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MYOINOSITOL IN PCOS

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ABSTRACT: Medical treatments for PCOS are usually aimed at improving the clinical, endocrine and metabolic effects of this disease. A combination of hormonal contraceptives, progestins, insulin sensitizing agents and statins is effective, and also has metabolic and endocrine benefits. However, their long-term effects in terms of preventing the complications of PCOS, such as cardiovascular disease and diabetes, are still unknown and their adverse effects limit long-term use. Additionally, their effects on ovulation rates and hirsutism varied in women with PCOS. Resistance to clomiphene citrate (CC) is quite common (15-20%) along with variable efficacy. Metformin, the commonly prescribed drug for insulin resistance poses the patient to risk of hypoglycemia and increase in serum homocysteine level. Thus, available treatment is not without dis advantages and their adverse effects can limit the success of the treatment. Therefore, new agents are needed which treats PCOS with minimal side effects. Myoinositol is an important constituent of follicular microenvironment, playing a determinant role in both nuclear and cytoplasmic oocyte development. It positively affects hyperinsulinemia and oocyte's quality. It improves ovarian function and pregnancy rate. NAC has got multiple mechanism of actions including antioxidant property, has anti-apoptotic effect, vaso dilating effect, anti-inflammatory effect etc. It not only improves insulin sensitivity in hyperinsulinemic patients with PCOS but also shows better improvement in acne, hirsutism and weight gain compared to metformin. It helps in restoring the menstrual regularity.

KEYWORDS: PCOS, myoinositol, oogenesis.

INTRODUCTION: POLYCYSTIC SYNDROME: Polycystic ovarian syndrome (PCOS) is defined as an ovarian dysfunction syndrome, which manifests as a wide spectrum of disorder with the combination of heterogeneous symptoms and signs. It is the most common endocrinopathy that affects women.[1] PCOS is also a leading cause of infertility. PCOS affects 5% to 10% of women in their reproductive years and is the most common endocrinopathy affecting women. The major features of PCOS include menstrual dysfunction, anovulation, and signs of hyperandrogenism. It is one of the most frequent causes of oligo-ovulatory symptoms. Once considered a cosmetic or fertility disorder, PCOS is now recognized to carry considerable morbidity and long-term risk, particularly for glycemic abnormalities and Type 2 diabetes mellitus. It is a major threat to woman's health and has substantial psychological, social, and economic consequences.[2]

ETIOLOGY: In 1935, Stein and Leventhal published a paper based on their findings in seven women with amenorrhea, hirsutism, obesity, and a characteristic polycystic appearance to their ovaries one of the first descriptions of a complex phenotype today known as the polycystic ovary syndrome. Insight into the pathogenesis and treatment of the polycystic ovary syndrome has increased substantially in the decade.

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The cause of PCOS is unknown, although some evidence suggests that patients have a functional abnormality of cytochrome P450c17, the 17-hydroxylase, which is the rate-limiting enzyme in androgen biosynthesis. Cytochrome P450c17 is active in the adrenals and ovaries, and excess activity of this enzyme could explain the increased androgen production from both sources in PCOS.[3]

PCOS is, in some cases, a familial disorder, but the genetic basis of the syndrome remains unclear. Studies of family members with PCOS indicate an autosomal dominant mode of inheritance. Full expression of the syndrome may require an insulin abnormality and a defect in androgen biosynthesis, but no gene (or genes) has been identified.[3]

PATHOLOGY: The pathophysiology of PCOS is not well understood, mainly due to lack of knowledge of the location of the primary defect. There are several candidates: ovary, adrenal, hypothalamus, pituitary, or insulin-sensitive tissues. It is possible that there are sub-sets of women with PCOS wherein each of these proposed mechanisms serves as the primary defect.

