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THE RESUMPTION OF MENSES TROUGH REDUCTION OF WEIGHT AND TREATMENT WITH METFORMIN TO A YOUNG GIRL WITH THE POLYCYSTIC OVARY SYNDROME – CASE REPORT

Ana Raluca Memu [1,✉]***, Mihaela Mîţoaica*** [2]***, Ioana Zosin*** [3]***, Gabriela Negrişanu*** [3]

[1] The County Emergency Hospital, Drobeta Turnu Severin
[2] "Prolife" Clinic, Drobeta Turnu Severin
[3] The University of Medicine and Farmacy "Victor Babeş", Timişoara

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Abstract

Objectives: *We aimed to evaluate the effect of reducing body weight by optimization of lifestyle and the utility of metformin association to a young obese woman with polycystic ovary syndrome (PCOS).* ***Material and Method:*** *A young obese woman diagnosed with PCOS (with amenorrhea at the time of the first visits) received a caloric restrictive diet for three months. After this period, metformin was associated.* ***Results:*** *After 3 months, just by optimization of lifestyle, weight loss was 4 kg, but amenorrhea remained. It was considered useful the association of 3x500mg/day of metformin. After another 3 months, in addition to decrease weight by up to 6 kg, the patient has regained menstruation, but the appearance of the ovaries has remained unchanged.* ***Conclusions:*** *The first therapeutic intervention to obese women with PCOS is lifestyle optimization. Association of metformin can bring additional benefits.*

key words*: polycystic ovary syndrome, obesity, amenorrhea, diet, metformin.*

Background

PCOS is characterized by disordered ovulation, usually resulting in oligomenorrhea or amenorrhea and diminished fertility, and hyperandrogenism, usually resulting in hirsutism, acne, or male pattern scalp hair loss [1]. Women with PCOS may be lean or obese, but obesity occurs about 2 times more frequently in women with PCOS than in control subjects with normal ovulation [2,3]. Recent studies have documented considerable insulin resistance (IR) in young women with PCOS; 40% of obese women with this disorder have impaired glucose tolerance or type 2 diabetes mellitus (DM) by the age of 40 years [4]. The IR is not attributable to obesity alone. Thin women with PCOS have appreciable IR as well, but obese women with the disorder are more insulin resistant than are their weight-matched normal-ovulating counterparts [5].

Metformin has been shown in several studies to improve insulin sensitivity, lower

✉ Drobeta Turnu Severin, Călăraşi Str. No. 22; *corresponding author e-mail: raluca_grecuus@yahoo.com*

androgen levels, and to induce menstrual cyclicity in adults [6, 7].

Here, we report a case of a young obese woman with PCOS who has been treated with diet and metformin and who has been lost weight and has been recovered the menses.

Material and Method

A 21 year old woman was admitted for investigation following the diagnosis of PCOS by gynecologist 2 months earlier. The patient was the second child in her family. Her mother had gestational DM, is obese and has arterial hypertension, dislipidemia and impaired fasting glucose (IFG). Her father has type 2 DM. Her older sister is obese and has IFG. The patient started a marked weight gain from 6 years of age. Menarche occurred at the age of 14, but she developed secondary amenorrhea soon thereafter.

She weighed 102 kg and is 165 cm tall (body mass index (BMI) was 37.5 kg/m^2). The waist circumference (WC) was 124 cm and the hip circumference (HC) was 125 cm (waist-to-hip ratio (WHR) was 0.99). Her blood pressure was 110/75 mm Hg. The patient was hirsute (Ferriman-Gallway score 10). She had no acne and no acanthosis nigricans.

Serum testosterone (T) was elevated, sex hormone binding globulin (SHBG) was reduced (Table 1), while follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), 17-OH progesterone levels remained normal. Also baseline serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), prolactin and 24-h free urinary cortisol were within normal limits. Serum transaminases and creatine were normal.

