INTEGRATED HEALTHCARE
PRACTITIONERS
Integrated Healthcare Practitioners' Dietary and Nutritional Supplement, and Herbal Remedies Management Program

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SUCCESSFUL COMPLETION OF THE QUESTIONS AT THE END OF THIS PAPER HAS BEEN APPROVED FOR CONTINUING EDUCATION BY THE BDDT-N; 0.5 CREDIT PHARMACOLOGY, 0.5 CREDIT NUTRITIONAL MEDICINE AND BY THE CNPBC; ONE CE HOUR.

Polycystic Ovary Syndrome

Role of Inositol in PCOS management

Polycystic ovary syndrome (PCOS), first identified in 1935 as Stein-Leventhal syndrome, is a complex neuroendocrine disorder affecting approximately 5% to 10% of women of reproductive age (Nardo 2008). PCOS is a heterogenous syndrome involving anovulation, ovarian cysts on ultrasound, hyperandrogenism, insulin resistance and obesity (Azziz 2009). These women may present with symptoms of infertility, oligomenorrhea or amenorrhea, acne, hirsuitism, androgenic alopecia and acanthosis nigricans (darkening of the skin usually seen in flexures such as behind the neck). Insulin resistance and secondary hyperinsulinemia are thought to be major contributing factors in the etiology of PCOS, and insulin-sensitizing drugs are frontline pharmacotherapy for this condition. This article provides a summary of PCOS and the evidence base for the use of inositol — a natural insulin-sensitizing agent — in the treatment of women with PCOS.

DIAGNOSTIC CRITERIA

Despite the above list of characteristic symptoms, presentation varies considerably between patients, and women may present without the expected symptoms and without all of the typical lab findings. Lab findings consistent with a diagnosis of PCOS include elevated LH with normal or low FSH, elevated estradiol, elevated testosterone and hyperinsulinemia, possibly with other lab markers of insulin resistance, which is present in 50% to 70% of women with PCOS (Azziz 2009). Although there is considerable controversy around the best way to test insulin resistance in PCOS, the two-hour oral glucose tolerance test (OGTT) measuring both insulin and glucose at one and two hours has been proposed (Azziz 2009). This is preferable to measures such as fasting blood glucose, since in young women, insulin resistance may be compensated for by increased insulin secretion. It is also increasingly recognized that a "lean phenotype" of PCOS exists, and in these women, basal LH levels may be within normal range, while LH pulsatility may be altered (Azziz 2009). Up to nine phenotypes or patterns of expression have been identified by Azziz et al (2009).

Previous definitions of PCOS have differed with respect to the precise diagnostic criteria, in an attempt to accommodate this phenotypical variability as it became better known. In 1990, the *National Institute of Health* redefined criteria as otherwise unexplained hyperandrogenism and anovulation (defined as either menstrual irregularity or infertility) (NIH criteria) (Rosenfield 2008). Because it was later found that a small number of PCOS patients have regular cycles, the presence of polycystic ovaries on ultrasound was subsequently added as a basis for diagnosis in the absence of menstrual irregularity (Rotterdam criteria) (Rosenfield 2008). It is important to note, however, that this ultrasound finding also occurs in up to 20% of healthy women without PCOS or related symptoms; therefore, ultrasound is not diagnostic without accompanying symptoms (Rosenfield 2008).

A recent review by the *PCOS Task Force*, an international body comprised of basic and clinical scientists and clinicians, attempted to clarify the definition of PCOS, and recommended that PCOS should be defined by the presence of hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), and the exclusion of related disorders, with the recognition that forms of PCOS may occur without overt evidence of hyperandrogenism (Azziz 2009). Diagnoses to exclude include congenital adrenal hyperplasia, idiopathic hyperandrogenism or hirsuitism, hyperprolactinemia, androgen-secreting neoplasms and thyroid disorders (Azziz 2009).

PATHOPHYSIOLOGY

The precise etiology of PCOS is unknown and is thought to be multifactorial and cyclical in nature. Elements of the syndrome are thought to include an inherent steroidogenic defect of theca (ovarian) cells leading to ovarian hyperandrogenism, adrenal hyperandrogenism, dysregulation of LH pulse frequency and amplitude, and peripheral insulin resistance, the last of which appears to be a triggering factor in aggravating the underlying steroidogenic defect (Diamanti-Kandarakis 2008). Diamanti-Kandarakis reports that even in lean women with PCOS and normal insulin sensitivity as determined by the euglycemic clamp procedure, "reducing insulin levels by diazoxide was associated with decreased androgen levels" (2008), suggesting that even in these apparently normo-glycemic, normo-insulinemic women, insulin is to some degree involved in perpetuating excess androgen production.

