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Polycystic Ovarian Syndrome

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Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders affecting women, occurring in up to 10% of the female population. It is classically characterized by symptoms of menstrual irregularity and hyperandrogenism.¹ Since the classical syndrome of PCOS was first described by Stein and Leventhal,² there has been increasing recognition of its broad clinical spectrum that has led to much debate regarding the precise definition and pathogenesis. Although excess adrenal and ovarian androgen production have been described as important factors contributing to the clinical picture, there is mounting evidence to suggest that insulin resistance (IR) plays a central role in the pathophysiology of both obese and nonobese PCOS. IR may have long-term implications by contributing to the development of multiple cardiac risk factors in this population. Most of the treatment modalities for PCOS to date have focused on improving symptoms of hirsutism, menstrual irregularity, and infertility. Recently, medications such as metformin and the thiazolidinediones have been recognized as having possible cardioprotective effects through insulin sensitization and subsequent modification of cardiac risk factors in PCOS. In light of these developments, the role of traditional treatments such as oral contraceptives has been questioned.

Definition and clinical features of PCOS

The main features of PCOS, as determined by a 1990 National Institutes of Health (NIH) Expert Panel Consensus, include either clinically or biochemically apparent hyperandrogenism, oligomenorrhea, and the absence of other endocrine disorders such as hyperprolactinemia or androgen-secreting tumours.³ The onset of clinical features of PCOS tend to occur during puberty. Hyperandrogenic features may include acne, alopecia, and male-pattern balding (Table 1). In extreme cases, signs of virilization may include clitoromegaly, increased muscle mass, and deepening of the voice. Menstrual irregularities range from primary amenorrhea, occurring in about 10% of women with PCOS, to oligomenorrhea, dysfunctional uterine bleeding, and secondary amenorrhea. Despite the possibility of intermittently fertile cycles, PCOS remains the most common cause of anovulatory infertility in women.⁴ Obesity is present in about 50% of women with PCOS and is associated with a greater risk of insulin resistance and accompanying features such as acanthosis nigricans.⁵ The distribution of fat tends to be central, with a waist-to-hip ratio >0.85. Ultrasonographic evidence of polycystic ovaries (PCO), although present in 80% of women with PCOS, is not considered necessary for a definition of the syndrome since there is a high prevalence in the normal population (up to 20%).⁶

Pathogenesis of PCOS

Although a number of theories have been proposed to explain the pathogenesis of PCOS, the exact mechanism remains unclear. Current evidence supports the premise that there are multifactorial influences on the syndrome, including a primary genetic predisposition in combination with external exacerbating factors.

Increased androgen production has been noted in approximately 70% of women with PCOS and yet, the origin of the hyperandrogenemia continues to be controversial. Both hyperinsulinemia and hyperandrogenism decrease sex hormone-binding globulin (SHBG) production in the liver, resulting in increased biologically-active free testosterone.⁷ Women with PCOS have been shown to have an exaggerated adrenal androgen response to adreno-



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Table 1: Clinical features of the polycystic ovarian syndrome

- **Hyperandrogenic features**
 - Acne
 - Alopecia
 - Male-pattern balding
 - Extreme cases (signs of virilization, eg, clitoromegaly, increased muscle mass, deepening of the voice)
- **Menstrual irregularities (in 10% of women)**
 - Primary amenorrhea
 - Oligomenorrhea
 - Dysfunctional uterine bleeding
 - Secondary amenorrhea
- **Anovulatory infertility**
- **Obesity (in 50% of women)**
 - Associated risk of insulin resistance
 - Accompanying features (eg, acanthosis nigricans)
 - Fat distribution tends to be central
 - Waist-to-hip ratio >0.85
- **Ultrasonographic evidence of polycystic ovaries (in 80% of women)**

corticotrophic hormone (ACTH), increased ovarian androgen responses to gonadotropin-releasing hormone (GnRH) agonists, and increased ovarian 5 α -reductase activity.^{8,9} Most recently, enhanced peripheral 5 α -reductase activity has also been demonstrated in PCOS, implicating both peripheral skin and intrahepatic steroidogenesis in the etiology of increased androgen levels.¹⁰

