European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2010; 14: 1101-1105

Letter to the Editor

Polycystic ovary syndrome: a vitamin deficiency? Floating a new pathogenesis hypothesis

Dear Editor,

Polycystic ovary syndrome (PCO'S) is a medical condition that causes irregular menstrual cycle, chronic anovulation most often manifested as oligo-amenorrhea, and androgen excess with the typical ovarian ultrasound features[1]. It is the most common cause of ovulatory disorders and female infertility and affects approximately 6-10% of women in childbearing age[2]. However, its pathogenesis is still poorly understood.

Recently many investigators focused both on impaired glucose tolerance, that affects 30 to 40% of patients with PCO'S[3], and insulin resistance, that is manifested in a significant proportion of women with PCO'S.

Insulin plays a direct role in the pathogenesis of hyperandrogenemia in the polycystic ovary syndrome, acting synergistically with luteinizing hormone to enhance the androgen production of theca cell[4]. Since the report by Burghen et al[5] in 1980 where PCOS was associated with hyperinsulinemia, it has become clear that this syndrome has major metabolic as well as reproductive morbidities. The recognition of this association has also instigated extensive investigation on the relationship between insulin and gonadal function. An inositol phosphoglycan molecule containing D-chiro-inositol is known to have a role in activating enzymes that control glucose metabolism[6]. A defect in tissue availability or utilisation of D-chiro-inositol (DCI) or inositolphosphoglycan (IPG) mediators may contribute to insulin resistance[7,8].

In turn, this association has led to the treatment of women with PCOS with insulin sensitizing agents such as troglitazone[9], inositol[8,10,11] and metformin[12].

Myionositol) (MI) and D-chiro-inositol (DCI), are isoforms of inositol and belong to the vitamin B complex. MI is widely distributed in nature whereas DCI, the product of epimerization of C_1 hydroxyl group of MI, is relatively rare[13]. We speculate that PCOS should be a clinic manifestation of a genetically determined vitamin (myionositol) deficiency. If that pathogenesis hypothesis would be true, the simply supplementation of myionositol should be the first line treatment of PCOS patients. Currently, in support of our hypothesis, clinical data show that all metabolic, endocrinology and ovarian changes observed in PCOS patients can be reversed by oraly supplement of myionositol (Table I).

References

1) Ehrmann DA. Polycystic Ovary Syndrome. N Engl J Med 2005; 352: 1223-1236.

2) Franks S. Polycystic Ovary Syndrome. N Engl J Med 1995; 333: 853-861.

3) Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 1999; 22: 141-146.

4) Baillargeon JP and Nestler JE. Commentary: polycystic ovary syndrome: a syndrome of ovarian hypersensitivity to insulin? J Clin Endocrinol Metab 2006; 91: 22-24.

(References continue on page 1105)

Corresponding Author: Vittorio Unfer, MD; e-mail: vunfer@gmail.com

Table I.