Between 50% and 70% of women with PCOS have demonstrable insulin resistance (Azziz 2009), and secondary hyperinsulinemia is thought to be a major contributor in reinforcing the cycle of hormonal dysregulation. Hyperinsulinemia and increased IGF-1 result in increased ovarian theca cell androgen production and decreased liver production of sex hormone binding globulin (SHBG), thereby increasing free estrogen and testosterone. Excess androgens are converted to estrogen by aromatase in adipose tissue, and the resultant excess estrogens feed back on the hypothalamus and pituitary, leading to the perturbations of GnRH, LH and FSH release that in turn cause anovulation and altered production of ovarian hormones. Recent evidence suggests that adrenal hyperfunction is also a significant contributor in reinforcing this complex cycle. Exaggerated adrenal cortisol response to ACTH stimulation has been found in patients with PCOS, and between 20% and 30% of PCOS patients have excess adrenal androgen production in addition to the typically elevated ovarian androgen production (Yildiz 2007).

CONVENTIONAL TREATMENT

A diagnosis of PCOS increases a woman's risk for infertility, dysfunctional bleeding, endometrial carcinoma, obesity, type 2 diabetes mellitus (DM), dyslipidemia, hypertension, metabolic syndrome and cardiovascular disease, as well as possibly irritable bowel syndrome (IBS) (Azziz 2009, Mathur 2009, Rosenfield 2008).

Table 1. Summary of Pharmacotherapy in PCOS

Drug Class	Examples	Indication	Mechanism	Adverse Effects/ Contraindications
Insulin-sensitizing agents	Metformin	Insulin resistance (indirectly improves other parameters)	↓hepatic gluconeogenesis, ↑peripheral glucose uptake and utilization	CI: impaired KI or LV function. May cause low vitamin B12 in a small number of individuals.
	Thiazolidine-odiones (TZDs): pioglitazone, rosiglitazone	Insulin resistance (comparable to metformin)	Effects similar to metformin; Acts on PPAR-γ signalling.	May ↑risk of angina, myocardial infarction and congestive heart failure.
Oral contraceptive pill (OCP)	Combined OCP (various) with or without the progestinoid cyproterone acetete	Regulate menstrual cycle, hirsuitism, acne, ↓risk of endometrial hyperplasia	Suppresses ovulation, induces withdrawal bleeding and shedding of endometrium.	May worsen insulin sensitivity, glucose tolerance and lipid profile.
Ovarian stimulant	Clomiphene citrate	Induction of ovulation, infertility	↑pituitary gonadotropin release, promoting follicular growth; estrogenic and anti-estrogenic.	Ovarian hyperstimulation syndrome may enlarge pre-existing uterine fibroids.
Anti-androgenic agents	Flutamide	Acne, hirsuitism, virilization	Androgen receptor blocker	Administered with OCP due to risk of feminization of male fetus in the event of pregnancy.
	Spironolactone	Acne, hirsuitism, virilization	Aldosterone antagonist, competitive androgen receptor antagonist	May cause hypotension, hyperkalemia. Precautions same as for flutamide.

Because of the multifactorial nature of the syndrome and its effects, treatment must be multifaceted. Conventional treatment consists of insulin-sensitizing drugs, most commonly metformin and less so thiazolineodiones; oral contraceptives (OCP) for regulation of menstruation, acne and hirsuitism; antiandrogenic agents such as flutamide and spironolactone as secondary agents for treatment of hirsuitism; and clomiphene citrate to induce ovulation if achieving pregnancy is desired. Metformin is the most widely studied prescription intervention for PCOS, and has been found to reduce fasting insulin levels, attenuate hyperandrogenemia and increase ovulation rates (Diamanti-Kandarakis 2008). Recently, trials of OCP as monotherapy for PCOS have uncovered concerning metabolic side effects, including worsened insulin sensitivity, glucose tolerance and lipid profile. Similar effects have been found for OCP (ethinylestradiol) combined with the progestinoid CA (cyproterone acetete), raising questions as to whether these are appropriate therapy in PCOS patients (Diamanti-Kandarakis 2008).

COMPLEMENTARY TREATMENT

Exercise, weight loss and dietary changes are foundational aspects of treatment, aimed at improving glucose metabolism and inhibiting the cycle of hyperinsulinemia-hyperandrogenemia, in addition to reducing the risk of developing cardiovascular complications. Amelioration of insulin resistance through diet, exercise and weight loss improves clinical and hormonal parameters of PCOS (Stamets 2004). Modest weight loss corresponding to 10% of initial body weight has been shown to increase frequency of ovulation and improve hormone levels (Diamanti-Kandarakis 2008). In addition to these dietary and lifestyle changes, exogenous inositol has been shown to act as a natural insulin-sensitizing agent.