Though the underlying defect in PCOS remains unknown, there is growing consensus that key features include insulin resistance, androgen excess and abnormal gonadotropin dynamics.[4]

Table 1: PATHOLOGY OF PCOS: (GnRH- Gonadotropin releasing hormone, IR- Insulin resistance, SHBG- sex hormone binding globulin, LH- luteinizing hormone):
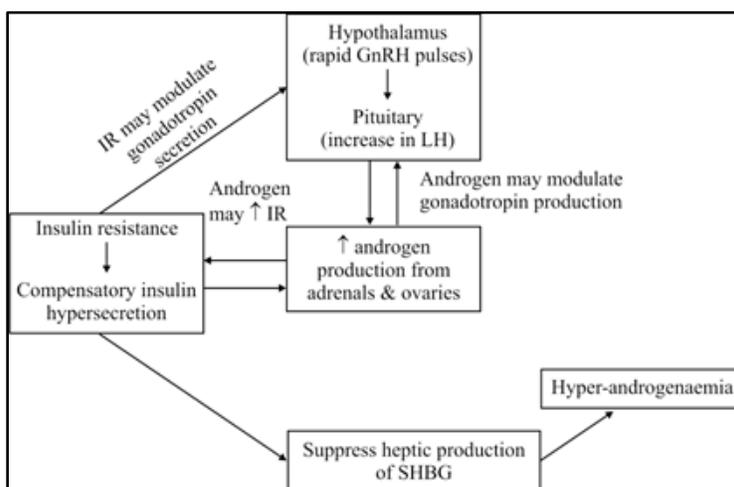
Investigations have elucidated some of the interactions between these systems. Recent evidence suggests that the principal underlying disorder is one of insulin resistance, with resulting hyperinsulinemia stimulating excess ovarian androgen production.[4] Insulin resistance leads to compensatory insulin hypersecretion by the pancreas in order to maintain normoglycemia. The resulting hyperinsulinaemia promotes ovarian androgen output and may also promote adrenal androgen output. High insulin levels also suppress hepatic production of sex hormone binding globulin (SHBG), which exacerbates hyper-androgenaemia by increasing the proportion of free circulating androgens. Another factor that promotes ovarian androgen output is the fact that women with PCOS are exposed long term to high levels of LH. This LH excess seems to be a

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result of an increased frequency of gonadotrophin-releasing hormone pulses from the hypothalamus. The abnormal hormonal milieu also probably contributes to incomplete follicular development which results in polycystic ovarian morphology.[5]

INSULIN & HYPOTHALAMO-PITUITARY-OVARIAN AXIS: Luteinizing hormone regulates the androgenic synthesis of theca cells; follicle-stimulating hormone is responsible for regulating the aromatase activity of granulosa cells, thereby determining how much estrogen is synthesized from androgenic precursors. When the concentration of luteinizing hormone increases relative to that of follicle-stimulating hormone, the ovaries preferentially synthesize androgen.

The frequency of the stimulus of hypothalamic gonadotropin-re leasing hormone (GnRH) determines, in part, the relative proportion of luteinizing hormone and follicle-stimulating hormone synthesized within the gonadotrope. Increased pulse frequency of hypothalamic GnRH favors production of LH. Because women with the polycystic ovary syndrome appear to have an increased luteinizing hormone pulse frequency, it has been inferred that the pulse frequency of GnRH must be accelerated in the syndrome. Insulin plays both direct and indirect roles in the pathogenesis of hyperandrogenemia in the polycystic ovary syndrome. Insulin acts synergistically with luteinizing hormone to enhance the androgen production of theca cells.[6]

Increased ovarian androgen biosynthesis in the polycystic ovary syndrome results from abnormalities at all levels of the hypothalamic-pituitary-ovarian axis. The increased frequency of luteinizing hormone (LH) pulses in the polycystic ovary syndrome appears to result from an increased frequency of hypothalamic gonadotropin-releasing hormone (GnRH) pulses. The latter can result from an intrinsic abnormality in the hypothalamic GnRH pulse generator, favoring the production of luteinizing hormone over follicle-stimulating hormone (FSH) in patients with the polycystic ovary syndrome, in whom the administration of progesterone can restrain the rapid pulse frequency. By whatever mechanism, the relative increase in pituitary secretion of luteinizing hormone leads to an increase in androgen production by ovarian theca cells.[6]

