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Fasting as possible complementary approach for polycystic ovary syndrome: Hope or hype?

Benito Chiofalo [a,b,*], Antonio Simone Laganà [a], Vittorio Palmara [a], Roberta Granese [a], Giacomo Corrado [b], Emanuela Mancini [b], Salvatore Giovanni Vitale [a], Helena Ban Frangež [c], Eda Vrtačnik-Bokal [c], Onofrio Triolo [a]

[a] Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy
[b] Department of Surgical Oncology, Gynecologic Oncology Unit, "Regina Elena" National Cancer Institute, Rome, Italy
[c] Department of Reproduction, University Medical Center Ljubljana, Ljubljana, Slovenia

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine system disorder among women of reproductive age. In several cases, PCOS women show infertility or subfertility and other metabolic alteration, such as insulin resistance (InsR), dyslipidaemia, hyperinsulinemia and obesity. Despite the aetiology of the syndrome is still far from be elucidated, it could be considered the result of concurrent endocrine modifications, lifestyle factors and genetic background. In particular, accumulating evidence suggests that InsR and compensatory hyperinsulinemia play a pivotal pathogenic role in the hyperandrogenism of many PCOS phenotypes, which in turn have a clear detrimental effect on chronic anovulation.

Different forms of fasting, such as intermittent fasting (IF, including alternate day fasting, or twice weekly fasting, for example) and periodic fasting (PF, lasting several days or longer every 2 or more weeks) are currently being tested in several *in vitro* and *in vivo* studies. Changes in the circulating levels of Insulin Growth Factor-1 (IGF-1), Insulin-like Growth Factor-Binding Protein 1 (IGFBP1), glucose and insulin are typical effects of fasting which may play a key role on aging and metabolic homeostasis.

Considering the paramount importance of InsR and compensatory hyperinsulinemia, different fasting regimens can reduce IGF-1, IGFBP1, glucose and insulin levels and consequently have beneficial effects on ovarian function, androgen excess and infertility in PCOS women.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder among women of reproductive age, first described in 1935 by Stein and Leventhal [1]. According to Rotterdam criteria proposed by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM), PCOS in characterized by the presence of two out of following parameters: oligo-anovulation, hyperandrogenism (clinical or biochemical), presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or an increased ovarian volume (>10 ml) [2]. In several cases, PCOS women show infertility or subfertility and other metabolic alterations, such as insulin resistance (InsR), dyslipidaemia, hyperinsulinemia and obesity [3]. Despite the aetiology of the syndrome is still far from be elucidated, it could be considered the result of concurrent endocrine modifications, lifestyle factors and genetic background [4]. In particular, accumulating evidence suggests that InsR and compensatory hyperinsulinemia play a pivotal pathogenic role in the hyperandrogenism of many PCOS phenotypes, which in turn have a clear detrimental effect on chronic anovulation [5]. Specifically, hyperinsulinemia acts synergistically with luteinizing hormone (LH), enhancing androgen production by theca and adrenal cells [6]. In addition, hyperinsulinemia decreases Sex Hormone Binding Globulin (SHBG) production with consequent increase of circulating (active) androgens, stimulates hypothalamic pulse generation with increase of LH synthesis and, finally, enhances Adrenocorticotropic Hormone action which causes an increase of adrenal androgens secretion [7].

In ovaries, insulin binds Insulin Growth Factor-1 (IGF-1) receptors: for this reason, these organs are not insulin-dependent and, consequently, are not affected by systemic InsR [8].

Assuming a broad spectrum, PCOS can be categorized into four main phenotypes [9]: type A, characterized by hyperandrogenism,

* Corresponding author at: Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy.
E-mail address: benitochiofalo@aol.com (B. Chiofalo).

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chronic anovulation and polycystic ovaries; type B, defined by hyperandrogenism and chronic anovulation; type C, with hyperandrogenism and polycystic ovaries; type D, characterized by chronic anovulation and polycystic ovaries. Although this classification does not include metabolic disturbance as the abovementioned hyperglicemia and compensatory hyperinsulinemia, the two conditions seem to be prevalent among type A patients (frank or classic PCOS) [10]. As widely accepted, early diagnosis and weight loss may contribute to reduce the risk of long-term complications, such as type 2 diabetes and heart disease, in PCOS women [11].

To date, several therapeutic strategies have been proposed for the treatment of PCOS, although some of them are focused only to ameliorate symptoms and signs: on one hand, antiandrogenic drugs (including progestins with antiandrogenic characteristic in combined oral contraceptives) are used to treat acne and hirsutism; on the other hands, ovulation inducing agents are used to treat infertility. Based on the accumulating evidence about metabolic disturbances in PCOS women, in the last years insulin-sensitizers gained increasing popularity: apart the already demonstrated efficacy of metformin [12], both Myo-Inositol and D-Chiro-Inositol proved to be effective in re-addressing metabolic and hormonal parameters to the homeostasis [13,14], alone or in combination with other nutraceuticals [15,16].