INOSITOL PHARMACOLOGY

Inositol is a "ubiquitous, cyclic carbohydrate with a basic 6-carbon ring structure" (Colodny 1998) and is related to the B vitamin family (MeSH database). There are nine isomers of inositol, of which the two main isoforms are D-chiro- and myo-inositol (Colodny 1998, Papaleo 2009). Myo-inositol is widely distributed in nature, while D-chiro-inositol, synthesized from the myo-isoform, is relatively rare (Papaleo 2009). In mammals, inositol exists as "phosphorylated derivatives, various phosphoinositides and in its free form" (Colodny 1998), present in cell membranes where it functions as a mediator in signalling cascades and in enzymatic reactions (Colodny 1998). Inositol is thought to exert its insulin-sensitizing effects through mediation of insulin signalling across the cell membrane.

Insulin signalling across the cell membrane requires the activation of inositol phosphoglycan mediators, which are released as second messengers in response to receptor binding. At least one of these D-chiro-inositol phosphoglycans (DCI-PG) is known to activate key enzymes that control the oxidative and non-oxidative metabolism of glucose, and it is thought that a deficiency of this DCI-PG mediator may result in insulin resistance. This hypothesis is further supported by the fact that insulin resistance has been associated with decreased urinary excretion of D-chiro-inositol in patients with impaired glucose tolerance or type 2 diabetes mellitus (Nestler 1999). Intramuscular levels of chiro-inositol have been found to be lower in patients with type 2 diabetes (Nestler 1999). Cheang et al (2008) have also found a positive correlation between the ratio of DCI-PG levels to insulin levels and insulin sensitivity in women with PCOS, supporting the role of DCI-PG as a mediator of insulin effects.

Possible explanations for such a proposed DCI-PG deficiency include a defective epimerase-type enzyme, which is responsible for the intracellular conversion of myo-inositol to chiro-inositol, or an accelerated breakdown and clearance of D-chiro-inositol. In either case, exogenous administration of D-chiro-inositol may replace intracellular D-chiro-inositol stores and restore the DCI-PG concentrations (Nestler 1999). Dietary inositol intake under normal circumstances approximates 1g/d; therefore, it is not considered a major source of the body's total inositol content (Colodny 1998).

Although D-chiro-inositol was the predominant form studied initially in PCOS, the focus of recent studies has been on myo-inositol. Myo-inositol is a precursor to D-chiro-inositol and is widely distributed in such compartments as human follicular fluid, where it appears to affect follicular maturity and production of good quality oocytes (Papaleo 2007).

CLINICAL TRIALS OF INOSITOL IN PCOS

The clinical trials of inositol in its D-chiro and myo isoforms for PCOS are described in Table 2. Inositol administration has been found to significantly decrease LH, prolactin, free and total testosterone, systolic and diastolic blood pressure, serum triglycerides and insulin levels, while increasing levels of sex hormone binding globulin (SHBG) and serum progesterone. Inositol has been found to increase measures of insulin sensitivity such as the AUC insulin after an oral glucose load, the insulin sensitivity index (ISI) and the HOMA index. Inositol has been shown to improve ovarian function, increasing frequency of ovulation and restoring normal ovarian rhythm in up to 70% of patients. Inositol has also demonstrated benefit on cutaneous symptoms of PCOS such as acne and hirsuitism, and has been associated with reduction in body mass index (BMI) in women with PCOS.

Dosages used range widely among the trials, from 200mg/d to 4g/d. Of the two trials by Gerli using different dosages, a better ovarian response appeared to be evoked by the higher dosage, with over 70% of the treated women receiving 4g/d

