [73, 74] since it acts through a specific effect on metabolism and on the reduction of hyperinsulinemia.

**Effects on fertility**

The fact that metformin improves metabolism, resolves hyperinsulinemia and all hormonal impairments induced by this latter, explains how it might be possible a specific effect of metformin on fertility. Recent reviews and data clearly reported that metformin is not better than clomiphene citrate (CC) to induce ovulation [61, 75-77], but it is fundamental to remember that these two compounds are affecting the hormonal profiles in completely different ways! It is important to remember that metformin and CC have completely different mechanisms of action, and metformin may act on the reproductive axis as a secondary hormonal effect, mainly related to the improved (i.e., lowered) insulin plasma levels and insulin resistance [7, 58, 59]. In fact, while metformin acts on insulin pathways, CC acts directly on the reproductive axis. Clinical data suggested that hyperinsulinemia and insulin resistance could be responsible for the ovarian abnormal response occurring in OHSS.
Although no clear evidence has been provided, hyperinsulinemic PCOS patients undergoing metformin administration before and/or during ovarian stimulation for the search of spontaneous pregnancy or IVF might benefit from metformin administration.

**Effects on hyperandrogenism**

Improvement of ovarian function under metformin treatment determines a relative improvement of hyperandrogenism and its clinical signs, such as acne and hirsutism. In general, hyperandrogenism and its signs are reduced by metformin administration because it reduces ovarian androgen production, ovarian P450c17a activity and free testosterone concentration [7], and within few months it also reduces the Ferriman–Gallway score [47, 48].

**Effects on body weight**

Metformin treatment and lifestyle intervention have been reported to be more effective in reducing body weight, BMI and visceral fat in obese subjects than lifestyle intervention alone [50, 65]. This means that metformin cannot be considered a specific antiobesity drug because lifestyle changes and a balanced diet together with physical activity are fundamental to metformin co-treatment and might improve the chances of success [79, 80]. However, it is of relevance to point out that metformin has been demonstrated to improve body weight control in obese PCOS patients by acting both directly on the CNS and indirectly via adiponectin modification [81], but in general it has a marginal effect on weight loss as monotherapy, as recently reviewed by Palomba et al., who stated that lifestyle modifications remain the cornerstone for weight loss in obese PCOS patients, although metformin cotreatment might improve the efficacy [7].

**Effects on the risk of Type 2 diabetes & CVD**

PCOS patients with insulin resistance have a higher risk for developing Type 2 diabetes [50, 80]. The prevalences of insulin resistance and diabetes in PCOS patients, especially if they are obese, is approximately 30-40% and 5-10%, respectively, and this is three- to seven-fold greater than the normal population [82, 79]. Since the incidence of cardiovascular diseases is quite high in diabetics, it has to be seriously considered that PCOS patients might also be exposed to a higher risk of CVD and/or its precursors such as hypertension [83, 37], since they are at a higher risk for diabetes than the normal population. This fact is enforced by the demonstration that both hyperandrogenism and impaired peripheral insulin sensitivity may increase the risk of CVD [84, 85], although prospective controlled data on CVD morbidity and mortality in PCOS patients has never been attentively evaluated.

**Effects on pregnancy & on risk of miscarriage**

Patients with PCOS are likely to develop gestational diabetes in 30-40% of cases [86, 87], with a higher chance than normal pregnant women [88]. Various data also demonstrated that metformin use during pregnancy reduced the risk of gestational diabetes through the reduction of preconceptional BMI, fasting insulin levels and insulin resistance [87, 89]. Various reports confirmed the efficacy of metformin treatment in PCOS pregnant women reducing significantly the risks of gestational diabetes [89-92] and of preeclampsia [93], although others did not show beneficial effects on miscarriage risk [76]. Although such data are of extremely great clinical relevance, not all of the reports studied large populations or were a placebo-controlled study. In any case, a recent meta-analysis confirmed that there is no difference in abortion risk in PCOS patients undergoing metformin treatment before pregnancy when compared with normal population [94, 95]. However, the safety of metformin administration during pregnancy was attentively evaluated, and no congenital abnormalities or adverse fetal outcomes were related to metformin [96, 97]. Moreover, no negative effects on growth, motor and social development in infants were reported when metformin was administered to PCOS women during the first months of breast feeding [97-99].

**Effects on mood & quality of life**

Last but not least, one important aspect is the quality of life. PCOS patients have been demonstrated to perceive life significantly worse than healthy controls or other patients affected by other diseases [100]. In general, women are nearly twice as likely to experience major depressive disorders as men [101], but it is of great interest to report that several studies suggest quality of life, body age concerns and sexual dissatisfaction in PCOS [100-103], as well as a high degree of occurrence of depressive state [104]. Obesity, clinical signs of hyperandrogenism (acne, hirsutism and alopecia) and infertility seem to be the main elements on which such great psychosocial discomfort find basis [105, 106], and when an adequate treatment improved all such features, quality of life and well-being improved again [107]. Interestingly, such a positive effect was also observed.
under metformin administration. Indeed, a significant improvement of quality of life in PCOS patients, especially for the psychological aspects, occurred and interesting correlations were observed between the clinical effects of metformin and the psychological improvement [108]. The reason for such a positive effect on the impaired psychological trait of PCOS patients seems to be related to the metformin-induced effects on neurosteroid synthesis and secretion, especially allopregnanolone.

The high frequency of anovulatory cycles in PCOS patients and the lack of adequate endogenous allopregnanolone production might be responsible for the aforementioned psychological state and depressive mood. Interestingly, when these PCOS patients were treated with metformin, allopregnanolone plasma levels increased [109]. At the basis of this effect there are the metformin-induced changes on insulin, on the local ovarian and adrenal environment and on the reproductive axis. The increase of allopregnanolone production and synthesis from its precursors and from endocrine tissues [109] might explain the efficacy of metformin treatment on PCOS quality of life [108].

In conclusion, the clinical use of metformin might be suggested in women with PCOS and abnormal insulin sensitivity. Metformin has been reported to induce positive modulation on peripheral tissues, improving metabolism and insulin sensitivity. The reproductive axis benefits the reduction of the insulin resistance since these facts restore a more efficacious recovery of the endocrine function of the ovary as well as of the hypothalamus-pituitary endocrine control. At the same time, metformin-induced insulin sensitivity counteracts the chance of being at risk of Type 2 diabetes and counteracts the negative effects of hyperinsulinism, hyperandrogenism and obesity on body health.

References


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