The patient had a normal fasting blood glucose with a normal blood glucose during an oral glucose tolerance test (OGTT). The serum lipid profile was normal.

Table 1. Baseline serum values of T and SHBG

	Serum value	Reference range
T (ng/ml)	1.19	0.13-1.08
SHBG (nmol/l)	17.9	19.8-155.2

Transabdominal ultrasound showed bilateral polycystic ovaries. The right ovary's volume was 11,3 ml and the left ovary's volume was 10,8 ml.

Secondary amenorrhea with hirsutism and an elevated T level, toghether with the appearance of polycystic ovaries on ultrasound established the diagnosis of PCOS according to the Rotterdam criteria: clinical or metabolic hyperandrogenism, oligo or anovulation, the echographyc critera of polycystic ovary (ovarian volume over 10 ml or the existence of more than 12 follicles on each section) [8, 9].

She was evaluated from the nutritional point of view. The caloric necessary was calculated based on the Harris-Benedict formula regarding the basal metabolism [the rate of the basal metabolism (RBM)= 655 + (9.6 X corporal weight in kg) + (1.8 X height in cm) – (4.7 X age in years)] [10]. She was advised to have a balanced hypocaloric diet with a 600 kcalories restriction in contrast with the ideal caloric necessary and to increase physical activity. After 3 months she has been reevaluated, weighed and the BMI has been recalculated [11, 12].

Results

The patient lost 4 kg and BMI was 36 kg/m^2 after 3 months of caloric restain and

increased physical activity. Menses didn't occure at that moment and the ultrasonographic images were unchanged. Metformin 1.5 g/day (500x3 p.o.) was added in order to induce menses. After another 3 months she lost 6 kg more and she recovered the menses.

Presently, 6 months after the initial presentation, the patient remains on diet, physical activity and 1.5 g/day of metformin. She is still obese (BMI=33.8 kg/m^2, WC=121 cm, HC=123 cm, WHR=0.98). The fasting blood glucose, OGTT and lipid profile are normal, T and SHBG values are in normal range, but the morphology of the ovaries didn't change (Table 2).

Table 2. The comparison of the parametres initially and after 6 months

	Initially	After 6 months
Weight (kg)	102	92
BMI (kg/m^2)	37.5	33.8
WC (cm)	124	121
HC (cm)	125	123
WHR	0.99	0.98
T (ng/ml)	1.19 (↑)	1.05 (normal)
SHBG (nmol/ml)	19.23 (↓)	20.18 (normal)
Lipid profile	normal	normal
Fasting plasma glucose (mg%)	88 (normal)	86 (normal)
OGTT	normal	normal
Ovarian ecographic morphology	polycystic	polycystic

Discussions

The Rotterdam 2004 Consensus Workshop [8] proposed that PCOS is a syndrome of ovarian dysfunction, and recommended that two of the following criteria should be present to establish a diagnosis: chronic oligo- or anovulation for more than 6 months, clinical and/or biochemical evidence of hyperandrogenism, and polycystic ovaries on ultrasound. Other disorders that mimic the PCOS phenotype should be excluded. The criteria for PCOS were fulfilled in this patient. She was amenorrhoic and had clinical and biochemical signs of hyperandrogenemia and polycystic ovaries on ultrasound. Gonadotropin and E2 levels were normal, thus excluding primary ovarian failure or hypo- or hypergonadotropic hypogonadism. Hyperprolactinemia and late-onset congenital adrenal hyperplasia were excluded because of normal prolactin and 17-OH progesterone levels. Furthermore, there was no evidence of hypercortisolism and thyroid disease.