Table 2. Clinical Trials of Inositol in PCOS

Reference	Study Design	Form & Dose	Outcomes
Costantino 2009 [Abst]	Double-blind, placebo-controlled trial in 42 women with PCOS	Myo-inositol + folic acid verses folic acid + placebo. Dose and duration not available.	Significant ↓ in free and total testosterone, systolic and diastolic BP, plasma TG, plasma insulin AUC, and improvement in the insulin sensitivity index (ISI) in the treatment group compared to placebo. 16 of 23 women in the inositol group ovulated verses four of 19 in placebo.
Zacche 2009	Prospective trial in 50 patients with PCOS	Myo-inositol 4g + 400mcg folic acid/d x six months	Acne improved after six months such that there was disappearance in 53%, and reductions in the number of patients with moderate (from 68 to 34%) and severe acne (from 32 to 13%). Hirsuitism disappeared in 30% of patients. LH, total and free testosterone, basal insulin levels and HOMA index ↓ significantly compared to baseline.
Papaleo 2009	Randomized controlled trial in 60 women with PCOS undergoing IVF	Myo-inositol 4g/d + folic acid 400mcg/d. Duration not specified.	The total number of recombinant FSH (given to induce ovulation) and the number of days of ovarian stimulation required to retrieve oocytes was significantly reduced in the inositol group. Only one cycle in the inositol group verses three in the placebo group was cancelled due to excessively elevated E2 levels (> 4000pg/ml). Mean number of oocytes retrieved did not differ between groups, but the inositol group showed reduced numbers of immature and degenerated oocytes. No significant difference in pregnancy rates.
Genazzani 2008	Randomized, controlled trial in 20 overweight women with PCOS	Myo-inositol 2g + 200mcg folic acid/d verses folic acid alone x 12 weeks	Serum LH, LH/ FSH ratio, prolactin, testosterone, and insulin levels were significantly decreased, and insulin sensitivity index and the HOMA index (another measure of insulin resistance) were improved in the treatment group. Insulin secretion and AUC in response to an oral glucose load was also significantly reduced compared to baseline. Menstrual cyclicity was restored in all amenorrheic or oligomenorrheic patients in the inositol group, while there was no change in the placebo group. The Ferriman-Gallway score of hirsuitism was not significantly decreased.
Papaleo 2007	Prospective trial in 25 women with subfertility due to PCOS	Myo-inositol 4g/d + folic acid 400 mcg/d x six months or until pregnancy	22 of the 25 women (88%) had at least one spontaneous menstrual cycle restored during the treatment period. 18 (72%) maintained normal ovulatory activity during this period. Serum progesterone ↑, while total and free testosterone ↓ significantly. During the six-month period, 10 biochemical single pregnancies occurred, including two spontaneous abortions. No multiple pregnancies occurred.
Gerli 2007	RCT trial in 92 patients with PCOS	Myo-inositol 4g/d + folic acid 400mcg/d verses folic acid alone x 16 weeks	The inositol group had significant ↑ in E2 (estradiol) levels, but not placebo, suggesting improved follicular maturation. No changes in testosterone levels were observed. BMI ↓ significantly in the inositol group, but ↑ in placebo. HDL also ↑ in the treatment group. Eight of 45 patients in the inositol group verses 17 of 47 in the placebo group failed to ovulate, a significant difference. > 70% patients receiving inositol established normal ovarian rhythm (three ovulations/16 weeks).
Gerli 2003	RCT trial in 283 women with PCOS	Inositol, 100mg twice per day for 16 weeks, form not specified	There was no change in fasting glucose, fasting insulin, or insulin AUC post glucose challenge in either group. BMI decreased significantly in the inositol group, while it increased in placebo. HDL also ↑ significantly in the inositol group. Eight of 136 patients in the inositol group verses 17 of 147 in the placebo group failed to ovulate, a significant difference. The inositol group also had significantly increased frequency of ovulation compared to placebo. Normal ovarian rhythm, defined as three ovulations over 16 weeks, was restored in 30% verses 18% of the inositol group verses placebo.
Iuorno 2002 [Abst]	RCT trial in 20 lean women with PCOS	D-chiro-inositol 600mg/d x six to eight weeks	Significant ↓ plasma insulin AUC, and concomitant 73% decrease in free testosterone in the treatment group vs placebo. There was a significant ↓ in systolic and diastolic BP and serum TG in the treatment group. 60% of the inositol group ovulated, as determined by serum progesterone levels, versus 20% of the placebo group.
Nestler 1999	RCT trial in 44 obese women with PCOS	D-chiro-inositol 1200mg/d x six to eight weeks	Normalization of glucose AUC in treatment group, versus no change in placebo, among patients with impaired glucose tolerance at baseline. Significant ↓ in LH response to leuprolide, peak 17α-hydroxyprogesterone levels, serum testosterone and DHEAS levels, and ↑ in SHBG levels in the inositol verses placebo groups. Serum TG, systolic and diastolic BP also decreased significantly compared to the placebo group. 19 of 22 women in the inositol group ovulated compared to six of 22 in the placebo group, as determined by serum progesterone levels.

establishing normal ovarian rhythm (defined as three cycles/16 weeks), compared to the 30% obtaining this result in the lower-dose study. An additional observation among the subset of study participants attempting to become pregnant was a non-significantly greater number of women in the treatment group achieved pregnancy: four patients in the inositol group versus one in the placebo group, in both studies (Gerli 2007, Gerli 2003).

