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Ovarian Hypertension: Polycystic Ovary Syndrome

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Introduction

Polycystic ovary syndrome (PCOS) was originally described by Stein and Leventhal in 1935 as a reproductive disorder characterized by oligo-amenorrhea, hirsutism, and polycystic ovary morphology.[1] Thirty years ago, it was first reported that women with PCOS had hyperinsulinemia.[2] Subsequent research indicated that PCOS was associated with a unique disorder of insulin action, as well as defects in insulin secretion, and together these abnormalities conferred a substantially increased risk of glucose intolerance.[3] Although the clinical manifestations of PCOS are heterogeneous, the hallmarks of the syndrome remain anovulation, androgen excess, and insulin resistance. Moreover, each of these features of the syndrome is responsible for the promotion of hypertension in this population. Therefore, therapy for hypertension should be targeted at treatment of these underlying abnormalities.

Diagnostic Criteria

The diagnostic criteria for PCOS have been a source of controversy. Outside the US, the diagnosis has been based on the presence of polycystic ovary morphology (PCO) by ovarian ultrasound examination; affected women are then further stratified based on ovulatory status. However, the finding that approximately 25% of normal women in many series can have PCO led investigators in the US to focus on the biochemical features of the syndrome for diagnostic criteria.[4-5] The 1990 NIH-NICHD conference on PCOS proposed what have become known as the NIH diagnostic criteria: hyperandrogenism (clinical and/or

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biochemical) and chronic anovulation with the exclusion of specific disorders of the ovary, adrenal and pituitary (Table 1).[4] PCO by ultrasound was not included as a criterion because of the lack of diagnostic specificity of this finding.[6] Ultrasonographically detected polycystic ovaries can be present in women with normal ovulation and sex hormone levels, whereas women with all the endocrine features of PCOS can have normal ovarian morphology by ultrasound exam.[6-7] The NIH criteria have been used to diagnose PCOS in the majority of the studies of hypertension in affected women.

In 2003, an international conference in Rotterdam reassessed the diagnostic criteria for PCOS and proposed revised criteria that included PCO.[8] The Rotterdam criteria require two of three of the following findings: hyperandrogenism, chronic anovulation, PCO (Table 1). Thus, these criteria would include all those women with PCOS by NIH criteria. However, the Rotterdam criteria also include women with hyperandrogenism and ovulatory cycles who would not be considered to have PCOS by NIH criteria. Since most ovulatory women with PCO have hyperandrogenism and increased LH levels, this additional group of women with PCOS according to Rotterdam criteria are analogous to the ovulatory PCO women identified by non-US investigators on the basis of ovarian ultrasound morphology. There are studies to suggest that ovulatory women with PCO are not insulin resistant compared to anovulatory women with PCO,[9] although recent studies suggest they may have milder metabolic abnormalities.[10] Therefore, it is unclear whether these women should be grouped with those with the classic anovulatory form of the disorder. Recently, the Androgen Excess Society (AES) developed diagnostic criteria for PCOS based on the feature of androgen excess, endorsing the NIH criteria but also recommending that women with regular ovulation and polycystic ovaries on ultrasound be included as a PCOS phenotype.[11]

Epidemiology

PCOS is one of the most common endocrine disorders affecting women of reproductive age.[12] A recent Australian study examined the prevalence of PCOS in a retrospective birth cohort employing the NIH, Rotterdam, and AES diagnostic criteria.[13] These data revealed prevalence based on NIH diagnostic criteria of 8.7 ± 2.0%, less than the 11.9 ± 2.4% and 10.2 ± 2.2% using Rotterdam and AES criteria, respectively. Prevalence estimates of PCOS among populations worldwide employing the NIH diagnostic criteria have been reported as approximately 6% in the Southeastern U.S.,[14] Spain,[15] the Mediterranean,[16] and Mexico.[17] Although studies have reported no statistically significant differences in the PCOS prevalence between black and white women,[14, 18] there are data suggesting an increased prevalence of PCOS among Hispanic[19] and Mexican-American[17] women compared to other racial and ethnic groups. Nonetheless, PCOS is likely underdiagnosed in clinical practice so the use of chart based data in prevalence estimate derivations is problematic.

Pathophysiology

The biochemical reproductive phenotype in PCOS consists of increased LH relative to FSH secretion and hyperandrogenism.[4-5] (Figure 1). There is increased frequency of LH pulsatile release indicating that the frequency of GnRH secretion is increased. There is also increased amplitude of LH pulses that is secondary, in part, to increased pituitary sensitivity to GnRH, which appears to be estrogen-mediated. It is possible that there is also an increased amount of GnRH secreted per pulse. FSH release is relatively suppressed and the late luteal and early follicular phase increases that are essential for normal follicular development are absent. One explanation for these FSH abnormalities is the increased frequency of GnRH secretion, which results in a selective suppression of FSH relative to LH release.[20] The elevated circulating androgens feedback on the hypothalamic-pituitary axis, both directly by decreasing sensitivity to the normal actions of estrogen and progesterone to slow the

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frequency of pulsatile GnRH release[21] and by extragonadal aromatization to estrogen, to increase LH relative to FSH release producing a self-sustaining syndrome.[4]

Under normal circumstances, the theca cells of the ovarian follicles produce androgens under the control of LH. These androgens are then aromatized into estrogens, primarily estradiol, by the adjacent granulosa cells.[22] FSH stimulates the granulosa cell growth and aromatase capacity. In PCOS, elevated LH levels stimulate enhanced theca cell androgen production. PCOS theca cells also have increased activity of multiple steroidogenic enzymes and produce increased amounts of androgens under basal circumstances as well as in response to LH.[22-23] Because of the acyclic FSH levels, there is arrested ovarian follicular development and decreased granulosa cell aromatase capacity resulting in decreased conversion of androgens to estrogens. Increased adrenal androgen secretion in a common finding is PCOS, most likely due to a shared defect in the steroid biosynthetic pathways common to the ovary and adrenals. The primary defect that initiates the reproductive features of PCOS remains unknown since it can be shown experimentally that either increasing androgen levels[4] or GnRH release[24] can produce features of PCOS. However, the intrinsic abnormalities in thecal steroidogenesis taken together with recent family and genetic studies suggest that abnormalities in androgen biosynthesis may be a primary defect in many cases.[25]

An additional biochemical hallmark of PCOS is increased ovarian and, frequently, adrenal androgen production.[26] There is increased activity of multiple steroidogenic enzymes common to the ovaries and the adrenal glands. This abnormality is accounted for in part by increased transcription of genes encoding for steroidogenic enzymes, including 3-β-hydroxysteroid dehydrogenase (3β-HSD), cytochrome P450 enzyme 17α-hydroxylase (P450c17), and 20α-hydroxysteroid dehydrogenase (20α-HSD), as well as increased mRNA accumulation of cholesterol side-chain cleavage enzyme (P450scc), 3β-HSD, P450c17, and 20α-HSD.

