

8-2008

# Diagnosis and Management of Polycystic Ovary Syndrome: A Literature Review

Brandy Cannon  
*Pacific University*

Follow this and additional works at: <http://commons.pacificu.edu/pa>



Part of the [Medicine and Health Sciences Commons](#)

---

## Recommended Citation

Cannon, Brandy, "Diagnosis and Management of Polycystic Ovary Syndrome: A Literature Review" (2008). *School of Physician Assistant Studies*. Paper 181.

This Capstone Project is brought to you for free and open access by the Theses, Dissertations and Capstone Projects at CommonKnowledge. It has been accepted for inclusion in School of Physician Assistant Studies by an authorized administrator of CommonKnowledge. For more information, please contact [CommonKnowledge@pacificu.edu](mailto:CommonKnowledge@pacificu.edu).

---

# Diagnosis and Management of Polycystic Ovary Syndrome: A Literature Review

## **Abstract**

**Purpose:** Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder that afflicts about 4-12% of women of reproductive age. First discovered by Stein and Leventhal in 1935, it is currently defined by the National Institute of Health as oligo- or anovulation with features of hyperandrogenism, when all other possible causes of menstrual irregularity and hyperandrogenism have been ruled out. PCOS can be distressing to women due to infertility issues and hyperandrogenism symptoms. PCOS can be challenging to diagnose by clinicians, and even more difficult to manage due to the large amount of presentations and treatment options. Currently there is no standard or universal course of therapy available.

**Methods:** An exhaustive literature search using the following search engines: Medline, NEJM, PudMed and CINAHL was conducted. Articles related to the topic but published more than 10 years ago were excluded.

**Results:** PCOS therapy should be appropriate for each patient taking into consideration her fertility, health and cosmetic desires. All PCOS patients should first be treated with lifestyle changes as this can yield improvement in all areas of pathogenesis. Diet, exercise and weight loss has proved efficacious in restoring ovulation, improving hyperandrogenism and decreasing insulin resistance. Management of anovulation and infertility will depend on whether or not the patient is attempting to conceive. If not, then oral contraceptives to decrease the risk of endometrial carcinoma will be the appropriate choice. If the individual is trying to conceive, then clomiphene citrate is considered first line in order to restore ovulation and promote fertility. If the patient is clomiphene resistant then, metformin should be tried as it has shown to improve ovulation although not as well as clomiphene. The next options include laparoscopic ovarian diathermy or gonadotropin therapy. When treating symptoms of hyperandrogenism such as: hirsutism, acne, seborrhea and male pattern baldness, anti-androgens should be used in all patients not attempting to conceive in order to reduce the amount of systemic testosterone causing the symptoms. Specifically, hirsutism is generally treated with mechanical methods. Metformin has also been shown to help improve hirsutism. Acne can be treated with topical and oral antibiotics and seborrhea can be managed with steroid creams. Rogaine should be used in women with male pattern baldness. Finally, and most importantly, women with PCOS should always be screened and treated for insulin resistance and syndrome X to prevent and slow the progression of diabetic and cardiovascular complications. If insulin resistance is found, patients should be put on metformin or TZDs to increase insulin sensitization. Also, if other disorders associated with metabolic syndrome are present, such as hyperlipidemia or hypertension, they should be treated appropriately.

**Conclusion:** If women with PCOS are diagnosed and managed properly with lifestyle changes and other pharmacological and surgical therapy, most distressing symptoms can be alleviated and future complications of diabetes and cardiovascular events can be slowed or prevented.

## **Degree Type**

Capstone Project

## **Degree Name**

Master of Science in Physician Assistant Studies

---

**First Advisor**

Mark Pedemonte, M.D.

**Second Advisor**

Jonathon W Gietzen MS PA-C

**Keywords**

Polycystic Ovarian Syndrome, PCOS, Stein-Leventhal Syndrome, Ovary, Polycystic

**Subject Categories**

Medicine and Health Sciences

**Rights**

This work is licensed under a [Creative Commons Attribution-Noncommercial-No Derivative Works 3.0 License](http://creativecommons.org/licenses/by-nc-nd/3.0/).