Insulin resistance has been found to play an increasingly pivotal role in the pathogenesis of PCOS. The observation that IR is associated with 70% of obese and up to 40% of nonobese women with PCOS suggests that it is central to PCOS even in the absence of excess adiposity.^{11,12} IR is tissue-specific, with both muscle and adipose tissue demonstrating decreased sensitivity to insulin, but organs such as the ovaries and adrenal glands paradoxically exhibit increased sensitivity to insulin. The hyperinsulinemic state has been linked to increased androgen synthesis in women with PCOS by the upregulation of cytochrome P450c17 α activity in both the ovaries and adrenal glands.¹³ In addition, cross-activation of IGF-1 and IGF-2 receptors by insulin has been proposed as a possible explanation of increased steroidogenic activity.^{14,15} Persistent hyperandrogenemia and peripheral conversion to estrone increase luteinizing hormone (LH) production without an increase in follicle-stimulating hormone (FSH), resulting in an LH to FSH ratio of >2.5. It is the increased local and systemic androgen production, often exacerbated by hyperinsulinemia, that is hypothesized to cause premature follicular atresia and anovulation in PCOS.

Abnormal regulation of adipocyte lipolysis has also been recognized as a possible contributor to the pathophysiology of PCOS. A recent study by Faulds et al of

lean women with PCOS demonstrated decreased catecholamine-induced lipolysis in subcutaneous fat, which suggests that this may play an important role in mediating the increased lipid content of adipocytes and the prevalence of obesity seen in PCOS.¹⁶

Long-term outcomes

Besides the direct effect of hyperinsulinemia on the ovaries and adrenal glands, IR predisposes women with PCOS to a number of metabolic abnormalities that are important to recognize. Women with PCOS have an increased prevalence of impaired glucose tolerance (31%-35%), type 2 diabetes (7.5%-10%),¹⁷ hypertension,¹⁸ and hyperlipidemia¹⁹ as compared to the general population. Similar to the diagnosis of diabetes in the general population, the oral glucose tolerance test has shown greater sensitivity compared to the fasting glucose alone in both adults and adolescents with PCOS.²⁰ The abnormal lipid profiles in PCOS tend to be characterized by elevated low-density lipoprotein (LDL) and triglycerides and low high-density lipoprotein (HDL), independent of body mass index (BMI) or waist circumference.¹⁹

The combination of insulin resistance, increased BMI, visceral adiposity, and hyperlipidemia may all contribute to the risk of early atherosclerosis. Surrogate markers of early atherosclerosis such as increased plasminogen activator inhibitor-1 (PAI-1), endothelin-1, homocysteine, and C-reactive protein (CRP) are elevated in women with PCOS.²¹⁻²⁴ Recent studies also provide evidence of endothelial dysfunction and abnormal platelet aggregation, potential contributors to plaque formation and rupture in women with PCOS.²⁵⁻²⁷ Endothelial dysfunction is directly related to increased insulin and androgen levels,^{25,26} while there is a negative correlation between insulin sensitivity and platelet aggregation,²⁷ further emphasizing the potential importance of insulin resistance in this syndrome. Additional definitive evidence of atherosclerosis (eg, increased carotid intimal medial thickness and coronary artery calcification) has also been demonstrated in this population.^{28,29} In this case, both waist circumference and LDL levels predict the increased coronary artery calcification seen in PCOS.²⁹ It should be noted, however, that there is continued debate over the extent of increased heart disease in PCOS and whether PCOS is an independent risk factor for cardiovascular mortality since, to date, studies have been negative. A retrospective study analyzed women with a diagnosis of PCOS (prior to 1979) over 30 years and although a higher level of cardiovascular risk factors was noted, mortality and morbidity from coronary heart disease did not differ significantly between women with PCOS and comparison groups.³⁰

In addition to cardiovascular risk, PCOS carries an increased risk of symptomatic obstructive sleep apnea (after controlling for obesity) and it is suggested that insulin resistance may play a pathogenic role.³¹ Finally, PCOS also carries an increased risk of both endometrial and ovarian cancer.³²