Insulin Resistance and Pancreatic β-cell Dysfunction

Although insulin resistance is a common feature of PCOS, not all women with PCOS are insulin resistant.[27] The insulin resistance in PCOS has been characterized in adipocytes by a post-binding defect in the insulin receptor-mediated signal transduction, which has also been confirmed in clinical studies of skeletal muscle action.[28] In addition, skin fibroblasts were used to demonstrate that defects in insulin signaling resulted from impaired insulin receptor tyrosine kinase activity.[27] This impairment has been determined to be secondary to increased receptor serine phosphorylation due to a serine kinase extrinsic to the receptor, which leads to selective resistance to the metabolic actions of insulin.[29]

In addition to insulin resistance, beta cell dysfunction is present in PCOS and it is the combination of these two derangements that contributes to the development of T2DM.[30] The beta cell dysfunction seen in women with PCOS has been evidenced by several methods demonstrating impaired insulin secretion response to glucose and exists independently of impairment in glucose tolerance. Notably, the impaired insulin secretory response was observed most convincingly among the women who had first degree family members with T2DM.

Impaired glucose tolerance (IGT) and T2DM are both increased in women with PCOS compared to women of similar BMI with regular menses.[31] In fact, in a large study of glucose intolerance among women with PCOS, 38.6% of the PCOS women had either IGT (31.1%) or diabetes (7.5%) by WHO criteria. Notably, when examining the non-obese women with PCOS, 10.3% had IGT and 1.5% had diabetes.[31]

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Obesity

Obesity is present in 30-70% of women with PCOS, depending on PCOS diagnostic criteria used and race/ethnicity of the population.[14, 22] Conversely, one study showed that 30% of morbidly obese women met criteria for PCOS compared to 5% of the lean population.[32] The role of obesity in the development of PCOS has been supported by a prospective study revealing that abdominal obesity and weight gain after puberty were associated with the development of PCOS.[33] Obesity has also been shown to exacerbate the clinical complications of PCOS, including insulin resistance,[27] hirsutism,[34] and the prevalence of infertility.[35] Notably, bariatric surgery and correction of obesity have been shown to result in resolution of PCOS characteristics.[32]

Genetic Susceptibility

The etiology of PCOS is unknown; however, several possible mechanisms have been postulated. In addition to the abnormal gonadotropin secretion and androgen excess previously discussed, the high heritability of PCOS characteristics suggests a genetic susceptibility to the disorder.[25, 36-37] Candidate gene studies were initiated which examined genes associated with steroid hormone biosynthesis, gonadotropin, obesity, energy regulation, and insulin action.[38-39] However, the only susceptibility locus that has been replicated is a dinucleotide repeat polymorphism within an intron of the fibrillin-3 gene on chromosome 19.[40-41]

Associated Metabolic Disorders

PCOS is characterized by multiple metabolic derangements, which may contribute to the development of hypertension and cardiovascular disease seen in this condition. However, it is important to note that, although women with PCOS manifest several cardiovascular disease risk factors, there have been no long-term prospective studies in women with PCOS that confirm the presence of increased cardiovascular disease events.[42] One study employed menstrual irregularity as a proxy for PCOS in a prospective cohort study of 82,439 female nurses ages 20-35 years old.[43] During a fourteen-year follow-up, women with “usually irregular” or “very irregular” menstrual cycles had an increased risk for nonfatal or fatal coronary heart disease compared to women with “very regular” menstrual cycles [age-adjusted relative risks (RR), 1.25 and 1.67, respectively; 95% confidence intervals (CI), 1.07-1.47 and 1.35-2.06, respectively]; a finding that was still significant after adjusting for BMI. There was also an insignificant increase in overall stroke risk (RR, 1.30; 95% CI, 0.97-1.74) and in ischemic stroke risk (RR, 1.40; 95% CI, 0.97-2.04) associated with “very irregular” menstrual cycles.

Metabolic syndrome

Metabolic syndrome has been variably defined by several international organizations[44-49]. However, all of the definitions include measures of central obesity, glucose intolerance, dyslipidemia, and high blood pressure. The prevalence of the metabolic syndrome in PCOS has been reported to be 43-47%, which is twice as high as the prevalence in the general population of comparable age, even after adjusting for BMI.[50] The components of the metabolic syndrome most commonly present in PCOS are central obesity and low serum high-density lipoprotein cholesterol (HDL); however, elevated blood pressure, impaired fasting glucose, and glucose intolerance are commonly present.[50] There is also an increased prevalence of metabolic syndrome among the sisters of women with PCOS.[51]

Dyslipidemia

The dyslipidemia in PCOS is similar to that seen in metabolic syndrome,[52] characterized by low levels of HDL, small particle size of low-density lipoprotein cholesterol (LDL), and

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high triglyceride cholesterol levels.[53] This pattern is more often seen in obese than in lean PCOS, likely secondary to the presence of greater insulin resistance in obesity.[4] The level of LDL cholesterol is also increased in women with PCOS and is less dependent on obesity than are HDL and triglyceride levels.[54] There is also evidence for heritability of dyslipidemia, so these lipid patterns can be seen not only in women with PCOS but also in their family members.[51]

Hypertension

Several studies suggest an increased prevalence of hypertension in women with PCOS compared to the general population[55-62] However, a factor complicating the interpretation of the studies is that obesity, which is common in PCOS, is itself a significant risk factor for hypertension and this variable was not consistently considered many studies. Moreover, in the studies which did adjust the analyses for BMI, either statistically or by study design involving matching control women by BMI, the association between hypertension and PCOS is not always clear.

Several studies demonstrated an association between PCOS and hypertension, but did not adjust for an elevated BMI. A Dutch study of PCOS women demonstrated a higher prevalence of hypertension among premenopausal women with PCOS compared to women without PCOS; however, the PCOS population was significantly more obese and the obesity could be responsible for the greater prevalence of hypertension in this population.[59] Additionally, hypertension was examined in menopausal women with PCOS who had undergone ovarian wedge resection.[63] This surgical procedure was the first established treatment for women with PCOS[64] and was commonly performed prior to the 1970s; however, it was discontinued due to the ovarian adhesions often following this procedure.[65] This study revealed that menopausal women post-ovarian wedge resection had a three-fold increased likelihood of being hypertensive compared to non-PCOS women.[63] These women with PCOS were also more obese than controls and this comparison was not adjusted for BMI. Although this study examines a postmenopausal population, the full burden of hypertension in PCOS has not been assessed since women with PCOS have not been followed prospectively beyond their reproductive years. One study which attempted to address this question was Wild *et al*. who conducted a retrospective examination of women with PCOS diagnosed an average of 31 years previously and found an increased prevalence of hypertension compared to a cohort of control women.[62] However, given the study design, BMI was not considered in the statistical analysis and differences in BMI may explain the association with hypertension.

Additional studies demonstrated an association between PCOS and hypertension controlling for the influence of BMI. In one study, women with PCOS were 40% more likely to have elevated blood pressure than the non-PCOS women, independent of age, BMI, diabetes or dyslipidemia, (OR 1.41, 95% CI 1.31-1.51).[19] Another population study from Brazil demonstrated similar findings in 69 women with PCOS when divided by BMI into normal, overweight, and obese categories and revealed a hypertension prevalence of 20.3%,;78.6% of these were obese and 21.4% were overweight.[66] An examination of a Czech population of PCOS women in their early 30s compared to non-PCOS women revealed that, after adjusting for BMI, PCOS women had higher blood pressure.[58] In a population of Dutch women with PCOS aged 45-54 yrs old, the prevalence of hypertension was 2.5 times greater than that of an age-matched Dutch female population.[59] Notably, the proportion of obese women with PCOS in this age group did not differ significantly from the control population.