The spectrum of PCOS phenotype is wide; this includes women with no evidence of clinical and biochemical hyperandrogenism despite dysfunctional polycystic ovaries. T is the principal circulating androgen in women, produced from ovarian and adrenal precursors (mainly androstenedione and dehydroepi-androstenedione (DHEA)), metabolized in peripheral tissues. Measurement of total T using a reliable immunoassay is recommended to establish hyperandrogenemia. Androgen-secreting tumors need to be excluded. A marked increase in serum T (two to three times the upper normal range), with a normal DHEA-sulfate (DHEAS) level, is highly suggestive of an androgen-secreting ovarian tumor. When DHEAS is also increased this suggests an adrenal androgen-secreting tumor. Most women with PCOS are overweight or obese, further enhancing androgen secretion while impairing metabolism and reproductive functions and possibly favouring the development of the PCOS phenotype [13]. Our patient is obese and has mild symptoms of hyperandrogenemia and the serum T level was initially elevated.

Many studies have investigated the link between IR and the hyperandrogenism characteristic of PCOS. These studies have made the interesting observation that hyperinsulinemia seems to drive ovarian production of androgen [14]. Clinical studies with insulin sensitizers, such as metformin, show that an improvement in insulin sensitivity, and the resulting decline in insulin, is accompanied by a decrease in serum T levels in women with PCOS [15]. This phenomenon may explain the decrease in serum T level in our patient. In this model, our patient's exercise and weight loss resulted in a decrease in IR, which in turn may have reduced the stimulus for excessive ovarian production of androgen. These studies support the idea that insulin may be an important driver of ovarian production of T in women with PCOS; thus, a potential link is offered between IR and androgen excess.

Other components of the IR syndrome are frequently, but not invariably, seen in women with PCOS. Many such patients have hypertension and hyperlipidemia, and some investigators have hypothesized that they face a higher-than-average risk for cardiovascular disease [16]. Those women with PCOS and other signs of the dysmetabolic syndrome, such as hypertension, hypertriglyceridemia in conjunction with low HDL, and central obesity, may be at highest risk for complications of the dysmetabolic syndrome, for example, early atherosclerosis, nonalcoholic steatohepatitis (NASH). Our patient is obese, has normal blood glucose levels, both fasting and during OGTT, has normal lipid profile and normal blood pressure, even she has a very high risc to develop metabolic syndrome due to PCOS, obesity and the very relevant family history for type 2 DM. A study of massively obese PCOS patients reported a genetic component to impaired glucose metabolism [17]. Therefore, our patient must perform OGTT biannual.

The treatment of first choice for overweight or obese women with PCOS is modification of diet and lifestyle [18]. In PCOS a low SHBG concentration reflects an elevation in IR and may be a useful marker to identify those individuals with PCOS who are insulin resistant and may therefore benefit from treatment with insulin-sensitizing agents [19].

Metformin ameliorates hyperandrogenism and irregular menses. This present case clearly benefited from such treatment and no side effects were observed until now. However, questions about how long treatment should be continued and long-term safety remain to be answered. It seems that the beneficial effects are lost soon after treatment is discontinued [20].

Conclusions

Testing for glucose intolerance and dyslipidemia is required, particularly in the presence of obesity in PCOS. Lifestyle changes are the first-line intervention in young women with PCOS, who are overweight. Management of the PCOS with metformin seems to be beneficial and well tolerated, especially if SHBG is low. It appears that PCOS is a lifelong condition. Consequently, patients should be counselled about long-term health risks, and obese women with PCOS should be periodically screened [21].

This case illustrates the presence of several markers of IR (central obesity, low SHBG level) in absence of impaired glucose metabolism. It also presents the observation

that the T level decresed and SHBG level increased with weight loss trough diet and physical activity associated with metformin therapy. Metformin accelerated the weight loss and induced menses.

REFERENCES

1. **Chang RJ, Katz SE.** Diagnosis of polycystic ovary syndrome. *Endocrinol Metab Clin North Am* 28:397-408. 1999.

2. **Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R.** Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab* 83:3078-3082. 1998.

3. **Marsden PJ, Murdoch AP, Taylor R.** Tissue insulin sensitivity and body weight in polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 55:191-199. 2001.

4. **Legro RS, Kunselman AR, Dodson WC, Dunaif A.** Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 84:165-169. 1999.