Genetics and molecular biology

A single defect resulting in excessive serine phosphorylation of both the insulin receptor and cytochrome P450c17 α has been hypothesized as playing a role in the pathogenesis of PCOS. Serine phosphorylation increases the activity of cytochrome P450c17 α , the rate-limiting step of androgen biosynthesis in both the adrenals and ovaries.³³ Increased serine phosphorylation of the insulin receptor can cause the hyperandrogenemia that is seen in the fibroblasts of about 50% of women with PCOS.³⁴ In addition, phosphorylation of factors extrinsic to the insulin receptor, such as the downstream signaling proteins, protein kinase C, or insulin receptor substrate proteins (IRS), may also contribute to IR.³⁵

Family studies support the idea of IR being a hereditary component of PCOS. First-degree female relatives of women with PCOS show an increased incidence of diabetes, impaired glucose tolerance, and IR in those with normal glucose tolerance.^{36,37} Genetic studies that have linked familial PCOS to an insulin regulatory locus on chromosome 11 suggest that PCOS is due, in part, to an inherited alteration in insulin production.³⁸ Other important findings in family studies of women with PCOS have included significantly increased LDL levels in hyperandrogenic sisters,³⁷ significantly increased androgen levels in mothers and sisters,³⁶ and increased levels of dehydroepiandrosterone (DHEA) in brothers.³⁹

Metformin in PCOS

Given the established role and implications of IR in PCOS, insulin-sensitizing drugs have been widely used in the therapeutic approach to PCOS. One of the most commonly used medications is metformin, a biguanide oral hypoglycemic. While its precise molecular mechanism for improving insulin sensitivity has yet to be defined, metformin has been shown to decrease hepatic glucose production, reduce gluconeogenesis by decreasing lipolysis and production of free fatty acids, and improve peripheral glucose utilization. Recent studies have demonstrated a potentially more direct effect of metformin on steroidogenesis through inhibition of cytochrome P450c17 α ⁴⁰ and by decreasing production of progesterone and estrogen in a dose-dependent fashion in ovarian granulosa cells.⁴¹ Thus, by improving insulin sensitivity, metformin reduces insulin resistance and compensatory hyperinsulinemia.

There have been several recent reviews of the use of metformin in women with PCOS.⁴²⁻⁴⁶ Early observational cohort studies, done primarily on obese women (BMI >27) demonstrated an improvement in cycle regularity in about 60% of subjects. Similar results were achieved in 4 randomized control trials (RCTs) of the effect of metformin on menstrual cycles, with improvement rates ranging from 41%-100%.⁴²⁻⁴⁶ The majority of the trials demonstrated a reduction in free or total testosterone, while the effect on BMI and fasting insulin remained variable.

Since improvements in menstrual cycles do not necessarily relate to ovulation, several studies have specifically

examined serum progesterone or LH levels as markers of ovulation. Metformin has shown improvement in ovulation in reviews of both observational studies and RCTs^{42,43,46} (60% and 56%, respectively) and decreases the time to first ovulation by approximately 1 additional ovulatory cycle over a 5-month period.⁴⁶ Again, while there is a consistent trend towards decreased testosterone levels, the effects on BMI and insulin levels are variable. In addition, a tendency toward increased menstrual cycles and ovulation are seen in women treated for 4 months or longer versus shorter periods of time.^{42,43}

Several trials have revealed that metformin is not beneficial in women with PCOS;⁴²⁻⁴⁶ however, it is hypothesized that in these studies, the significant obesity (BMI >30) of the subjects may have limited the benefits of medication and that a reduction of BMI in these patients could have improved their insulin sensitivity.

Metformin has also been shown to improve infertility in women with PCOS when studied alone, in combination with clomiphene citrate, or in combination with gonadotropins for ovulation induction. Uncontrolled trials have suggested improved pregnancy rates while on metformin, but a single, small RCT demonstrated nonsignificant increased rates with metformin versus placebo (17.5% versus 5.3%).⁴⁷ The combination of metformin and clomiphene citrate has resulted in increased ovulation and rates of pregnancy in randomized trials, as compared to clomiphene citrate alone in both unselected women⁴⁸ and in those who are clomiphene-resistant (67% versus 24%).^{43,49,50} Metformin pretreatment has also been shown to improve responses to ovulation induction with exogenous FSH stimulation⁵¹ and possibly improve outcomes in women undergoing *in vitro* fertilization (IVF) with increased fertilization and pregnancy rates.⁵² A recent study provided a direct comparison of metformin with clomiphene citrate and human menopausal gonadotropin (hMG) ovulation induction in clomiphene citrate-resistant women. It showed no difference in pregnancy rates, suggesting that sequential treatment with metformin and clomiphene citrate may be an effective treatment option for ovulation induction in infertile women with PCOS.⁵³