Additionally, an investigation of daytime ambulatory blood pressure monitoring (ABPM) among young (mean age approximately 26 yrs) overweight women (mean BMI approximately 26 kg/m^2) revealed women with PCOS had higher blood pressures compared

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to regularly-menstruating control women. The women with PCOS compared to controls, although all normotensive, had systolic blood pressures in the prehypertensive range (mean ± SD, 126 ± 11 *vs*. 119 ± 12 mmHg, $p < 0.05$) and was independent of BMI.[60]

In addition to BMI, hypertension among women with PCOS may be affected by other background characteristics of the individual, such as race and ethnicity.[19] The investigation by Lo *et al*. demonstrated that, among women with PCOS, the prevalence of hypertension or elevated blood pressure was lowest among Asians and Hispanics and highest among Blacks. Even after adjusting for age, BMI, and diabetes status, Blacks had the highest (OR 1.32, 95% CI 1.19-1.38) and Hispanics had the lowest (OR 0.68, 95% CI 0.62-0.75) prevalence of blood pressure elevation compared to the White population.[19]

There are data to suggest that the nocturnal decrease in blood pressure characteristic of healthy vasculature is absent in women with PCOS, both in adolescent[67] and adult[68] women. In the study examining adolescent women with PCOS, there was no difference in BMI between the women who had normal glucose tolerance (NGT) compared to IGT. However, all of the women with NGT manifested normal systolic blood pressure nocturnal dipping, whereas only 40% of those PCOS women with IGT demonstrated this normal blood pressure response.[67] In adult women with PCOS, ABPM was found to be increased in 30% of women with PCOS, a finding largely explained by the increased prevalence of obesity in affected women.[68]

Other studies controlling for BMI have not revealed an association between PCOS and hypertension. A small study of 14 women with PCOS and 18 control obese women demonstrated no difference in blood pressures.[69] Another study of young lean PCOS compared to age-matched control women did not reveal an increased blood pressure among the PCOS women.[70] Conversely, a study of similarly overweight PCOS and control women did demonstrate a blood pressure discrepancy; however, the 50% prevalence of hypertension among PCOS women compared to 39% among control women did not reach statistical significance.[71] One study demonstrated that obese women with PCOS were hypertensive compared to lean PCOS and lean control women. However, the lean PCOS women were not hypertensive compared to the lean control women.[56] Similarly, in a study of 244 PCOS and an equal number of control women, BMI was a significant predictor of both systolic and diastolic blood pressure among women with PCOS.[57] Additionally, there was no difference observed in ambulatory blood pressure in women with PCOS compared to control women with adjustment for BMI.[72]

Hypertension in Pregnancy

Pregnant women with PCOS have a greater risk of perinatal morbidity from pregnancy-induced hypertension (PIH) and preeclampsia (PE) than non-PCOS pregnancies as demonstrated in a meta-analysis of pregnancy outcomes in women with PCOS compared to controls.[73] The studies included in the meta-analysis defined PIH as blood pressure ≥ 140/90 mmHg without proteinuria at a gestational age of >20 weeks) and defined PE as blood pressure ≥ 140/90 mmHg with proteinuria, either >0.3 g/24h urine or ≥ 2 + albustick at a gestational age of >20 weeks. The meta-analysis revealed an increased odds ratio of nearly 3.5-fold for both PIH (odds ratio, OR 3.67; 95% CI: 1.98-6.81), and PE (OR 3.47; 95% CI: 1.95-6.17). All of the women with PCOS in the preeclampsia studies included in the meta-analysis had higher BMI than controls. However, of the eight PIH studies included in the metanalysis, four studies matched PCOS and control women on BMI, while the other four studies had PCOS women with significantly higher BMI than the control women. In addition, the control groups were mainly spontaneous conceptions as opposed to the variable assisted reproductive therapies used among the PCOS women, which may[74] or may not[75] also increase the risk of preeclampsia.

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Cardiovascular Disease Risk Factors

In studies that have examined more non-traditional risk factors for coronary heart disease, including inflammatory biomarkers,[76-77] impaired vascular function,[78] and arterial stiffness,[79] derangements were not observed in the PCOS populations independent of obesity. Adiponectin, an adipokine inversely associated with atherosclerosis[80] was also examined in PCOS and was found to be associated with insulin resistance and BMI, not with PCOS or testosterone levels.[81] An examination of plasminogen activator inhibitor 1 (PAI-1) activity and tissue plasminogen activator (tPA) mass concentration between patients with PCOS and control women demonstrated that obese women with PCOS had increased levels of PAI-1 and tPA compared to controls; however, the lean PCOS levels of these two factors did not differ compared to the levels seen among the control women.[82]

However, age-matched populations of women with PCOS have been found to have increased carotid intima media thickness (cIMT) compared to control women, even after adjusting for BMI.[83-85] Another study observed that cIMT was increased and brachial artery flow-mediated dilation was decreased in women with PCOS compared to age- and BMI-matched control women.[86] Coronary artery calcification has also been observed to be greater among women with PCOS compared control women, even after adjusting for age and BMI.[87-89]

Pathophysiology of Hypertension in PCOS

Although the pathogenesis of PCOS has not yet been fully elucidated,[90] there are several mechanisms potentially responsible for the development of hypertension in PCOS (Box 1). Thus, the etiology of hypertension that occurs in the setting of PCOS is also multifactorial, including factors such as hyperandrogenemia, insulin resistance, obesity, and increased sympathetic nervous system activity.

Androgen Excess

There are data demonstrating that the hyperandrogenemia in PCOS women is associated with systolic and diastolic blood pressures in women with PCOS, independent of obesity or insulin resistance.[91] Androgen excess has also been associated with an increase in cIMT in women with PCOS.[85] Increased cIMT has been widely used as a reflection of preclinical atherosclerotic disease, a contributor to the development of hypertension.[92] A small study explored the relative impact of insulin resistance, another proposed etiology of hypertension in this population, compared to hyperandrogenism by studying PCOS women treated with an oral contraceptive containing 35 mcg of ethinyl estradiol and 2 mg of the antiandrogen cyproterone acetate (CPA-EE), to the insulin-sensitizer, metformin, then measuring ABPM and cIMT. The study revealed that CPA-EE use resulted in an increase in systolic, diastolic and mean arterial blood pressures during the day whereas metformin decreased all of these measures. No differences were observed in the nighttime parameters in response to either of these therapies. In addition, there was no statistically significant change in cIMT, although there was a tendency towards reduction in PCOS women treated with either CPA-EE or metformin. This study suggests that insulin resistance is more responsible than androgen levels for the hypertension seen in women with PCOS. However, the increase in blood pressure seen with the CPA-EE relative to the metformin group may have been due to the estrogen component and may not reflect the antiandrogenic effect.