Study	Patients	Treatment	Period	Other treatment product	Results	Conclusions
"Efficacy of Myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome" Martino M. Zacchè et al, Gynecol Endocrinol 2009; 25: 508-513	50	2 g/day	3+6 months	200 mcg folic acid	After 3 months of Myo administration, plasma LH, testosterone, free testosterone, insulin and HOMA index resulted significantly reduced. No significant changes were observed in plasma FSH and androstenedione levels. Both hirsutism and acne decreased after 6 months of therapy.	Myo-inositol administration is a simple and safe treatment that ameliorates the metabolic profile of patients with PCOS, reducing hirsutism and acne.
"Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome" Genazzani et al, Gynecol Endocrinol, 2008; 24: 139–144	20	2 g/day	12 weeks	200 mcg folic acid	After 12 weeks of Myo administration plasma LH, PRL, T, insulin levels and LH/FSH resulted significantly reduced. Insulin sensitivity, expressed as glucose-to-insulin ratio and HOMA index resulted significantly improved after 12 weeks of treatment. Menstrual cyclicity was restored in all amenorrheic and oligomenorrheic subjects. No changes occurred in the patients treated with folic acid.	Myo administration improves reproductive axis functioning in PCOS patients reducing the hyperinsulinemic state that affects LH secretion.
"Myo-inositol in patients with polycystic ovary syndrome: a novel method for ovulation induction" Papaleo E et al, Gynecol Endocrinol 2007; 23: 700-703	25	2 g/day (twice a day)	6 months	200 mcg folic acid twice a day	Twenty-two out of the 25 (88%) patients restored at least one spontaneous menstrual cycle during treatment, of whom 18 (72%) maintained normal ovulatory activity during the follow-up period. A total of 10 singleton pregnancies (40% of patients) were obtained. Nine clinical pregnancies were assessed with fetal heart beat at ultrasound scan. Two pregnancies evolved in spontaneous abortion.	Myo-inositol is a simple and safe treatment that is capable of restoring spontaneous ovarian activity and consequently fertility in most patients with PCOS. This therapy did not cause multiple pregnancy.
"Myo-inositol is an effective first-line approach for inducing ovulation in women with polycystic ovary syndrome" Papaleo et al, Gynecol Endocrinol 2008; 24 (Suppl 1): Issn: 0951-3590 OP 4	51	2 g/day (twice a day)	6 months	200 mcg folic acid twice a day	Forty-two out of 51 patients restored at least one spontaneous menstrual cycle during treatment while nine patients showed Myo-inositol resistance. Thirty-four out of 42 women maintained monthly ovulatory activity during the follow-up period corresponding at 66.6% of patients with PSO. A total of 18 pregnancies were obtained.	Comparing results with data presented in literature, Myo-inositol is a simple and safe treatment that is capable to restore a spontaneous ovarian activity and consequently fertility in most patients with polycystic ovary syndrome. This therapy did not cause multiple pregnancy.

Table I. *(Continue)*

Study	Patients	Treatment	Period	Other treatment product	Results	Conclusions
"Myo-inositol in the treatment of obesity and insulin resistance in PCOS adolescent girls: a randomized, controlled trial" Nigro et al, Gynecol Endocrinol 2008; 24 (Suppl 1): Issn: 0951-3590 OP 6	49	2 g/day (twice a day)	6 months	200 mcg folic acid twice a day	Myo-inositol had a greater treatment effect over placebo for weight, body mass index, waist circumference, sc abdominal adipose tissue and fasting insulin. Si improved in 55% of subjects while on Myo-inositol and 17% of subjects while on placebo (P=0.21).	Myo-inositol therapy for obese insulin-resistant young PCOS patients results in significant improvement in body composition and fasting insulin.
"The effects of Myo-inositol on ovarian stimulation and in vitro fertilization: a pilot study" Gerli et al, Gynecol Endocrinol 2008; 24 (Suppl 1): Issn: 0951-3590 OP 281	104	4 g/day	3 weeks	400 mcg folic acid then recombinant FSH	Bayesian analysis showed probabilities of 0.05 that Myo-inositol reduces FHS requirement by at least 12% and of that 10% oocytes are collected after Myo-inositol co-treatment.	Co-administration of Myo-inositol is therefore likely to increase the number of oocytes collected after ovarian stimulation in insulin-resistant women with PCOS and reduce the requirement for FSH.
"Metabolic and hormonal effects of Myo-inositol in women with polycystic ovary syndrome: a double-blind trial" D. Costantino et al, Eur Rev Med Pharmacol Sci 2009; 13: 105-110	42	4 g/day	12-16 weeks	400 mcg folic acid	There was a decrement in systolic pressure in Myo-inositol group (from 131±2 to 127±2 mmHg) while an increment in placebo group (from 128±1 to 130±1 mmHg; P=0.002); similarly about the diastolic blood pressure, with decrement (from 88±1 to 82±3 mmHg) in Myoinositol group and increment (from 86±7 to 90±1 mmHg) in placebo group respectively (P=0.001). In the Myo-inositol group plasmatriglycerides decreased by 52% (from 195±20 to 95±17 mg/dl) and total cholesterol decreased significantly (from 210±10 to 171±11 mg/dl). Sixteen (69,5%) and four (21%) women ovulated in the Myo-inositol group and the placebo group respectively. The different is statistically significant (P=0.001). There was an important decrement of the serum dehydroepiandrosterone sulphate in the Myo-inositol group (from 366±47 to 188±24 µg/dl; P=0.003) while it wasn't significant in the placebo group (from 384± 63 to 320±35 µg/dl; P=0.06).	Myo-inositol decreases serum androgen concentrations, reduces circulating insulin and improves glucose tolerance and other metabolic values altered associated with insulin resistance in women affected by Polycystic ovary syndrome.