Increased efficiency in the conversion of androgenic precursors in theca cells leads to enhanced production of androstenedione, which is then converted by 17β -hydroxy steroid dehydrogenase (17β) to form testosterone or aromatized by the aromatase enzyme to form estrone. Within the granulosa cell, estrone is then converted into estradiol by 17β. Numerous autocrine, paracrine, and endocrine factors modulate the effects of both luteinizing hormone and insulin on the androgen production of theca cells; insulin acts synergistically with luteinizing hormone to enhance androgen production. Insulin also inhibits hepatic synthesis of sex hormone-binding globulin, the key circulating protein that binds to testosterone and thus increases the proportion of testosterone that circulates in the unbound, biologically available, or "free", state. Testosterone inhibits and estrogen stimulates hepatic synthesis of sex hormone binding globulin.[6]

Evidence suggests that some actions of insulin are mediated by putative inositolphosphoglycan (IPG) mediators, also known as second messengers. The IPG signaling system transduces insulin's stimulation of human the cal androgen biosynthesis, thus offering a mechanism by which insulin can stimulate ovarian androgen production even in women with PCOS whose tissues are resistant to insulin's stimulation of glucose metabolism. Several studies suggest that some abnormal action of insulin might be dependent from inositolphosphoglycan

(IPG) mediators of insulin action and suggest that a deficiency in a specific D-chiro-inositol (DCI)-containing IPG may underlie insulin resistance, similarly to type 2 diabetes.[7]

SYMPTOMS: Although anovulation, obesity, hirsutism and bilateral polycystic ovaries are considered classic manifestations, polycystic ovary syndrome is perhaps best viewed as a spectrum of symptoms, pathologic findings and laboratory abnormalities. Women with polycystic ovary syndrome may display a wide range of clinical symptoms, but they are usually present for three primary reasons: menstrual irregularities, infertility and symptoms associated with androgen excess (e.g., hirsutism and acne).[8]

MENSTRUAL ABNORMALITIES: Patients have abnormal menstruation patterns attributed to chronic anovulation. (The patient usually has a history of menstrual disturbance dating back to menarche.) Some women have oligomenorrhea (i.e. menstrual bleeding that occurs at intervals of 35 days to 6 months, with < 9 menstrual periods per year) or secondary amenorrhea (an absence of menstruation for 6 months). Oligomenorrhea has been observed in 85-90% of women with PCOS and as many as 30-40% of amenorrehic patients have PCOS. Dysfunctional uterine bleeding and infertility are the other consequences of anovulatory menstrual cycles. The menstrual irregularities in PCOS usually manifest around the time of menarche.[8]

ANOVULATION: In patients with PCOS, the ratio of follicular androstenedione to estradiol is high, suggesting an aromatization defect. As a result, there is an increase in intra-ovarian androgens resulting in hyperandrogenism.[4] Hyperandrogenism interferes with follicular maturity in women with PCOS and results in anovulation.[1,9]

Table 2: THE PATHOLOGY OF ANOVULATION IN PCOS.
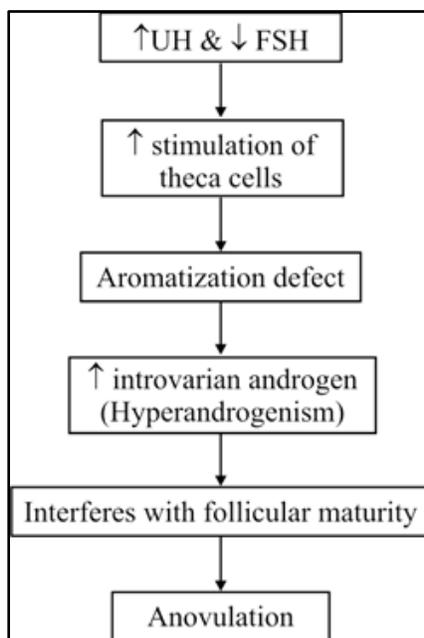
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POLYCYSTIC OVARIES: When any anovulatory state exists for a period of time, the "polycystic ovary" emerges. As an end result, affected women develop bilaterally enlarged polycystic ovaries, defined by the presence of more than eight follicles per ovary, with the follicles less than 10 mm in diameter.