Insulin Resistance

Hypertension may be secondary to enhanced sodium retention occurring in the setting of hyperinsulinemia.[93] High insulin levels have been associated with a subsequent increase in intracellular sodium and calcium.[94] as well as an increased insulin-like growth factor-1

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(IGF-1) which may be associated with vascular smooth muscle hypertrophy. In support of the role of insulin resistance in mediating hypertension in women with PCOS, the beneficial effects of metformin on blood pressure have been reported.[95] Additionally, the insulin sensitizing effects of metformin lead to a decrease in serum advanced glycated end products (AGEs),[96] molecules that permit the proliferation and migration of smooth muscles cells to the vascular intima.[97] Subsequently, the decrease in AGEs seen in the setting of insulin sensitizer therapy may lead to a decrease in cIMT. Moreover, other investigators have found an improvement in cIMT in response to metformin therapy on women with PCOS.[98]

Obesity

Obesity is a well-established risk factor for hypertension[99] and it has been considered the primary etiology implicated in the increased blood pressure in women with PCOS.[68] Current estimates internationally report greater than 60% of women with PCOS are overweight or obese.[100-102] One population study demonstrated that women with PCOS were more than four times more likely to be obese (body mass index ≥ 30 kg/m2) than non-PCOS women. Additionally, blood pressure was more likely to be elevated among women who were obese compared to those who were non-obese (43.1% vs. 12.4%, $p < 0.001$).

Sympathetic Nervous System

In addition, the sympathetic nervous system has been implicated in the etiology of hypertension in this population. Greater sympathetic nerve activity was found in a study of 20 women with PCOS who were compared to 18 weight- and age-matched control women.[103] The sympathetic nerve activity to the muscle vascular bed among women with PCOS was increased and highly correlated with testosterone level and to a lesser degree the cholesterol level. In addition, androgen excess[104] as well as insulin resistance[105] and obesity[106] have been implicated in stimulating the autonomic nervous system, thereby, each serving as a potential mediator of the hypertension observed in PCOS.

Therapeutic Considerations

Therapy for PCOS is targeted towards ameliorating or eliminating the symptoms for each individual woman. Consequently, given the association of hypertension with all of the common PCOS manifestations, treating the manifestations of PCOS may treat concomitant hypertension or the risk for hypertension as well. In addition, one needs to assess hypertension in the context of assessing other CV risk factors as well.[107]

Treatment of hyperandrogenism revolves around the use of combination oral contraceptives (COC) or antiandrogens. However, the response to oral contraceptives has been inconsistent. The use of drospirenone, an antimineralocorticoid progestin, in combination with ethinyl estradiol compared to the vaginal contraceptive ring was associated with a minimal but statistically significant increase of diurnal and 24-hour systolic blood pressure in women with PCOS (drospirenone, 5 mmHg for both time periods, $p = 0.001$; and contraceptive ring, 6 mmHg for both time periods).[108] Another study demonstrated a more convincing decrease in systolic blood pressure in response to a drospirenone containing COC of 1.9 mmHg compared to a 1.7 mmHg increase in systolic blood pressure in the desogestrel-containing COC group of women with PCOS.[109] However, other investigations in PCOS demonstrated no change in blood pressure with a drospirenone-containing COC.[110-111]

Another antiandrogenic therapy used in women with PCOS is spironolactone. This aldosterone antagonist has been used as a potassium-sparing diuretic in the setting of hypertension since the 1950s. It was serendipity that associated its use with improvement in hirsutism in a woman with PCOS undergoing treatment of hypertension[112] and it has since become the most widely used antiandrogen for female pattern hair loss in the US.[113] Studies

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have demonstrated the efficacy in the treatment of hirsutism in women with PCOS[114] so its use for this indication exceeds that for hypertension among women with PCOS. In studies examining the effect of spironolactone on blood pressure, one Indian study of spironolactone vs. metformin, no change in blood pressure was evident with either drug.[115] In another investigation of PCOS women treated with spironolactone 100 mg daily for 2 months, mean blood pressure decreased significantly from 118 ± 5/82 ± 4 mmHg to 113 ± 4/72 ± 5 mmHg ($p < 0.05$).[116]

Lifestyle modifications, including diet and physical activity, are critical for women with PCOS who are overweight or obese in preventing hypertension.[117] In addition, other methods of weight loss have shown promise for improving hypertension in the PCOS population. In a retrospective analysis of PCOS women who underwent a Roux-en-Y gastric bypass, normalization of blood pressure was observed in 78% of the previously hypertensive population.[118]

Conclusions

Hypertension is a significant contributor to the risk for cardiovascular disease. The increased prevalence of hypertension in women with PCOS may contribute to the increased risk of cardiovascular disease in women with PCOS. Thus, the Androgen Excess and Polycystic Ovarian Societies recommend that blood pressure be obtained in women with PCOS at every visit and that prehypertension be detected and treated given the potential benefit of lowering blood pressure for the prevention of CVD.[107] Whether hypertension is associated with PCOS independent of obesity remains controversial. Nevertheless, detection and subsequent treatment of hypertension in this population should decrease the adverse sequelae from hypertensive cardiovascular disease. Moreover, treatment of the risk factors inherent to PCOS, such as hyperandrogenism, insulin resistance, and obesity, may minimize the risk not only for the development of hypertension but also for incident cardiovascular disease independent of hypertension.[107] Treatment of hypertension in the PCOS population may take the form of lifestyle modification or pharmacotherapy.

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References

1. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. American Journal of Obstetrics and Gynecology. 1935; 19:181–191.
2. Burghen GA, Givens JR, Kitabchi AE. Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. J Clin Endocrinol Metab. Jan; 1980 50(1):113–116. [PubMed: 7350174]
3. Dunaif A, Graf M, Mandeli J, Laumas V, Dobrjansky A. Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance, and/or hyperinsulinemia. J Clin Endocrinol Metab. Sep; 1987 65(3):499–507. [PubMed: 3305551]
4. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. Dec; 1997 18(6):774–800. [PubMed: 9408743]
5. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med. Mar 24; 2005 352(12):1223–1236. [PubMed: 15788499]
6. Polson DW, Adams J, Wadsworth J, Franks S. Polycystic ovaries--a common finding in normal women. Lancet. Apr 16; 1988 1(8590):870–872. [PubMed: 2895373]
7. Legro RS, Chiu P, Kunselman AR, Bentley CM, Dodson WC, Dunaif A. Polycystic ovaries are common in women with hyperandrogenic chronic anovulation but do not predict metabolic or

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reproductive phenotype. J Clin Endocrinol Metab. May; 2005 90(5):2571–2579. [PubMed: 15713728]

8. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. Jan; 2004 81(1):19–25.
9. Robinson S, Kiddy D, Gelding SV, Willis D, Niththyananthan R, Bush A, Johnston DG, Franks S. The relationship of insulin insensitivity to menstrual pattern in women with hyperandrogenism and polycystic ovaries. Clin Endocrinol (Oxf). Sep; 1993 39(3):351–355. [PubMed: 8222298]
10. Adams JM, Taylor AE, Crowley WF Jr, Hall JE. Polycystic ovarian morphology with regular ovulatory cycles: insights into the pathophysiology of polycystic ovarian syndrome. J Clin Endocrinol Metab. Sep; 2004 89(9):4343–4350. [PubMed: 15356031]
11. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF. Criteria for Defining Polycystic Ovary Syndrome as a Predominantly Hyperandrogenic Syndrome: An Androgen Excess Society Guideline. J Clin Endocrinol Metab. 2006; 91(11):4237–4245. [PubMed: 16940456]
12. 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. [PubMed: 10372683]
13. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod. Feb; 2010 25(2):544–551. [PubMed: 19910321]
14. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab. Jun; 2004 89(6):2745–2749. [PubMed: 15181052]
15. Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab. 2000; 85(7):2434–2438. [PubMed: 10902790]
16. Diamanti-Kandarakis E, Kouli CR, Bergiele AT, Filandra FA, Tsianateli TC, Spina GG, Zapanti ED, Bartzis MI. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. J Clin Endocrinol Metab. Nov; 1999 84(11):4006–4011. [PubMed: 10566641]
17. Moran C, Tena G, Moran S, Ruiz P, Reyna R, Duque X. Prevalence of polycystic ovary syndrome and related disorders in mexican women. Gynecol Obstet Invest. 2010; 69(4):274–280. [PubMed: 20110726]
18. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab. 1998; 83(9):3078–3082. [PubMed: 9745406]
19. Lo JC, Feigenbaum SL, Yang J, Pressman AR, Selby JV, Go AS. Epidemiology and adverse cardiovascular risk profile of diagnosed polycystic ovary syndrome. J Clin Endocrinol Metab. Apr; 2006 91(4):1357–1363. [PubMed: 16434451]
20. Marshall JC, Eagleson CA. Neuroendocrine aspects of polycystic ovary syndrome. Endoc Meta Clinic North Am. 1999; 28:295–324.
21. Eagleson CA, Gingrich MB, Pastor CL, Arora TK, Burt CM, Evans WS, Marshall JC. Polycystic ovarian syndrome: evidence that flutamide restores sensitivity of the gonadotropin-releasing hormone pulse generator to inhibition by estradiol and progesterone. J Clin Endocrinol Metab. 2000; 85(11):4047–4052. [PubMed: 11095431]
22. Franks S. Polycystic ovary syndrome. Trends Endocrinol Metab. Nov-Dec; 1989 1(2):60–63. [PubMed: 18411091]
23. Nelson VL, Qin KN, Rosenfield RL, Wood JR, Penning TM, Legro RS, Strauss JF 3rd, McAllister JM. The biochemical basis for increased testosterone production in theca cells propagated from patients with polycystic ovary syndrome. J Clin Endocrinol Metab. Dec; 2001 86(12):5925–5933. [PubMed: 11739466]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

24. Reid RL, Leopold GR, Yen SS. Induction of ovulation and pregnancy with pulsatile luteinizing hormone releasing factor: dosage and mode of delivery. Fertil Steril. Nov; 1981 36(5):553–559. [PubMed: 6796436]
25. Legro RS, Driscoll D, Strauss JF 3rd, Fox J, Dunaif A. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. Proc Natl Acad Sci U S A. Dec 8; 1998 95(25): 14956–14960. [PubMed: 9843997]
26. Wickenheisser JK, Quinn PG, Nelson VL, Legro RS, Strauss JF 3rd, McAllister JM. Differential activity of the cytochrome P450 17alpha-hydroxylase and steroidogenic acute regulatory protein gene promoters in normal and polycystic ovary syndrome theca cells. J Clin Endocrinol Metab. Jun; 2000 85(6):2304–2311. [PubMed: 10852468]
27. Dunaif A. Insulin action in the polycystic ovary syndrome. Endoc Meta Clinic North Am. 1999; 28:341–359.
28. Dunaif A, Wu X, Lee A, Diamanti-Kandarakis E. Defects in insulin receptor signaling in vivo in the polycystic ovary syndrome (PCOS). Am J Physiol Endocrinol Metab. Aug; 2001 281(2):E392–399. [PubMed: 11440917]
29. Book CB, Dunaif A. Selective insulin resistance in the polycystic ovary syndrome. J Clin Endocrinol Metab. Sep; 1999 84(9):3110–3116. [PubMed: 10487672]
30. Ehrmann DA, Sturis J, Byrne MM, Karrison T, Rosenfield RL, Polonsky KS. Insulin secretory defects in polycystic ovary syndrome. Relationship to insulin sensitivity and family history of non-insulin-dependent diabetes mellitus. J Clin Invest. 1995; 96:520–527. [PubMed: 7615824]
31. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab. Jan; 1999 84(1):165–169. [PubMed: 9920077]
32. Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millán JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. J Clin Endocrinol Metab. Dec; 2005 90(12):6364–6369. [PubMed: 16189250]
33. Laitinen J, Taponen S, Martikainen H, Pouta A, Millwood I, Hartikainen AL, Ruokonen A, Sovio U, McCarthy MI, Franks S, Järvelin MR. Body size from birth to adulthood as a predictor of self-reported polycystic ovary syndrome symptoms. Int J Obes Relat Metab Disord. Jun; 2003 27(6): 710–715. [PubMed: 12833115]
34. Hoeger KM. Obesity and lifestyle management in polycystic ovary syndrome. Clin Obstet Gynecol. Mar; 2007 50(1):277–294. [PubMed: 17304042]
35. Grodstein F, Goldman MB, Cramer DW. Body mass index and ovulatory infertility. Epidemiology. Mar; 1994 5(2):247–250. [PubMed: 8173001]
36. Legro RS, Kunselman 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. May; 2002 87(5):2134–2138. [PubMed: 11994353]
37. 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. May; 2002 87(5):2128–2133. [PubMed: 11994352]
38. Urbanek M, Legro RS, Driscoll DA, Azziz R, Ehrmann DA, Norman RJ, Strauss JF 3rd, Spielman RS, Dunaif A. Thirty-seven candidate genes for polycystic ovary syndrome: strongest evidence for linkage is with follistatin. Proc Natl Acad Sci U S A. Jul 20; 1999 96(15):8573–8578. [PubMed: 10411917]
39. Urbanek M, Wu X, Vickery KR, Kao LC, Christenson LK, Schneyer A, Legro RS, Driscoll DA, Strauss JF 3rd, Dunaif A, Spielman RS. Allelic variants of the follistatin gene in polycystic ovary syndrome. J Clin Endocrinol Metab. 2000; 85(12):4455–4461. [PubMed: 11134093]
40. Urbanek M, Sam S, Legro RS, Dunaif A. Identification of a polycystic ovary syndrome susceptibility variant in fibrillin-3 and association with a metabolic phenotype. J Clin Endocrinol Metab. Nov; 2007 92(11):4191–4198. [PubMed: 17785364]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