Table I.

Study	Patients	Treatment	Period	Other treatment product	Results	Conclusions
"Myo-inositol may improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial" Papaleo E et al, Fertil Steril 2009; 91:1750-1754	30+30	4 g/day	12 months	400 mcg folic acid	Total r-FSH units (1,958 ± 695 vs. 2,383 ± 578) and number of days of stimulation (11.4±0.9 vs. 12.4±1.4) were significantly reduced in the Myo-inositol group. Furthermore, peak E(2) levels (2,232±510 vs. 2,713±595 pg/mL) at hCG administration were significantly lower in patients receiving Myo-inositol. The mean number of oocytes retrieved did not differ in the two groups, whereas in the group cotreated with Myo-inositol the mean number of germinal vesicles and degenerated oocytes was significantly reduced (1.0 ± 0.9 vs. 1.6 ± 1.0), with a trend for increased percentage of oocytes in metaphase II (0.82 ± 0.11% vs. 0.75 ± 0.15%).	These data show that in patients with PCOS, treatment with Myo-inositol and folic acid, but not folic acid alone, reduces germinal vesicles and degenerated oocytes at ovum pick-up without compromising total number of retrieved oocytes. This approach, reducing E(2) levels at hGC administration, could be adopted to decrease the risk of hyperstimulation in such patients.
"Randomized, double blind placebo-controlled trial: effects of Myo-inositol on ovarian function and metabolic factors in women with PCOS" S. Gerli et al, Eur Rev Med Pharmacol Sci 2007; 11: 347-354	92	4 g/day	14 weeks	400 mcg folic acid	After 14-wk Myo-inositol or placebo therapy, no change in fasting glucose concentrations, fasting insulin, or insulin responses to glucose challenge was recorded. There was an inverse relationship between body mass and treatment efficacy. In fact a significant weight loss (and leptin reduction) ($P < 0.01$) was recorded in the Myo-inositol group, whereas the placebo group actually increased weight ($P < 0.05$).	These data support a beneficial effect of Myo-inositol in women with oligomenorrhea and polycystic ovaries in improving ovarian function.

5) Burghen GA, Givens JR, Kitabchi AE. Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. J Clin Endocrinol Metab 1980; 50: 113-116.

6) Larner J. Multiple pathways in insulin signalling-fitting the covalent and allosteric puzzle pieces togheter. Endocr J 1994; 2: 167-171.

7) Baillargeon JP, Diamanti-Kandarakis E, Ostlund RE Jr, Apridonidze T, Iuorno MJ, Nestler JE. Altered D-chiro-inositol urinary clearance in women with polycystic ovary syndrome. Diabetes Care 2006; 29: 300-305.

8) Iuorno MJ, Jakubowicz DJ, Baillargeon JP, Dillon P, Gunn RD, Allan G, Nestler JE. Effects of d-chiro-inositol in lean women with the polycystic ovary syndrome. Endocr Pract 2002; 8(6): 417-423.

9) Hasegawa I, Murakawa H, Suzuki M, Yamamoto Y, Kurabayashi T, Tanaka K. Effect of troglitazone on endocrine and ovulatory performance in women with insulin resistance-related polycystic ovary syndrome. Fertil Steril 1999; 71(2): 323-327.

10) Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. N Engl J Med 1999; 340: 1314-1320.

11) Gerli S, Mignosa M, Di Renzo GC. Effects of inositol on ovarian function and metabolic factors in women with PCOS: a randomized double blind placebo-controlled trial. Eur Rev Med Pharmacol Sci 2003; 7: 151-159.

12) Ng EH, Wat NM, Ho PC. Effects of metformin on ovulation rate, hormonal and metabolic profiles in women with clomiphene-resistant polycystic ovaries: a randomized, double-blinded placebo-controlled trial. Hum Reprod 2001; 16(8): 1625-1631.

13) Yoshida K, Yamaguchi M, Morinaga T, Ikeuchi M, Kinehara M, Ashida H. Genetic modification of Bacillus subtilis for production of D-chiro-inositol, an investigation drug candidate for treatment of type 2 diabetes and polycystic ovary syndrome. Appl Environ Microbiol 2006; 1310-1315.

V. Unfer
AGUNCO Obstetrics & Gynecology Center,
Via G. Cassiani 15, Rome (Italy)