---

### Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

**If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:**

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

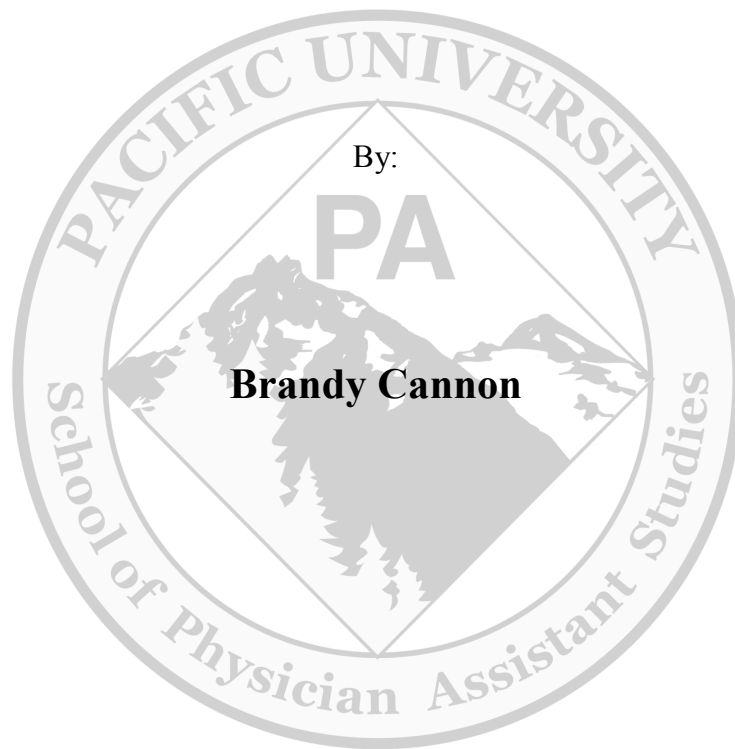
Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: [copyright@pacificu.edu](mailto:copyright@pacificu.edu)

## NOTICE TO READERS

This work is not a peer-reviewed publication. The Master's Candidate author(s) of this work have made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author(s) nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author(s) and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student authors attest that this work is completely their original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.

# **Diagnosis and Management of Polycystic Ovary Syndrome: A Literature Review**



A Clinical Research Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University, Forest Grove, OR

For the Masters of Science Degree August, 2008

Faculty Advisor: Mark Pedemonte, M.D.

Clinical Project Advisor: Jonathon W Gietzen MS PA-C



**School of Physician Assistant Studies**

222 SE 8<sup>th</sup> Ave, Suite 551, Hillsboro, OR 97123

(503) 352-7272

E-Mail: [pa@pacificu.edu](mailto:pa@pacificu.edu)

***STATEMENT OF ACCEPTANCE:***

This project is hereby accepted as a requirement for completion of the degree of:  
Masters of Science in Physician Assistant Studies at Pacific University School of Physician Assistant  
Studies on this day the sixteenth of August, 2008.

---

Brandy Cannon, PA-S  
Author

Date

---

Jonathon W Gietzen MS, PA-C  
Clinical Project Coordinator

Date

---

H. F. Randolph III, PA-C, MPAS  
Program Director

Date

---

---

## **Biography**

---

Brandy Cannon is a native of Washington State where she attended the University of Washington in Seattle. After earning her B.S. in cellular biology, she moved back home to the town of Camas, WA where she worked as a CNA while taking a few prerequisite courses to prepare for PA school. She gained acceptance into Pacific University's Physician Assistant Program in 2006, but made the decision to stay in Washington and commute during her training. During her clinical year she has gained interest in family practice and urgent care. Brandy is married and the mother of two boys; ages 5 years and 6mo old. Her interests include camping, sports and family activities. She plans to stay in Washington and work in Primary Care after graduation.



---

## Abstract

---

**Purpose:** Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder that afflicts about 4-12% of women of reproductive age. First discovered by Stein and Leventhal in 1935, it is currently defined by the National Institute of Health as oligo- or anovulation with features of hyperandrogenism, when all other possible causes of menstrual irregularity and hyperandrogenism have been ruled out. PCOS can be distressing to women due to infertility issues and hyperandrogenism symptoms. PCOS can be challenging to diagnose by clinicians, and even more difficult to manage due to the large amount of presentations and treatment options. Currently there is no standard or universal course of therapy available.

**Methods:** An exhaustive literature search using the following search engines: Medline, NEJM, PubMed and CINAHL was conducted. Articles related to the topic but published more than 10 years ago were excluded.