41. Ewens KG, Stewart DR, Ankener W, Urbanek M, McAllister JM, Chen C, Baig KM, Parker SC, Margulies EH, Legro RS, Dunaif A, Strauss JF 3rd, Spielman RS. Family-based analysis of candidate genes for polycystic ovary syndrome. J Clin Endocrinol Metab. May; 2010 95(5):2306–2315. [PubMed: 20200332]
42. Legro RS. Polycystic ovary syndrome and cardiovascular disease: a premature association? Endocr Rev. Jun; 2003 24(3):302–312. [PubMed: 12788801]
43. Solomon CG, Hu FB, Dunaif A, Rich-Edwards JE, Stampfer MJ, Willett WC, Speizer FE, Manson JE. Menstrual cycle irregularity and risk for future cardiovascular disease. J Clin Endocrinol Metab. May; 2002 87(5):2013–2017. [PubMed: 11994334]
44. National Cholesterol Education Program (NCEP) Expert Panel on Detection E and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106:3143–3421. [PubMed: 12485966]
45. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. Oct 25; 2005 112(17):2735–2752. [PubMed: 16157765]
46. Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, Handelsman Y, Hellman R, Jellinger PS, Kendall D, Krauss RM, Neufeld ND, Petak SM, Rodbard HW, Seibel JA, Smith DA, Wilson PW. American College of Endocrinology position statement on the insulin resistance syndrome. Endocr Pract. May-Jun; 2003 9(3):237–252. [PubMed: 12924350]
47. International Diabetes Federation. Worldwide definition of the metabolic syndrome. 2005. Available at: http://www.idf.org/webdata/docs/IDF_Metabolic_syndrome_definition.pdf
48. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistace (EGIR). Diab Med. 1999; 16:442–443.
49. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998; 15:539–553. [PubMed: 9686693]
50. Essah PA, Nestler JE. Metabolic syndrome in women with polycystic ovary syndrome. Fertil Steril. 2006; 86:S18–19. [PubMed: 16798277]
51. Sam S, Legro RS, Bentley-Lewis R, Dunaif A. Dyslipidemia and metabolic syndrome in the sisters of women with polycystic ovary syndrome. J Clin Endocrinol Metab. Aug; 2005 90(8):4797–4802. [PubMed: 15899949]
52. Bentley-Lewis R, Koruda K, Seely EW. The metabolic syndrome in women. Nat Clin Pract Endocrinol Metab. Oct; 2007 3(10):696–704. [PubMed: 17893688]
53. Legato MJ. Dyslipidemia, gender, and the role of high-density lipoprotein cholesterol: implications for therapy. Am J Cardiol. Dec 21; 2000 86(12A):15L–18L.
54. Valkenburg O, Steegers-Theunissen RP, Smedts HP, Dallinga-Thie GM, Fauser BC, Westerveld EH, Laven JS. A more atherogenic serum lipoprotein profile is present in women with polycystic ovary syndrome: a case-control study. J Clin Endocrinol Metab. Feb; 2008 93(2):470–476. [PubMed: 18056772]
55. Carmina E. Cardiovascular risk and events in polycystic ovary syndrome. Climacteric. 2009; 12(Suppl 1):22–25. [PubMed: 19811236]
56. Conway GS, Agrawal R, Betteridge DJ, Jacobs HS. Risk factors for coronary artery disease in lean and obese women with the polycystic ovary syndrome. Clin Endocrinol (Oxf). Aug; 1992 37(2): 119–125. [PubMed: 1395062]
57. Talbott E, Clerici A, Berga SL, Kuller L, Guzick D, Detre K, Daniels T, Engberg RA. Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: results of a case-control study. J Clin Epidemiol. May; 1998 51(5):415–422. [PubMed: 9619969]
58. Vrbíková J, Cífková R, Jirkovská A, Lánská V, Platilová H, Zamrazil V, Stárka L. Cardiovascular risk factors in young Czech females with polycystic ovary syndrome. Hum Reprod. May; 2003 18(5):980–984. [PubMed: 12721172]

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NIH-PA Author Manuscript

59. Elting MW, Korsen TJ, Bezemer PD, Schoemaker J. Prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of a Dutch PCOS population. Hum Reprod. Mar; 2001 16(3):556–560. [PubMed: 11228228]
60. Holte J, Gennarelli G, Berne C, Bergh T, Lithell H. Elevated ambulatory day-time blood pressure in women with polycystic ovary syndrome: a sign of a pre-hypertensive state? Hum Reprod. Jan; 1996 11(1):23–28. [PubMed: 8671152]
61. Orbetzova MM, Shigarminova RG, Genchev GG, Milcheva BA, Lozanov LB, Genov NS, Zacharieva SZ. Role of 24-hour monitoring in assessing blood pressure changes in polycystic ovary syndrome. Folia Med (Plovdiv). 2003; 45(3):21–25. [PubMed: 15366662]
62. 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. [PubMed: 11844363]
63. Dahlgren E, Johansson S, Lindstedt G, Knutsson F, Odén A, Janson PO, Mattson LA, Crona N, Lundberg PA. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. Fertil Steril Mar. 1992; 57(3):505–513.
64. Farquhar C, Lilford RJ, Marjoribanks J, Vandekerckhove P. Laparoscopic ‘drilling’ by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. Cochrane Database Syst Rev. Jul 18.2007 3 CD001122.
65. Buttram VC, Vaquero C. Post-ovarian wedge resection adhesive disease. Fertility and Sterility. 1975; 26:874–876. [PubMed: 1183643]
66. Barcellos CR, Rocha MP, Hayashida SA, Mion Junior D, Lage SG, Marcondes JA. Impact of body mass index on blood pressure levels in patients with polycystic ovary syndrome. Arq Bras Endocrinol Metabol. Oct; 2007 51(7):1104–1109. [PubMed: 18157386]
67. Arslanian SA, Lewy VD, Danadian K. Glucose intolerance in obese adolescents with polycystic ovary syndrome: roles of insulin resistance and beta-cell dysfunction and risk of cardiovascular disease. J Clin Endocrinol Metab. Jan; 2001 86(1):66–71. [PubMed: 11231980]
68. Luque-Ramírez M, Alvarez-Blasco F, Mendieta-Azcona C, Botella-Carretero JI, Escobar-Morreale HF. Obesity is the major determinant of the abnormalities in blood pressure found in young women with the polycystic ovary syndrome. J Clin Endocrinol Metab. Jun; 2007 92(6):2141–2148. [PubMed: 17389696]
69. Zimmermann S, Phillips RA, Dunaif A, Finegood DT, Wilkenfeld C, Ardeljan M, Gorlin R, Krakoff LR. Polycystic ovary syndrome: lack of hypertension despite profound insulin resistance. J Clin Endocrinol Metab. Aug; 1992 75(2):508–513. [PubMed: 1639952]
70. Sampson M, Kong C, Patel A, Unwin R, Jacobs HS. Ambulatory blood pressure profiles and plasminogen activator inhibitor (PAI-1) activity in lean women with and without the polycystic ovary syndrome. Clin Endocrinol (Oxf). Nov; 1996 45(5):623–629. [PubMed: 8977761]
71. Cibula D, Cífková R, Fanta M, Poledne R, Zivny J, Skibová J. Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome. Hum Reprod. Apr; 2000 15(4):785–789. [PubMed: 10739820]
72. Meyer C, McGrath BP, Teede HJ. Overweight women with polycystic ovary syndrome have evidence of subclinical cardiovascular disease. J Clin Endocrinol Metab. Oct; 2005 90(10):5711–5716. [PubMed: 16046590]
73. Boomsma CM, Fauser BC, Macklon NS. Pregnancy complications in women with polycystic ovary syndrome. Semin Reprod Med. Jan; 2008 26(1):72–84. [PubMed: 18181085]
74. Ludwig M. Risk during pregnancy and birth after assisted reproductive technologies: an integral view of the problem. Semin Reprod Med. Nov; 2005 23(4):363–370. [PubMed: 16317625]
75. Sun LM, Walker MC, Cao HL, Yang Q, Duan T, Kingdom JC. Assisted reproductive technology and placenta-mediated adverse pregnancy outcomes. Obstet Gynecol. Oct; 2009 114(4):818–824. [PubMed: 19888040]
76. Möhlig M, Spranger J, Osterhoff M, Ristow M, Pfeiffer AF, Schill T, Schlösser HW, Brabant G, Schöfl C. The polycystic ovary syndrome per se is not associated with increased chronic inflammation. Eur J Endocrinol. Apr; 2004 150(4):525–532. [PubMed: 15080783]