Additionally, metformin has proven to be beneficial in nonobese women with PCOS, resulting in improved menstrual cycles and ovulatory rates with lower serum testosterone and fasting insulin levels.⁵⁴⁻⁵⁶ A combination of metformin and flutamide has also been shown to increase ovulation with increased insulin sensitivity and improved lipid profiles and body fat redistribution (preferential loss of abdominal fat) in lean women with PCOS.^{57,58} Only one study has examined the use of metformin and clomiphene citrate in clomiphene-resistant women and it showed no improvement in ovulation or pregnancy.⁵⁹ This study, however, was small (n=20) and strictly Chinese, and it has been suggested that these patients may have been particularly resistant to treatment.

The thiazolidinediones (TZDs) in PCOS

TZDs sensitize tissue to insulin action by binding to the nuclear receptor PPAR γ (peroxisome proliferator-activated receptor gamma) and by upregulating genes for lipid and glucose metabolism. Initial studies done with troglitazone (no longer available due to hepatotoxicity) showed improvements in glucose tolerance, insulin sensitivity, lipid and fibrinolytic abnormalities, reproductive function, hirsutism, and decreased levels of free testosterone (20%-40%) and adrenal androgen production (DHEA-S) in women with PCOS.⁶⁰⁻⁶³ Currently available TZDs – pioglitazone and rosiglitazone – have been studied in women with PCOS. Pioglitazone has been shown to improve acne and hirsutism, menstrual cycles, insulin sensitivity, lipid profiles, and androgen levels, with a greater effect observed in hyperinsulinemic versus normoinsulinemic women.⁶⁴ Rosiglitazone therapy is also effective in inducing spontaneous (33%) and clomiphene citrate-induced (77%) ovulation in clomiphene-resistant women with rates similar to metformin.^{43,65}

Safety of insulin sensitizers and pregnancy

It should be noted that metformin is a category B agent with respect to pregnancy (ie, no evidence of human fetal toxicity or teratogenicity); however, continued use during pregnancy remains controversial.⁶⁶ While retrospective studies have suggested reduced rates of pregnancy loss in the first trimester with continued metformin treatment, prospective data does not support this conclusion. The TZDs, on the other hand, are category C agents (teratogenicity in animal studies) and extreme caution is advised during human studies and pregnancy.

Insulin sensitizers and CV risk modification

In individuals with diabetes, evidence for a possible cardioprotective role for metformin was observed in the United Kingdom Prospective Diabetes Study (UKPDS),⁶⁷ in which metformin reduced the risk of coronary heart disease more than insulin or sulfonylureas. In women with PCOS, metformin has been shown to decrease fasting insulin, increase HDL, decrease LDL, and decrease free fatty acids.^{40,47,68,69} Studies of TZDs in women with PCOS have also demonstrated decreased insulin levels, improved lipid profiles, and most recently, a reversal of endothelial dysfunction characterized by a lack of normal vasodilatory response of the arteries.^{64,70} Given the potential increased CV risk in this high-risk group, metformin and TZDs may provide benefits in terms of CV risk factor modification and long-term outcomes.

Controversies surrounding oral contraceptives

Oral contraceptive pills (OCPs) are frequently used in women with PCOS because they are effective for improving menstrual regularity, potentially protecting from endometrial cancer, increasing SHBG, decreasing free testosterone, and improving hirsutism. However, OCPs have been related to a decrease in insulin sensitivity in women with PCOS.⁶⁸ As information surrounding the long-term sequelae of IR grows, the use of OCPs is being increasingly questioned.⁷¹ Studies have shown a relative risk of up to 1.6 for developing diabetes in women using low-dose OCPs over 4 years.⁷² A meta-analysis of case control studies examining the risk of myocardial infarction and ischemic stroke with the use of low-dose OCPs revealed an odds ratio of >2 for both.⁷³ PCOS is associated with a number of CV risk factors and, therefore, there is growing concern that the use of OCPs may further increase the risk in an already susceptible population. When examining long-term risks such as endometrial cancer, a large percentage of women with PCOS can achieve significantly improved menstrual regularity and ovulation with metformin. Therefore, the role of OCPs as first-line therapy for endometrial protection in these women may need to be re-evaluated.

