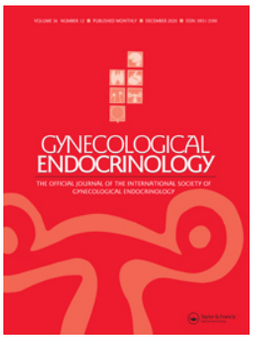

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EDITORIAL

Inositols: reflections on how to choose the appropriate one for PCOS

Although the polycystic ovary syndrome (PCOS) is clinically defined by the presence of at least 2 out of 3 Rotterdam Consensus Conference criteria (i.e. hyperandrogenemia, oligo/amenorrhea, polycystic ovaries upon ultrasound), recently insulin resistance (IR) has been reported as new feature of the syndrome, being more frequent in overweight/obese patients but also occurring among PCOS women with normal weight [1]. IR is due to the reduction of tissue sensitivity to the glucose plasma levels thus requiring higher insulin levels to stimulate glucose upload into the cells in order to maintain a normal glycemia.

The relevance given to IR is due to the fact that it is central for the onset of the metabolic syndrome (MS), both in young adults as well as in older women [2]. In addition is associated to many health risks such as diabetes, hypertension, stroke, etc. These risks are related to the onset of the MS if no prevention is applied in terms of lifestyle and treatment [2]. It is now clear that PCOS patients, especially those with IR, have at least twice the incidence of the MS than the normal population [3].

In these last 20 years, a number of evidences have suggested that the use of insulin sensitizers, especially metformin, might be absolutely of help not only for individuals with MS but also those with PCOS and IR [4]. The real problem related to the use of metformin is the fact that it induces a number of gastrointestinal side effects when given at doses as high as 2–3 gr/day, situation that determines a high percentage of drop out among patients, especially obese ones that were supposed to benefit greatly from the treatment.

As a putative solution, with no such side effects, the integrative treatment using inositols was proposed. Inositols are a large family of nine stereoisomers belonging to a sugar alcohol family. Practically, inositols have the same chemical structure of glucose and once entered in the cells they provide the structural basis for inositol phosphates, important secondary messengers and relevant components of the structural lipids phosphatidylinositol and phosphatidylinositol phosphate [5]. Among the nine isomers myo-inositol (MYO) and D-chiro-inositol (DCI) have been demonstrated to have good therapeutic effectiveness in PCOS patients and no side effects [6]. Since the use of both inositols for treating PCOS is quite widespread, a better understanding about this treatment option is needed.

Recently, reviews and expert's point of view have defined the importance not only of the appropriate use of these inositols but also how relevant is the anamnestic investigation to select which is the most appropriate [1,7]. In fact, in human biology both MYO and DCI are needed since both play specific important roles over glucose metabolism. Once in the cell, MYO is transformed into phosphatidyl-myo-inositol and then into inositol-triphosphate that is the post receptor messenger for insulin as well as for FSH and TSH [8,9]. DCI is created from MYO conversion through a specific enzyme named epimerase [10]. MYO activates the uptake of glucose through GLUT4-vesicles location on the cell membrane; whereas DCI, through other pathways, induces the storage of glucose as glycogen and induces energy production from glucose (inside the mitochondrion) through oxidative processes [1].

These events decrease glucose concentration inside the cytoplasma and create a gradient of concentration that allows a higher flow of glucose from outside the cell. It is evident that if both isomers are present, the control of the glucose homeostasis is improved as well as insulinemia. These combined activities are in perfect equilibrium if the epimerase permits the appropriate production of DCI.

Recently it has been demonstrated that patients with familial diabetes (i.e. first-degree relatives) and/or being diabetic show an altered urinary MYO-to-DCI ratio that suggests an abnormal reduced expression/synthesis of the epimerase enzyme thus impairing the MYO conversion to DCI [11,12]. Such fact is supported by the observation that not all PCOS patients show reduction of the hyperinsulinemia under oral glucose tolerance test (OGTT) when administered MYO [13]. Moreover, when DCI was administered alone, it was effective in reducing the hyperinsulinemic response in all PCOS subjects, especially in those with familial diabetes [14].

These data support the evidence that DCI administration reduces IR, restoring almost normal insulin sensitivity and that epimerase is the 'weak point' of the enzymatic cascade that regulates DCI synthesis from MYO, suggesting that predisposition to diabetes negatively modulates insulin sensitivity in PCOS women due to the impaired DCI synthesis.

Clinically speaking, aside evaluating hormonal, metabolic profiles and insulin response to OGTT among PCOS women, performing an appropriate familial anamnesis, and that of the intrauterine and postnatal life, assumes a relevant importance. In fact, being born with intrauterine growth restriction or small-for-gestational age, or from a pregnancy complicated with gestational diabetes, predisposes greatly to a defensive hyperinsulinemic state that protects the newborn and allows a recovery of body weight. If such event occurs, the compensatory hyperinsulinemia is triggered, especially in the case of a female, predisposing to a subliminal IR and not only to a PCOS but to a great variety of dismetabolic diseases that might impair the health and the quality of life if not resolved early [15].

According to all these observations, avoiding metformin administration, the integrative approach to IR in PCOS women using inositols seems to be an optimal solution since MYO appears to be proper for all PCOS patients with no familial diabetes, while DCI results adequate in case of PCOS women with familial diabetes, being also useful in general to all PCOS cases [6,14]. It is obvious that everyday life style rules are needed especially if overweight and/or obesity are present.

In addition, recently it has been pointed out that, being inositols chemically and structurally similar to glucose, they compete with glucose for intestinal absorption especially if administered during meals [16]. For this reason whatever inositol is prescribed, it has to be taken far from breakfast and lunch. Moreover, exactly for the same reason, combinations of MYO and DCI should be avoided, since both compete to be absorbed in the intestine [17] and probably only administering higher dosages of both compounds can an adequate absorption be granted. From what has been exposed in turns out that inositols are really

useful integrative tools for the prevention of IR and the occurrence of the MS in PCOS women, if chosen properly.

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