NIH-PA Author Manuscript

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NIH-PA Author Manuscript

77. Escobar-Morreale HF, Villuendas G, Botella-Carretero JI, Sancho J, San Millán JL. Obesity, and not insulin resistance, is the major determinant of serum inflammatory cardiovascular risk markers in pre-menopausal women. Diabetologia. May; 2003 46(5):625–633. [PubMed: 12739017]

78. Ketel IJ, Stehouwer CD, Serné EH, Korsen TJ, Hompes PG, Smulders YM, de Jongh RT, Homburg R, Lambalk CB. Obese but not normal-weight women with polycystic ovary syndrome are characterized by metabolic and microvascular insulin resistance. J Clin Endocrinol Metab. Sep; 2008 93(9):3365–3372. [PubMed: 18593766]

79. Ketel IJ, Stehouwer CD, Henry RM, Serné EH, Hompes P, Homburg R, Smulders YM, Lambalk CB. Greater Arterial Stiffness in Polycystic Ovary Syndrome (PCOS) Is an Obesity--But Not a PCOS-Associated Phenomenon. J Clin Endocrinol Metab. 2010

80. Libby P, Okamoto Y, Rocha VZ, Folco E. Inflammation in atherosclerosis: transition from theory to practice. Circ J. Feb; 2010 74(2):213–220. [PubMed: 20065609]

81. Spranger J, Möhlig M, Wegewitz U, Ristow M, Pfeiffer AF, Schill T, Schlösser HW, Brabant G, Schöfl C. Adiponectin is independently associated with insulin sensitivity in women with polycystic ovary syndrome. Clin Endocrinol (Oxf). Dec; 2004 61(6):738–746. [PubMed: 15579189]

82. Lindholm A, Bixo M, Eliasson M, Hudecova M, Arnadottir R, Holte J, Poromaa IS. Tissue plasminogen activator and plasminogen activator inhibitor 1 in obese and lean patients with polycystic ovary syndrome. Gynecol Endocrinol. 2010

83. Guzick DS, Talbott EO, Sutton-Tyrrell K, Herzog HC, Kuller LH, Wolfson SK Jr. Carotid atherosclerosis in women with polycystic ovary syndrome: initial results from a case-control study. Am J Obstet Gynecol. 1996; 174:1224–1232. [PubMed: 8623850]

84. Talbott EO, Guzick DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE, Kuller LH. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. Arterioscler Thromb Vasc Biol. 2000; 20:2414–2421. [PubMed: 11073846]

85. Luque-Ramírez M, Mendieta-Azcona C, Alvarez-Blasco F, Escobar-Morreale HF. Androgen excess is associated with the increased carotid intima-media thickness observed in young women with polycystic ovary syndrome. Hum Reprod. Dec; 2007 22(12):3197–3203. [PubMed: 17933750]

86. Carmina E, Orio F, Palomba S, Longo RA, Cascella T, Colao A, Lombardi G, Rini GB, Lobo RA. Endothelial dysfunction in PCOS: role of obesity and adipose hormones. Am J Med. Apr; 2006 119(4):356.e351–356. [PubMed: 16564785]

87. Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy PF 2nd, Fitzpatrick LA. Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2003; 88:2562–2568. [PubMed: 12788855]

88. Talbott EO, Zborowski JV, Rager JR, Boudreaux MY, Edmundowicz DA, Guzick DS. Evidence for an association between metabolic cardiovascular syndrome and coronary and aortic calcification among women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2004; 89:5454–5461. [PubMed: 15531497]

89. Talbott EO, Zborowski J, Rager J, Stragand JR. Is there an independent effect of polycystic ovary syndrome (PCOS) and menopause on the prevalence of subclinical atherosclerosis in middle aged women? Vasc Health Risk Manag. 2008; 4(2):453–462. [PubMed: 18561521]

90. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet. Aug 25; 2007 370(9588):685–697. [PubMed: 17720020]

91. Chen MJ, Yang WS, Yang JH, Chen CL, Ho HN, Yang YS. Relationship between androgen levels and blood pressure in young women with polycystic ovary syndrome. Hypertension. Jun; 2007 49(6):1442–1447. [PubMed: 17389259]

92. Riccioni G. The effect of antihypertensive drugs on carotid intima media thickness: an up-to-date review. Curr Med Chem. 2009; 16(8):988–996. [PubMed: 19275607]

93. Zavaroni I, Coruzzi P, Bonini L, Mossini GL, Musiari L, Gasparini P, Fantuzzi M, Reaven GM. Association between salt sensitivity and insulin concentrations in patients with hypertension. Am J Hypertens. Aug; 1995 8(8):855–858. [PubMed: 7576404]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

94. Resnick LM. Cellular ions in hypertension, insulin resistance, obesity, and diabetes: a unifying theme. J Am Soc Nephrol. Oct; 1992 3(4 Suppl):S78–85. [PubMed: 1457764]

95. Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database Syst Rev. 2003; 3 CD003053.

96. Diamanti-Kandarakis E, Alexandraki K, Piperi C, Aessopos A, Paterakis T, Katsikis I, Panidis D. Effect of metformin administration on plasma advanced glycation end product levels in women with polycystic ovary syndrome. Metabolism. Jan; 2007 56(1):129–134. [PubMed: 17161235]

97. Hattori Y, Suzuki M, Hattori S, Kasai K. Vascular smooth muscle cell activation by glycated albumin (Amadori adducts). Hypertension. Jan; 2002 39(1):22–28. [PubMed: 11799073]

98. Orio F Jr, Palomba S, Cascella T, De Simone B, Manguso F, Savastano S, Russo T, Tolino A, Zullo F, Lombardi G, Azziz R, Colao A. Improvement in endothelial structure and function after metformin treatment in young normal-weight women with polycystic ovary syndrome: results of a 6-month study. J Clin Endocrinol Metab. Nov; 2005 90(11):6072–6076. [PubMed: 16118336]

99. Kannel WB. Fifty years of Framingham Study contributions to understanding hypertension. J Hum Hypertens. Feb; 2000 14(2):83–90. [PubMed: 10723112]

100. Cupisti S, Kajaia N, Dittrich R, Duezenli H, W Beckmann M, Mueller A. Body mass index and ovarian function are associated with endocrine and metabolic abnormalities in women with hyperandrogenic syndrome. Eur J Endocrinol. May 5.2008 158:711–719. [PubMed: 18426831]

101. Glintborg D, Henriksen JE, Andersen M, Hagen C, Hangaard J, Rasmussen PE, Schousboe K, Hermann AP. Prevalence of endocrine diseases and abnormal glucose tolerance tests in 340 Caucasian premenopausal women with hirsutism as the referral diagnosis. Fertil Steril. Dec; 2004 82(6):1570–1579. [PubMed: 15589862]

102. Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, Stephens KC, Taylor K, Boots LR. Androgen excess in women: experience with over 1000 consecutive patients. J Clin Endocrinol Metab. Feb; 2004 89(2):453–462. [PubMed: 14764747]

103. Sverrisdottir YB, Mogren T, Kataoka J, Janson PO, Stener-Victorin E. Is polycystic ovary syndrome associated with high sympathetic nerve activity and size at birth? Am J Physiol Endocrinol Metab. 2008; 294:E576–581. [PubMed: 18198350]

104. Yildirir A, Aybar F, Kabakci G, Yarali H, Oto A. Heart rate variability in young women with polycystic ovary syndrome. Ann Noninvasive Electrocardiol. Oct; 2006 11(4):306–312. [PubMed: 17040278]

105. Muniyappa R, Montagnani M, Koh KK, Quon MJ. Cardiovascular actions of insulin. Endocr Rev. Aug; 2007 28(5):463–491. [PubMed: 17525361]

106. Müller-Wieland D, Kotzka J, Knebel B, Krone W. Metabolic syndrome and hypertension: pathophysiology and molecular basis of insulin resistance. Basic Res Cardiol. 1998; 93(Suppl 2): 131–134. [PubMed: 9833175]

107. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, Lobo R, Norman RJ, Talbott E, Dumesic DA. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab. May; 2010 95(5):2038–2049. [PubMed: 20375205]

108. Battaglia C, Mancini F, Fabbri R, Persico N, Busacchi P, Facchinetti F, Venturoli S. Polycystic ovary syndrome and cardiovascular risk in young patients treated with drospirenone-ethinylestradiol or contraceptive vaginal ring. A prospective, randomized, pilot study. Fertil Steril. Sep; 2010 94(4):1417–1425. [PubMed: 19591981]

109. Kriplani A, Periyasamy AJ, Agarwal N, Kulshrestha V, Kumar A, Ammini AC. Effect of oral contraceptive containing ethinyl estradiol combined with drospirenone vs. desogestrel on clinical and biochemical parameters in patients with polycystic ovary syndrome. Contraception. Aug; 2010 82(2):139–146. [PubMed: 20654754]

110. Fruzzetti F, Perini D, Lazzarini V, Parrini D, Gambacciani M, Genazzani AR. Comparison of effects of 3 mg drospirenone plus 20 mug ethinyl estradiol alone or combined with metformin or cyproterone acetate on classic metabolic cardiovascular risk factors in nonobese women with polycystic ovary syndrome. Fertil Steril. 2009 Nov 18. Epub ahead of print.

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111. Guido M, Romualdi D, Giuliani M, Suriano R, Selvaggi L, Apa R, Lanzone A. Drospirenone for the treatment of hirsute women with polycystic ovary syndrome: a clinical, endocrinological, metabolic pilot study. J Clin Endocrinol Metab. Jun; 2004 89(6):2817–2823. [PubMed: 15181063]

112. Ober KP, Hennessy JF. Spironolactone therapy for hirsutism in a hyperandrogenetic woman. Ann Intern Med. 1978; 89:643–644. [PubMed: 717935]

113. Rathnayake D, Sinclair R. Innovative use of spironolactone as an antiandrogen in the treatment of female pattern hair loss. Dermatol Clin. JUL 01; 2010 28(3):611–618. [PubMed: 20510769]

114. Christy NA, Franks AS, Cross LB. Spironolactone for hirsutism in polycystic ovary syndrome. Ann Pharmacother. 2005; 39(9):1517–1521. [PubMed: 16076921]

115. Ganie MA, Khurana ML, Eunice M, Gupta N, Gulati M, Dwivedi SN, Ammini AC. Comparison of efficacy of spironolactone with metformin in the management of polycystic ovary syndrome: an open-labeled study. J Clin Endocrinol Metab. Jun; 2004 89(6):2756–2762. [PubMed: 15181054]

116. Armanini D, Castello R, Scaroni C, Bonanni G, Faccini G, Pellati D, Bertoldo A, Fiore C, Moghetti P. Treatment of polycystic ovary syndrome with spironolactone plus licorice. Eur J Obstet Gynecol Reprod Biol. Mar; 2007 131(1):61–67. [PubMed: 17113210]

117. Norman RJ, Davies MJ, Lord J, Moran LJ. The role of lifestyle modification in polycystic ovary syndrome. Trends Endocrinol Metab. Aug; 2002 13(6):251–257. [PubMed: 12128286]

118. Eid GM, Cottam DR, Velcu LM, Mattar SG, Korytkowski MT, Gosman G, Hindi P, Schauer PR. Effective treatment of polycystic ovarian syndrome with Roux-en-Y gastric bypass. Surg Obes Relat Dis. Mar-Apr; 2005 1(2):77–80. [PubMed: 16925218]

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Box 1. Potential Causes of Hypertension in Women with PCOS

- Hyperandrogenism
- Insulin resistance
- Obesity
- Increased Sympathetic Nervous System Activity

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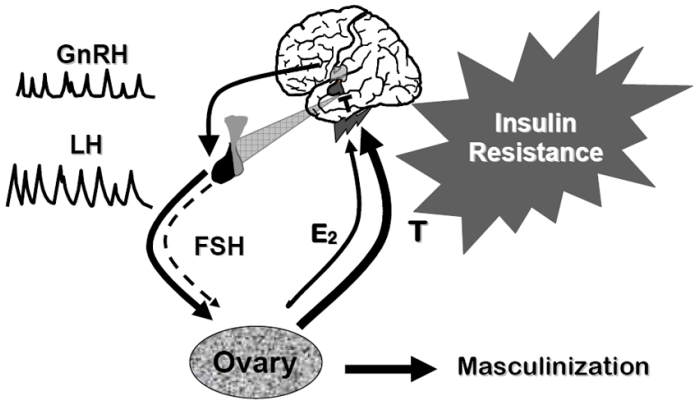

Figure 1.

Schema for the pathophysiology of PCOS. Increased GnRH pulsatility leads to a selective increase in LH pulsatility while suppressing FSH secretion. These gonadotropin secretory changes result in arrested follicular development and increased LH-dependent ovarian androgen production, increased theca cell androgen secretion, and decreased conversion of androgens to estrogens by the immature granulosa cells. These changes lead to increased ovarian androgen production, which feedback on the hypothalamic-pituitary axis, both directly by decreasing sensitivity to the normal actions of estrogen and progesterone to slow the frequency of pulsatile GnRH release and by extragonadal aromatization to estrogen, to increase LH relative to FSH release producing a self-sustaining syndrome. This figure is used with the permission of Andrea Dunaif.

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Table 1

Diagnostic Criteria for PCOS[a]

NIH Criteria[b]	Hyperandrogenism/Hyperandrogenemia Chronic anovulation
Rotterdam Criteria	Two of the following: hyperandrogenism/hyperandrogenemia, chronic anovulation, polycystic ovaries
Androgen Excess Society criteria	Hyperandrogenism/Hyperandrogenemia Infrequent or irregular ovulation OR regular ovulation and polycystic ovaries

[a] All criteria include the exclusion of other medical conditions, including thyroid or pituitary dysfunction, androgen–secreting tumors, Cushing's syndrome, or congenital adrenal hyperplasia

[b] NIH criteria developed with National Institute of Child Health and Human Development