These ultrasound findings are present in more than 90 percent of women with PCOS, but they are also present in up to 25 percent of normal women.

HYPERANDROGENISM: Hyperandrogenism clinically manifests as excess terminal body hair in a male distribution pattern. Hirsutism can be defined as hair in locations in women where it is usually not found. There is excessive growth of terminal, medullated, and pigmented hair on androgen-sensitive areas of skin such upper lip, chin, around the nipples, and along the linear alba of the lower abdomen. The prevalence of hirsutism in PCOS woman ranges from 17-83%.[10] It is recognized that hirsutism in part is ethnically determined, being more common in women with dark skin. Some patients have acne and/or male-pattern hair loss (androgenic alopecia).

Other signs of hyperandrogenism (e.g. clitoromegaly, increased muscle mass, voice deepening) are more characteristic of an extreme form of PCOS termed hyperthecosis. These signs and symptoms could also be consistent with androgen-producing tumors, exogenous androgen administration, or virilizing congenital adrenal hyperplasia.

Premature adrenarche is a common occurrence and, in some cases, may represent a precursor to PCOS. Hirsutism and obesity may be present in premenarchal adolescent girls with PCOS.[8]

INFERTILITY: A subset of women with PCOS is infertile. The prevalence of infertility caused mainly by anovulation in PCOS women varies between 35-94%.[11] Conception may take longer than in other women, or women with PCOS may have fewer children than they had planned.[8]

OBESITY: Obesity is now commonly defined in adults as a BMI >30 kg/m[6,11] Obesity is present in nearly half of all women with PCOS,[8] ranging from 30% to 60%.

DIABETES MELLITUS: Approximately 10% of women with PCOS have type 2 diabetes mellitus, and 30-40% of women with PCOS have impaired glucose tolerance by age 40 years. Hyperinsulinemia is present in more than 50% of patients with PCOS. Although about 70% of obese women with PCOS exhibit exaggerated insulin secretion, this feature is also present in 20%-40% of lean PCOS subjects.

ACANTHOSIS NIGRICANS: Patients with PCOS may have dark, pigmented skin on the nape of their neck, skin folds, knuckles, and/or elbows. This is called as acanthosis nigricans.[8] It is a cutaneous marker of hyperinsulinemia.[6]

METABOLIC SYNDROME: The National Cholesterol Education Program's Adult Treatment Panel III report identified 6 components of the metabolic syndrome that relate to cardio vascular disease: abdominal obesity, atherogenic dyslipidemia, raised blood pressure, Insulin resistance

and/or glucose intolerance, proinflammatory state, and prothrombotic state. Numerous patients with PCOS have characteristics of metabolic syndrome. Aziz et al showed 43% prevalence of metabolic syndrome in women with PCOS. Women with PCOS have increased prevalence of coronary artery calcification and a thickened carotid intima media, which may be responsible for subclinical atherosclerosis.[8]

SLEEP APNEA: Many women with PCOS have obstructive sleep apnea syndrome.[8] These patients have excessive daytime somnolence and experience apnea/ hypopnea episodes during sleep.[12,13]

DIAGNOSIS:
DIAGNOSTIC CRITERIA: A 1990 expert conference sponsored by National Institute of Child Health and Human Disease (NICHD) of the United States, National Institutes of Health (NIH) proposed the following criteria for the diagnosis of PCOS[3]:
1. Oligo-ovulation or anovulation manifested by oligomenorrhea or amenorrhea.
2. Hyperandrogenism (clinical evidence of androgen excess) or hyperandrogenemia (biochemical evidence of androgen excess).
3. Exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism.