Conclusion

In summary, PCOS is a common disorder in women with both short-term consequences of hirsutism and infertility, and long-term metabolic consequences of developing multiple cardiac risk factors. Insulin resistance has been shown to contribute to the development of many features of the metabolic syndrome in this population, including an increased incidence of obesity, diabetes, IGT, dyslipidemia, hypertension, and coronary artery disease. Further support for the role of insulin resistance is demonstrated by the beneficial effects of insulin sensitizers, such as metformin and TZDs that have been shown to improve fertility and potentially alter cardiovascular risk factors in this population. Traditionally, treatment in this population has been tailored to the patients' symptoms. However, early recognition and modification of potential metabolic processes continue to play an increasingly important role. Thus, in managing women with PCOS, introduction of an insulin sensitizer, such as metformin, as a standard component of treatment may be the preferred treatment strategy.

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References

- Franks S. Polycystic ovary syndrome. *N Engl J Med* 1995;333:853-61.
- Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol* 1935;29:181.
- Dunaif A, Thomas A. Current concepts in the polycystic ovary syndrome. *Annu Rev Med* 2001;52:401-419.
- Knochenhauer ES, Key TJ, Kahsar-Miller M, et al. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab* 1998;83:3078-3082.
- Dale PO, Tanbo T, Vaaler S, Aveholm T. Body weight, hyperinsulinemia, and gonadotropin levels in the polycystic ovarian syndrome: evidence of two distinct populations. *Fertil Steril* 1992;58:487-491.
- Polson DW, Adams J, Wadsworth J, Frank S. Polycystic ovaries – a common finding in normal women. *Lancet* 1988;1:870-872.
- Nestler JE, Powers LP, Matt DW, et al. A direct effect of hyperinsulinemia on serum sex hormone-binding globulin levels in obese women with the polycystic ovary syndrome. *J Clin Endocrinol Metab* 1991;72(1):83-9.
- Azziz R, Black V, Hines GA, Fox LM, Boots LR. Adrenal androgen excess in the polycystic ovary syndrome: sensitivity and responsivity of the hypothalamic-pituitary-adrenal axis. *J Clin Endocrinol Metab* 1998;83(7):2317-23.
- Ehrmann DA, Rosenfield RL, Barnes RB, Brigell DF, Sheikh Z. Detection of functional ovarian hyperandrogenism in women with androgen excess. *N Engl J Med* 1992;327(3):157-62.
- Fassnacht M, Schlenz N, Schneider SB, Wudy SA, Allolio B, Arlt W. Beyond adrenal and ovarian androgen generation: Increased peripheral 5 alpha-reductase activity in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;88(6):2760-6.
- Dunaif A, Segal KR, Futterweit W, et al. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 1989;38:1165-1174.
- Campbell PJ, Gerich JE. Impact of obesity on insulin action in volunteers with normal glucose tolerance: demonstration of a threshold for the adverse effect of obesity. *J Clin Endocrinol Metab* 1990;70:1114-1118.
- Barbieri RL, Makris A, Randall RW, Daniels G, Kistner RW, Ryan KJ. Insulin stimulates androgen accumulation in incubations of ovarian stroma obtained from women with hyperandrogenism. *J Clin Endocrinol Metab* 1986;62:904-910.
- Cara JF, Rosenfield RL. Insulin-like growth factor I and insulin potentiate luteinizing hormone-induced androgen synthesis by rat ovarian thecal-interstitial cells. *Endocrinology* 1988;123:733-739.
- Marx T, Mehta A. Polycystic ovary syndrome: Pathogenesis and treatment over the short and long-term. *Clev Clin J Med* 2003;70(1):31-45.
- Faulds G, Ryden M, Ek I, Wahrenberg H, Arner P. Mechanisms behind lipolytic catecholamine resistance of subcutaneous fat cells in the polycystic ovarian syndrome. *J Clin Endocrinol Metab* 2003;88:2269-2273.
- Legro RS, Kinselmann 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* 1999;84:165-169.
- Carmina E, Lobo RA. Polycystic ovary syndrome (PCOS): arguably, the most common endocrinopathy is associated with significant morbidity in women. *J Clin Endocrinol Metab* 1999;84:1897-1899.
- Talbott E, Clerici A, Berga SL, et al. Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: results of a case-control study. *J Clin Epidemiol* 1998;51:415-422.
- Palmert MR, Gordon CM, Kartashov AI, Legro RS, Emans SJ, Dunaif A. Screening for abnormal glucose tolerance in adolescents with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2002;87(3):1017-23.
- Legro RS, Kinselmann AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. *Am J Med* 2001;111:607-613.