Different forms of fasting, such as intermittent fasting (IF, including alternate day fasting, or twice weekly fasting, for example) and periodic fasting (PF, lasting several days or longer every 2 or more weeks) are currently being tested in several *in vitro* and *in vivo* studies and gained significant media attention [17,18]. Despite metabolic disturbances are key elements of PCOS pathophysiology, to the best of our knowledge there is not a robust study which investigated the possible role of IF or PF in this syndrome, apart a very limited report about Ramadhan Fasting [19].

The hypothesis

Considering the available evidence, we hypothesize that fasting may ameliorate PCOS-related symptoms and signs and have a beneficial role in preventing medium- and long-term complications, especially in patients affected by InsR and compensatory hypersinsulinemia.

Evaluation of the hypothesis

Regarding IF, various terms are currently used for this style of diet, including "alternate-day fasting" and "5:2 diet" [17]. Its effect on disease prevention and lifespan has been studied mainly in rodent models, using a range of experimental protocols from alternate fasting (the so-called "every other day fasting") to 3 weeks of partial energy restriction and subsequent refeeding. In these studies, IF appears equally or more effective than isoenergetic continuous energy restriction in improving insulin sensitivity [20], preventing spontaneous or genetically engineered mammary tumours [21,22], delaying the onset of prostate cancer [23], increasing resistance to neuronal damage [20], reducing cognitive impairment [24], protecting cardiovascular system [25] and increasing lifespan of rodents [26]. PF is more effective in reversing multiple features of the metabolic syndrome in humans: it enhances insulin sensitivity, stimulates lipolysis and reduces blood pressure [27]. In addition, observational studies and some randomized trials [28–30] indicate that modest weight reduction (>5% of body weight) reduces the incidence and progression of many diseases, including diabetes, cardiovascular and neurological disorders.

Changes in the circulating levels of IGF-1, Insulin-like Growth Factor-Binding Protein 1 (IGFBP1), glucose and insulin are typical effects of fasting which may play a key role on aging and metabolic homeostasis [27]. In particular, IGF-1 is the major growth factor in mammals and acts in combination with insulin to promote aging and the progression of other diseases, including a potential detrimental role in cancer [31–33]. Recent data suggest that fasting for 3 or more days causes 30% or more reduction of circulating insulin and glucose levels, as well as rapid decrease of IGF-1 [34]. In addition, different fasting regimens, reducing IGF-1, IGFBP1, glucose and insulin levels, may have beneficial effects on ovarian function: corroborating this hypothesis, it was recently found that women affected by PCOS have an increased endometrial expression of IGF1 and IGFBP1, which orchestrate the insulin signalling pathway [35]. Considering the paramount importance of InsR and compensatory hyperinsulinemia in inducing androgen excess in PCOS women, fasting may improve also hyperandrogenism-related symptoms and signs. In addition, weight loss reduces adipose tissue and may negatively modulate the conversion of androgens in oestrone: in this was, fasting may reduce the hypothalamic and hypophyseal dysregulation, which underlie subfertility in PCOS women.

Considering the four different PCOS phenotypes, probably IF or PF may have the most marked effects in type A (frank or classic PCOS), since these patients are most often affected by InsR and metabolic disturbances, but also the other PCOS phenotypes could benefit of fasting regimens. Although several studies investigated the correlation between insulin signalling pathways and fasting, current data are still not so robust to suggest a clear fasting regime for PCOS patients. Nevertheless, considering that most of the abovementioned fasting-related modifications occur through epigenetic modulation of key genes which regulate the metabolism [36], probably the PF regimen may have more robust effects in the medium and long-term in PCOS women.

Consequences of the hypothesis and discussion

To the best of our knowledge, data about ovarian function after fasting (IR or PF) are still lacking, even in the animal models. Although IR and PF do not cause common or severe adverse effects, the studies in humans should be performed under careful medical control, checking in particular basal and under-treatment glycaemia, plasmatic insulin and IGF-1. About this point, it is necessary to stress that compliance of the patients would be fundamental, since IF or PF may have positive effects only with a strict and accurate adherence to the proposed alimentary regimen. In this view, we solicit future observational studies with adequate statistical power, which may clarify the effects of IF, or PF in women with different PCOS phenotypes. Finally, it would interesting to compare the efficacy of fasting regimens and usual insulin sensitizers in randomized controlled trials and, last but least, to evaluate the combination of fasting with common pharmacologic strategies in PCOS.

Conflict of interest

The authors have no proprietary, financial, professional or other personal interest of any nature in any product, service or company. The authors alone are responsible for the content and writing of the paper.

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