Gerli et al also attempted to identify characteristics of women most likely to respond to inositol treatment. When comparing responders to non-responders, no differences in fasting insulin, glucose concentrations or OGTT response were observed. However, responders had significantly lower testosterone (2.5 versus 3.5nmol/L), higher SHBG (36.5 versus 26.3nmol/L) and lower free androgen index (7.2 versus 11.9). This suggests that the least androgenic patients have a higher likelihood of responding to inositol.

Papaleo et al investigated the use of myo-inositol in subfertile patients undergoing IVF treatment. Although no significant differences were seen in the number of oocytes retrieved or in the number of pregnancies achieved, co-administration of myo-inositol with pharmaceutical gonadotropins used to induce ovulation was found to significantly reduce E2 estradiol levels, suggesting that myo-inositol may decrease the risk of ovarian hyperstimulation syndrome, a potentially serious acute condition for which PCOS patients undergoing ovulation induction are at increased risk (Papaleo 2009).

CLINICAL CONSIDERATIONS

No significant adverse events were reported in these studies of inositol administered at a therapeutic doses of up to 4g/d myo-inositol for up to six months. Inositol appears to be well tolerated. Inositol has been used successfully to achieve pregnancy in women with PCOS (Papaleo 2007). However, there is a lack of information pertaining to use throughout pregnancy. Preclinical studies found inositol to reduce the incidence of neural tube defects in diabetic animal models (Colodny 1998).

SUMMARY

PCOS is a common cause of menstrual irregularity, female infertility and hyperandrogenism, and is strongly associated with insulin resistance, secondary hyperinsulinemia, and risk for developing diabetes or cardiovascular disease. There is considerable variability in presentations of PCOS, and diagnostic criteria have attempted to accommodate this. Inositol as D-chiro-inositol or myo-inositol has been demonstrated to positively impact multiple parameters affected by this condition, including levels of LH, total and free testosterone, progesterone and markers of insulin sensitivity. Inositol is effective in restoring normal ovarian cyclicity in up to 70% of affected women, and has been shown to improve acne and hirsuitism. Doses of myo-inositol range from 2-4g/d and appear to be well tolerated.

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Questions

1. Amenorrhea must be present to make a diagnosis of PCOS.
   A) True
   B) False

2. Insulin resistance is seen in approximately ___ % of women with PCOS.
   A) 15%
   B) 35%
   C) 60%
   D) 90%

3. Select the combination of symptoms and findings most likely to predict a diagnosis of PCOS.
   A) Obesity, acne, hypertension, impaired glucose tolerance.
   B) Amenorrhea, hirsuitism, ultrasound reveals multiple ovarian cysts, impaired glucose tolerance.
   C) Hirsuitism, elevated plasma testosterone, androgenic alopecia, acne.
   D) Obesity, impaired glucose tolerance, major depressive disorder, generalized anxiety disorder.

4. Oral contraceptives (OCP's) and insulin-sensitizing medications (Metformin, for example) are commonly prescribed medications for women with PCOS.
   A) True
   B) False

5. Select the option below which best describes potential adverse effects associated with OCP administration among women with PCOS.
   A) Weight gain, hypertension.
   B) Sudden coronary death, pulmonary embolism.
   C) Worsening of glucose tolerance, insulin sensitivity and lipid profile.
   D) Aggravation of hirsuitism.

6. Caloric restriction, exercise and fibre are appropriate diet and lifestyle-based interventions for women with PCOS.
   A) True
   B) False

7. Mechanistically, inositol is hypothesized to benefit outcomes among women with PCOS through which of the following?
   A) Inositol acts as a testosterone antagonist.
   B) Inositol inhibits hepatic synthesis of triglyceride.
   C) Inositol inhibits adrenal synthesis and secretion of cortisol.
   D) Inositol facilitates insulin signalling across cell membranes.

8. Inositol levels in urine and tissues have been shown to be lower among patients with PCOS relative to healthy controls.
   A) True
   B) False

9. Select the clinical outcome(s) least likely to be positively impacted by inositol among women with PCOS.
   A) Increased likelihood of conception.
   B) Improved glucose tolerance, insulin sensitivity.
   C) Lowering of plasma testosterone levels.
   D) Improvement in acne.

10. Select the most appropriate daily dosage of inositol, based on dosage used in available human trials for management of PCOS.
    A) 500mg inositol per day.
    B) 4,000mg inositol per day.
    C) 10,000mg inositol per day.
    D) 15,000mg inositol per day.

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