ROTTERDAM CRITERIA: In 2003, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) recommended that at least 2 of the following 3 features are required for PCOS to be diagnosed. This is commonly known as Rotterdam criteria.[3]
1. Oligo-ovulation or anovulation manifested as oligomenorrhea or amenorrhea.
2. Hyperandrogenism (clinical evidence of androgen excess) or hyperandrogenemia (biochemical evidence of androgen excess).
3. Polycystic ovaries (as defined on ultrasonography).

MANAGEMENT: The management of the patients with PCOS includes weight loss, medical treatment and surgical treatment.

WEIGHT LOSS: Women with a BMI of greater than 27 kg/m^6 are considered overweight, and they are often insulin resistant. Women with a BMI of > 30 kg/m^6 are considered obese and are almost always insulin resistant. Weight loss, even as a little as 5% to 7%, can decrease the amount of circulating androgens and, thus, will induce ovulation. Weight loss is also associated with decreased insulin and testosterone levels and an improved lipoprotein profile.[14]

MEDICAL MANAGEMENT: Medical management of polycystic ovarian syndrome (PCOS) is aimed at the treatment of metabolic derangements, anovulation, hirsutism, and menstrual irregularity.
1. Hormonal Treatments - OC pills.
2. Insulin-Sensitizing Agents – Metformin.

3. Fertility Therapy-Clomiphene citrate.
4. Treatment of Hirsutism - OC pills, Spironolactone, Flutamide, finasteride.

The following table shows various classes of drugs with example that are used in the management of PCOS and in what symptom/pathology they will be useful.[6]

SURGICAL TREATMENT: Various laparoscopic methods, including electrocautery, laser drilling, and multiple biopsies have been used with the goal of creating focal areas of damage in the ovarian cortex and stroma.

DISADVANTAGES OF THE AVAILABLE TREATMENT OPTION:
- Combinations of estrogen & progesterone: May increase risk of thrombosis & metabolic abnormalities, Gastrointestinal distress, breast tenderness, decreases insulin sensitivity, impairs glucose tolerance and alters lipid profiles.
- Antiestrogen (Clomiphene citrate): Resistance occurs in 15-20% of patients, multiple births, hot flushes, Ovarian hyperstimulation, Ocular toxicity, Moderately effective as monotherapy, Less effective in obese patients, Not equally successful in all situations/variable success rate.
- Biguanide (Metformin): Fear of hypoglycemia and increase in S. homocysteine level, Less effective for hirsutism, Gastrointestinal distress, Unpleasant metallic taste, Numerous drug interactions.
- Antiandrogens (Spironolactone): Risk of hyperkalemia or hepatitis, Gastrointestinal (GI) discomfort, irregular menstrual bleeding, Potential abnormal sexual differentiation of a male fetus.
- 5α- Reductase inhibitors: Do not specifically target the isoenzyme of 5α - reductase in the pilosebaceous unit.
- Glucocorticoids: Long-term risks of glucose intolerance insulin resistance, osteopenia, weight gain.
- Thiazolidinediones: Modest effects on hirsutism, Associated with weight gain, Increases in S. homocysteine levels.
- Ornithine decarboxylase Inhibitors: Minimal documented efficacy

Thus, the available treatment is not without disadvantages. In addition, their adverse effects can limit the success of the treatment. Exploring other mechanisms to induce or augment ovulation along with symptom control is a desirable goal in reproductive medicine. Besides, the drug should have a very good safety profile. In these lines myoinositol seems to be a promising therapy.

MYOINOSITOL: Inositol is a six fold alcohol (polyol) of cyclohexane occurring in nature in the form of nine possible isomers, of which the most widespread is "Myoinositol" (MI). Main organ of its synthesis is kidney (2g every day for each kidney), that is responsible for its catabolism too. Also brain and testes are two important sites of synthesis. In nature inositol can be found in free form, or phospholipids-linked, or as phytic acid.
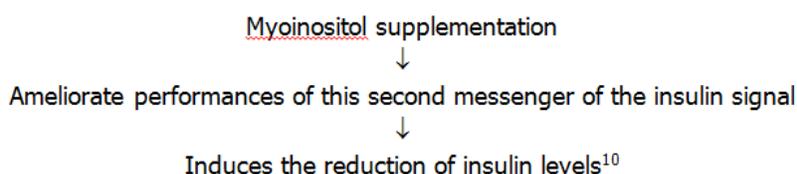
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Phospholipids containing inositol (inositides) have important role in chemical signals transmissio systems from outside to inside of cells.