**Results:** PCOS therapy should be appropriate for each patient taking into consideration her fertility, health and cosmetic desires. All PCOS patients should first be treated with lifestyle changes as this can yield improvement in all areas of pathogenesis. Diet, exercise and weight loss has proved efficacious in restoring ovulation, improving hyperandrogenism and decreasing insulin resistance. Management of anovulation and infertility will depend on whether or not the patient is attempting to conceive. If not, then oral contraceptives to decrease the risk of endometrial carcinoma will be the appropriate choice. If the individual is trying to conceive, then clomiphene citrate is considered first line in order to restore ovulation and promote fertility. If the patient is clomiphene resistant then, metformin should be tried as it has shown to improve ovulation although not as well as clomiphene. The next options include laparoscopic ovarian diathermy or gonadotropin therapy. When treating symptoms of hyperandrogenism such as: hirsutism, acne, seborrhea and male pattern baldness, anti-androgens should be used in all patients not attempting to conceive in order to reduce the amount of systemic testosterone causing the symptoms. Specifically, hirsutism is generally treated with mechanical methods. Metformin has also been shown to help improve hirsutism. Acne can be treated with topical and oral antibiotics and seborrhea can be managed with steroid creams. Rogaine should be used in women with male pattern baldness. Finally, and most importantly, women with PCOS should always be screened and treated for insulin resistance and syndrome X to prevent and slow the progression of diabetic and cardiovascular complications. If insulin resistance is found, patients should be put on metformin or TZDs to increase insulin sensitization. Also, if other disorders associated with metabolic syndrome are present, such as hyperlipidemia or hypertension, they should be treated appropriately.

**Conclusion:** If women with PCOS are diagnosed and managed properly with lifestyle changes and other pharmacological and surgical therapy, most distressing symptoms can be alleviated and future complications of diabetes and cardiovascular events can be slowed or prevented.

**Keywords:** Polycystic Ovarian Syndrome, PCOS, Stein-Leventhal Syndrome, Ovary, Polycystic, Management, Treatment, Therapy, Diagnosis.

---

---

## Acknowledgements

---

To *my husband, Michael*, Thank you for being my support when I needed it most, for picking up the slack when I couldn't, for telling me it would be alright, and most of all, for believing in me even when I didn't.

To *my mother*: Thank you for helping me to succeed all of my life, and giving me all those words of encouragement and prayers even though I didn't always appreciate it in the moment.

To *my boys*: Thank you for bringing so much joy into my life and keeping me on my toes.

---

# Table of Contents

---

Statement of Approval .....	1
Biography .....	2
Abstract .....	3
Acknowledgements .....	4
Table of Contents .....	5
List of Tables .....	6
List of Figures .....	7
List of Abbreviations.....	8
Introduction and Background.....	9
Methods .....	10
Results .....	10
Discussion .....	18
Tables .....	21
Figures .....	22
References .....	24

---

## List of Tables

---

Table I: Etiology Hypotheses of Polycystic Ovarian Syndrome

Table II: Symptoms and Signs of Polycystic Ovarian Syndrome

Table III: Differential Diagnosis for PCOS and Associated Laboratory Tests and Values

---

---

# List of Figures

---

Figure I: Examples of Polycystic Ovaries; a) Ultrasound view, b) Gross view

Figure II: Age-adjusted prevalence of metabolic syndrome criteria in women with PCOS

Figure III: An Overview of PCOS Management

---

---

## List of Abbreviations

---

PCOS.....	Polycystic Ovary Syndrome
HDL-C.....	High Density Lipoprotein Cholesterol
DVT.....	Deep Vein Thrombosis
TZDs.....	Thiazolidinediones
FDA.....	Food and Drug Administration
CRP.....	C-Reactive Program
ACE-inhibitors.....	Angiotensin Converting Enzyme Inhibitors
ARBs.....	Angiotensin II Receptor Blockers

# **Diagnosis and Management of Polycystic Ovary Syndrome: A Literature Review**

## **INTRODUCTION**

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder that afflicts about 4-12% of women of reproductive age.<sup>1</sup> The disorder was first noted by Stein and Leventhal in 1935 when the link between amenorrhea, hirsutism, infertility and ovarian cysts was discovered. Despite much debate in defining this disorder, most clinicians use the definition set forth by the National Institutes of Health in 1990. Their diagnostic criteria included: oligo- or anovulation with features of hyperandrogenism, when all other possible causes of menstrual irregularity and hyperandrogenism have been ruled out.<sup>2,3</sup> Some investigators have included the presence of polycystic ovaries in this definition, while others classify this finding as nonspecific.<sup>2,4</sup>