- Diamanti-Kandaraki E, Spina G, Kouli C, Migdalis I. Increased endothelin-1 levels in women with polycystic ovary syndrome and the beneficial effect of metformin therapy. *J Clin Endocrinol Metab* 2001;86:4666-4673.
- Yarali H, Yildirim A, Aybar F, et al. Diastolic dysfunction and increased serum homocysteine concentrations may contribute to increased cardiovascular risk in patients with polycystic ovary syndrome. *Fertil Steril* 2001;76:511-516.
- Kelly CC, Lyall H, Petrie JR, Gould GW, Connell JM, Sattar N. Low grade chronic inflammation in women with polycystic ovarian syndrome. *J Clin Endocrinol Metab* 2001;86:2453-2455.
- Paradisi G, Steinberg HO, Hempfling A, et al. Polycystic ovary syndrome is associated with endothelial dysfunction. *Circulation* 2001;103:1410-1415.
- Paradisi G, Steinberg HO, Shepard MK, Hook G, Baron AD. Troglitazone therapy improves endothelial function to near normal levels in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;88:576-580.
- Dereli D, Ozgen G, Buyukkececi F, Guney E, Yilmaz C. Platelet dysfunction in lean women with polycystic ovary syndrome and association with insulin sensitivity. *J Clin Endocrinol Metab* 2003;88(5):2263-8.
- Talbott EO, Guzick DS, Sutton-Tyrrell K, et al. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. *Arterioscler Thromb Vasc Biol* 2000;20(11):2414-21.
- Christian RC, Dumesic DA, Behrenbeck T, Ober AL, Sheedy PF, Fitzpatrick LA. Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;88:2563-2568.
- Wild S, Pierpoint T, McKeigue P, Jacobs H. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. *Clin Endocrinol (Oxf)* 2000;52(5):595-600.
- Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. *J Clin Endocrinol Metab* 2001;86(2):517-20.
- Wild S, Pierpoint T, Jacobs H, McKeigue P. Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. *Hum Fertil (Camb)* 2000;3(2):101-105.
- Zhang LH, Rodriguez H, Ohno S, Miller WL. Serine phosphorylation of human P450c17 increases 17,20-lyase activity: implications for adrenarche and the polycystic ovary syndrome. *Proc Natl Acad Sci USA* 1995;92(23):10619-23.
- Dunaif A, Xia J, Book CB, Schenker E, Tang Z. Excessive insulin receptor serine phosphorylation in cultured fibroblasts and in skeletal muscle. A potential mechanism for insulin resistance in the polycystic ovary syndrome. *J Clin Invest* 1995;96(2):801-10.
- Venkatesan AM, Dunaif A, Corbould A. Insulin resistance in polycystic ovary syndrome: progress and paradoxes. *Recent Prog Horm Res* 2001;56:295-308.
- 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* 2003;88(5):2031-6.
- Legro RS, Bentley-Lewis R, Driscoll D, Wang SC, Dunaif A. Insulin resistance in the sisters of women with polycystic ovary syndrome: association with hyperandrogenemia rather than menstrual irregularity. *J Clin Endocrinol Metab* 2002;87(5):2128-33.
- Waterworth DM, Bennett ST, Gharani N, et al. Linkage and association of insulin gene VNTR regulatory polymorphism with polycystic ovary syndrome. *Lancet* 1997;349(9057):986-90.
- Legro RS, Kinselmann AR, Demers L, Wang SC, Bentley-Lewis R, Dunaif A. Elevated dehydroepiandrosterone sulfate levels as the reproductive phenotype in the brothers of women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2002;87(5):2134-8.
- Moggetti 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* 2000;85(1):139-46.
- Mansfield R, Galea R, Brincat M, Hole D, Mason H. Metformin has direct effects on human ovarian steroidogenesis. *Fertil Steril* 2003;79(4):956-62.
- Haas D, Carr BR, Attia GR. Effects of metformin on body mass index, menstrual cyclicity, and ovulation induction in women with polycystic ovary syndrome. *Fertil Steril* 2003;79(3):469-481.
- Costello MF, Eden JA. A systematic review of the reproductive system effects of metformin in patients with polycystic ovary syndrome. *Fertil Steril* 2003;79(1):1-13.
- Barbieri RL. Metformin for the treatment of polycystic ovary syndrome. *Obstet Gynecol* 2003;101(4):785-93.
- Baillargeon JP, Iuorno MJ, Nestler JE. Insulin sensitizers for polycystic ovary syndrome. *Clin Obstet Gynecol* 2003;46(2):325-40.
- Harborne L, Fleming R, Lyall H, Norman J, Sattar N. Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. *Lancet* 2003;361(9372):1894-901.
- Fleming R, Hopkinson ZE, Wallace AM, Greer IA, Sattar N. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. *J Clin Endocrinol Metab* 2002;87(2):569-74.
- Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med* 1998;338(26):1876-80.
- Vandermolen DT, Ratts VS, Evans WS, Stovall DW, Kauma SW, Nestler JE. Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone. *Fertil Steril* 2001;75(2):310-5.