Myo-lnositol is involved in several biological processes[15]:

a. Transmission of signals mediated by insulin-receptor link.
b. Cytoskeleton assembly;
c. Gametogenesis;
d. Intracellular calcium concentration control;
e. Membrane potential maintaining;
f. Gene expression regulation.

MECHANISM OF ACTION: Myoinositol is an important constituent of follicular microenvironment, playing a determinant role in both nuclear and cytoplasmatic oocyte development. Therefore higher myoinositol level in the follicular fluid can be well indicative of oocytes quality.

Myoinositol supplementation
↓
Ameliorate performances of this second messenger of the insulin signal
↓
Induces the reduction of insulin levels[10]

Myoinositol administration, besides DCI, has a modulatory role on insulin sensitivity, gonadotropin) and androgen secretion.[16]

Myoinositol mechanism of action appears to mainly based on improving insulin sensitivity of targ tissues, resulting in a positive effect on the reproductive axis (Myoinositol restores ovulation an, improves oocyte quality) and hormonal function! (Myoinositol reduces clinical and biochemica hyperandrogenism and dyslipidemia) through tin reduction of insulin plasma levels.

MYOINOSITOL AND OOGENESIS: Several evidences emphasize the crucial role q inositol during oocyte maturation.

Chiu et al showed that increase in intracellular Ca^{++} levels precedes germinal vesicle rupture and oocyst maturation progression. Culture medium supplementation with Ml seems able to indirectly promote meiotic maturation. On the contrary, inositol depletion in culture media considerably reduces signal transduction mechanisms and alters regulation of Ca^{++} intracellular oscillations. In addition, it seems that follicles with high Ml levels contain good quality oocytes. Presence in follicular fluids of high Ml levels, therefore, could be a potential marker not only of a correct follicular development, but also of good oocyte quality. Some studies stress the effects of Ml supplementation in patients submitted to IVF cycles who in previous cycles produced poor quality oocytes; in particular, positive effect of Ml supplementation is represented by reduction of germinal vesicles and degenerate oocytes number.

Preliminary data showed that, in PCOS patients the treatment with myo-inositol and folic acid, compared with folic acid alone, reduces the number of germinal vesicles and degenerated

oocytes, without compromising the total number of retrieved oocytes. These results, as other trials', suggest that myoinositol has a positive effect on mature oocytes development.

In patients treated with myo-inositol plus exogenous gonadotropins a significant reduction in E_2 levels at hCG administration was found.[10]

MYOINOSITOL AND POLYCYSTIC OVARY SYNDROME (PCOS): Women affected by PCOS frequently show an insulin resistance pattern with hyperinsulinemia and glucidic metabolism alterations, till evident pictures of diabetes. In PCOS patients, hyperinsulinemia and insulin resistance play a direct role in hyperandrogenism pathogenesis, since insulin is able to stimulate internal theca cells to produce high levels of androgens. D-chiro-Inositol (DCI), produced by MI, is an insulin-mediator. A reduced availability or an altered use of DCI or MI could lead therefore to insulin resistance. Many clinical trials underline the association between insulin tissue sensitivity increment and DCI or MI oral administration for at least 3 months.[16]

PHARMACOKINETICS: Inositol phosphates are synthesized from the parent molecule inositol, with daily dietary consumption of inositol estimated at one gram. Once inositol reaches the cells of the intestinal tract, it is phosphorylated to create inositol hexaphosphate, and then subsequently dephosphorylated to its lower forms (IP1-5), which play important roles in signal transduction. Independent of the route of administration, myoinositol has been found to be absorbed almost instantaneously, transported intracellular and dephosphorylated into lower inositol phosphates. Myoinositol can reach targeted tumor tissue as early as one hour post-administration.

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