5. **Dunaif A, Segal KR, Futterweit W, Dobrjansky A.** Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 38:1165-1174. 1989.

6. **Morin-Papunen *LC, Koivunen RM, Ruokonen A & Martikainen HK.*** *Metformin therapy improves the menstrual pattern with minimal endocrine and metabolic effects in women with polycystic ovary syndrome. Fertil Steril* 69:691–*696*. 1998.

7. **Diamanti-Kandarakis E, *Kouli C, Tsianateli T & Bergiele A.*** *Therapeutic effects of metformin on insulin resistance and hyperandrogenism in polycystic ovary syndrome. Eur J of Endocrinol* 138:269–*274*. 1998.

8. **The 2003 Rotterdam Consensus Workshop.** Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 19(1):41-47. 2004.

9. **Zosin Ioana, Bottermann P.** Afecţiunile sistemului endocrin. In: Compendiu de endocrinologie clinică, Eds. Excelsior 4-17. 1996.

10. **Radulian Gabriela.** Metabolismul energetic. In: Gabriela Negrişanu, Tratat de nutriţie, eds. Brumar 23-32. 2005.

11. **Negrişanu Gabriela, Memu Raluca.** Evaluarea clinică şi nutriţională. In: Gabriela Negrişanu, Tratat de nutriţie, eds. Brumar 359-378. 2005.

12. **Negrişanu Gabriela, Păcuraru Simona.** Nutriţia pentru controlul greutăţii corporale. In: Gabriela Negrişanu, Tratat de nutriţie, eds. Brumar 421-460. 2005.

13. **Renato Pasquali; Elisabet Stener-Victorin; Bulent O. Yildiz; Antoni J. Duleba; Kathleen Hoeger; Helen Mason; Roy Homburg; Theresa Hickey; Steve Franks; Juha S. Tapanainen; Adam Balen;David H. Abbott; Evanthia Diamanti-Kandarakis; Richard S. Legro.** Research in Polycystic Ovary Syndrome Today and Tomorrow. *Clin Endocrinol* 74(4):424-433. 2011.

14. **Franks S, Gilling-Smith C, Watson H, Willis D.** Insulin action in the normal and polycystic ovary. *Endocrinol Metab Clin North Am* 28:361-378. 1999.

15. **Moghetti P, Castello R, Negri C, et al.** Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J Clin Endocrinol Metab* 85:139-146. 2000.

16. **Mather KJ, Kwan F, Corenblum B.** Hyperinsulinemia in polycystic ovary syndrome correlates with increased cardiovascular risk independent of obesity. *Fertil Steril*.73:150-156. 2000.

17. **Yildiz BO, *Yarali H, Oguz H & Bayraktar M.*** *Glucose intolerance, insulin resistance, and hyperandrogenemia in first degree relatives of women with polycystic ovary syndrome. J Clin Endocrinol Metab* 88:2031–*2036*. 2003.

18. Stephen Franks. When Should an Insulin Sensitizing Agent Be Used in the Treatment of Polycystic Ovary Syndrome? *Clin Endocrinol* 74(2):148-151. 2011.

19. V. Jayagopal, E. S. Kilpatrick, P. E. Jennings, D. A. Hepburn, And S. L. Atkin. The Biological Variation of Testosterone and Sex Hormone-Binding Globulin (SHBG) in Polycystic Ovarian Syndrome: Implications for SHBG as a Surrogate Marker of Insulin Resistance. *J Clin Endocrinol Metab* 88(4):1528–1533. 2003.

20. Ibanez L, ***Valls C, Potau N, Marcos MV & de ZF.*** *Sensitization to insulin in adolescent girls to normalize hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism after precocious pubarche. J Clin Endocrinol Metab* 85:3526–*3530.* 2000.

21. Bhathena RK. Insulin resistance and the long-term consequences of polycystic ovary syndrome. *J Obstet Gynaecol* 31(2):105-10. 2011.