50. Kocak M, Caliskan E, Simsir C, Haberal A. Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with polycystic ovary syndrome. *Fertil Steril* 2002;77(1):101-6.
51. De Leo V, La Marca A. Metformin and FSH for induction of ovulation in women with polycystic ovarian syndrome. *Hum Reprod* 2002;17(9):2481-2.
52. Stadtmauer LA, Toma SK, Riehl RM, Talbert LM. Impact of metformin therapy on ovarian stimulation and outcome in 'coasted' patients with polycystic ovary syndrome undergoing in-vitro fertilization. *Reprod Biomed Online* 2002;5(2):112-6.
53. George SS, George K, Irwin C, et al. Sequential treatment of metformin and clomiphene citrate in clomiphene-resistant women with polycystic ovary syndrome: a randomized, controlled trial. *Hum Reprod* 2003;18(2):299-304.
54. Ibanez L, Valls C, Ferrer A, Marcos MV, Rodriguez-Hierro F, de Zegher F. Sensitization to insulin induces ovulation in nonobese adolescents with anovulatory hyperandrogenism. *J Clin Endocrinol Metab* 2001;86(8):3595-8.
55. Nestler JE, Jakubowicz DJ. Lean women with polycystic ovary syndrome respond to insulin reduction with decreases in ovarian P450c17 alpha activity and serum androgens. *J Clin Endocrinol Metab* 1997;82(12):4075-9.
56. Morin-Papunen L, Vauhkonen I, Koivunen R, Ruokonen A, Martikainen H, Tapanainen JS. Metformin versus ethinyl estradiol-cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized study. *J Clin Endocrinol Metab* 2003;88(1):148-56.
57. Ibanez L, Valls C, Ferrer A, Ong K, Dunger DB, De Zegher F. Additive effects of insulin-sensitizing and anti-androgen treatment in young, nonobese women with hyperinsulinism, hyperandrogenism, dyslipidemia, and anovulation. *J Clin Endocrinol Metab* 2002;87(6):2870-74.
58. Ibanez L, Ong K, Ferrer A, Amin R, Dunger D, De Zegher F. Low-dose flutamide-metformin therapy reverses insulin resistance and reduces fat mass in nonobese adolescents with ovarian hyperandrogenism. *J Clin Endocrinol Metab* 2003;88(6):2600-6.
59. 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):1625-31.
60. Dunaif A, Scott D, Finegood D, Quintana B, Whitcomb R. The insulin-sensitizing agent troglitazone improves metabolic and reproductive abnormalities in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 1996;81(9):3299-306.
61. Ehrmann DA, Schneider DJ, Sobel BE, et al. Troglitazone improves defects in insulin action, insulin secretion, ovarian steroidogenesis, and fibrinolysis in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 1997;82(7):2108-16.
62. Azziz R, Ehrmann D, Legro RS, et al; PCOS/Troglitazone Study Group. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2001;86(4):1626-32.
63. Azziz R, Ehrmann DA, Legro RS, Fereshetian AG, O'Keefe M, Ghazzi MN; PCOS/Troglitazone Study Group. Troglitazone decreases adrenal androgen levels in women with polycystic ovary syndrome. *Fertil Steril* 2003;79(4):932-7.
64. Romualdi D, Guido M, Ciampelli M, et al. Selective effects of pioglitazone on insulin and androgen abnormalities in normo- and hyperinsulinaemic obese patients with polycystic ovary syndrome. *Hum Reprod* 2003 Jun;18(6):1210-8.
65. Ghazeeri G, Kutteh WH, Bryer-Ash M, Haas D, Ke RW. Effect of rosiglitazone on spontaneous and clomiphene citrate-induced ovulation in women with polycystic ovary syndrome. *Fertil Steril* 2003;79(3):562-6.
66. Hellmuth E, Damm P, Molsted-Pedersen L. Oral hypoglycaemic agents in 118 pregnancies. *Diabet Med* 2000;17:507-511.
67. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-865.
68. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, Tapanainen JS. Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. *J Clin Endocrinol Metab* 2000;85(9):3161-8.
69. Lord J, Flight I, Norman R. Insulin-sensitizing drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. *Cochrane Database Syst Rev* 2003;3:CD003053.
70. Paradisi G, Steinberg HO, Shepard MK, Hook G, Baron AD. Troglitazone therapy improves endothelial function to near normal levels in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;88(2):576-80.
71. Diamanti-Kandaraki E, Baillargeon JP, Luomo MJ, Jakubowicz DJ, Nestler JE. A modern medical quandary: polycystic ovary syndrome, insulin resistance, and oral contraceptive pills. *J Clin Endocrinol Metab* 2003;88(5):1927-32.
72. Chasan-Taber L, Willett WC, Stampfer MJ, et al. A prospective study of oral contraceptives and NIDDM among US women. *Diabetes Care* 1997;20:330-335.
73. Baillargeon JP, Luomo MJ, Nestler JE. Insulin sensitizers for polycystic ovary syndrome. *Clin Obstet Gynecol* 2003;46(2):325-340.

Abstract of interest

Platelet dysfunction in lean women with polycystic ovary syndrome and association with insulin sensitivity.

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Platelet dysfunction and its association with insulin resistance and/or hyperandrogenemia were evaluated in 50 women with polycystic ovary syndrome (PCOS), 50 women with nonclassic congenital adrenal hyperplasia (NC-CAH), and 30 women in the control group. Agonist-induced platelet aggregation was measured. Women with PCOS had significantly higher levels of platelet aggregations induced by ADP (77.4 ± 3.3 vs. 67.3 ± 2.8), collagen (79.7 ± 1.8 vs. 69.1 ± 3.9), and epinephrine (84.7 ± 2.6 vs. 67.8 ± 3.8), compared with controls. However platelet aggregations of women with NC-CAH because of ADP (68.2 ± 4.22), collagen (69.5 ± 5.4), or epinephrine (68.6 ± 4.3) were similar to those in the control group. There were negative correlations between aggregations induced by agonists and the insulin sensitivity in women with PCOS. These correlations also appeared significant after androgen levels with covariance analysis were excluded. These covariance analyses were performed because serum androgen levels might affect platelet function. Any significant correlations were not found between androgen levels and agonist-induced platelet aggregation in women with NC-CAH. We conclude that platelet dysfunction may be an important reason for the possible cardiovascular heart diseases in women with PCOS.

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