The etiology of PCOS is unclear, but 3 hypotheses have been suggested by the Polycystic Ovary Syndrome Writing Committee (Table I).<sup>5</sup> Although the specific cause is unknown, much of the symptoms of PCOS stem from hyperandrogenism and insulin resistance.<sup>4</sup> Disorders linked to insulin resistance include increased risk for Metabolic Syndrome or Syndrome X. The characteristics of this disorder include: central obesity with a waist circumference greater than 88cm, elevated triglycerides over 150 mg/dL, an HDL-C below 50 mg/dL, Hypertension, over 130/85 mmHg, and impaired fasting glucose higher than 110 mg/dL. Having Metabolic Syndrome puts women at a much higher risk of cardiovascular complications and type 2 diabetes.<sup>1,4</sup> Conditions associated with hyperandrogenism include hirsutism, which is excessive hair growth in women in a normally male pattern,<sup>6</sup> acne, male pattern baldness, oligo- or anovulation, menstrual irregularity and infertility.<sup>4</sup>

PCOS can be challenging to diagnose, and even more difficult to manage due to the large amount of presentations and treatment options. Currently there is no standard or universal course of therapy available. The treatment for each patient must be tailored to each individual and the importance she places on certain symptoms and signs. Another challenge is continuing to adjust

treatment in the face of changing symptoms.<sup>1</sup> This paper will present the diagnosis and management options for PCOS. Diagnostic criteria should include oligo- or anovulation with symptoms of hyperandrogenism, while other causes of both should be ruled out initially.<sup>2</sup> Therapy should be targeted at controlling distressing symptoms for the patient such as those caused by hyperandrogenism, managing ovulation and infertility to allow patient to have children if desired and to prevent endometrial cancer, and finally, managing the long term effects of insulin resistance to prevent future cardiovascular and diabetic complications.<sup>1,4</sup>

## **Methods**

An exhaustive literature search using the following search engines: Medline, NEJM, PudMed and CINAHL was conducted. The following search terms were used: Polycystic Ovarian Syndrome, PCOS, Stein-Leventhal Syndrome, Ovary, Polycystic, Management, Treatment, Therapy, Lifestyle change, Infertility, Insulin Resistance, and Hyperandrogenism. Articles related to the topic but published more than 10 years ago were excluded.

## **Results**

### **Diagnosis and Laboratory Evaluation**

Women with PCOS may have varied presentations including infertility, irregular menses, excess hair growth, etc or signs may be discovered during a routine physical exam including acanthosis nigricans, hirsutism, obesity, etc. An in depth history should be taken paying special attention to menstrual and pregnancy history, medication use, social history including diet, smoking and alcohol use, and family history of cardiovascular disease and diabetes.<sup>1,4</sup> Unfortunately, there is no specific study or laboratory test that is diagnostic for PCOS so the clinician must rely on his knowledge of the signs and symptoms of the disease (Table II) to begin the proper workup for the disorder.<sup>1</sup>



PCOS laboratory evaluation should seek positive labs that confirm the diagnosis while other disorders causing similar symptoms must be ruled out. Hypothyroidism, Hyperprolactinemia, pregnancy and Cushings Syndrome can mimic the presentation of PCOS. Also, adrenal, ovarian, and stomach tumors can cause similar findings. Other less common causes include acromegaly, late onset congenital adrenal hyperplasia, hyperthecosis, primary hypothalamic amenorrhea, and primary ovarian failure. The corresponding laboratory tests and studies should be done and any abnormal values should be followed-up properly (Table III). Also, in an attempt to confirm the diagnosis of PCOS and rule out an ovarian tumor, a pelvic ultrasound should be ordered to investigate the presence of polycystic ovaries (figure I).<sup>1,3,7</sup> However, this test may not be very specific as over 20% of women without PCOS have this finding. If all of the aforementioned disorders are ruled out and hyperandrogenism and chronic anovulation persist, PCOS should be diagnosed.<sup>1</sup> In addition to the previous studies, a fasting lipid panel and a two-hour oral glucose tolerance test should be done to screen for dyslipidemias and diabetes or impaired fasting glucose.<sup>4</sup>

### **Management of PCOS**

The management PCOS can be broken down into three categories: 1) correction of oligo-/anovulation or irregular menses in association with infertility, 2) controlling symptoms of hyperandrogenism, and 3) management of the lifelong effects of insulin resistance. This can be a difficult task due to the varying symptoms and emphasis placed on each symptom by individual women, in addition to the many treatment options available with lack of standardization.<sup>1</sup>

### **Control of Irregular Menses and Anovulation in Women Not Attempting to Conceive**

Irregular menses can be very troublesome for women due to the variable start times. Also, infrequent menses can cause more severe cramping and have heavier flow.<sup>1</sup> Having irregular

menses can also be a great health risk for patients because it can put them at increased risk of endometrial cancer. The lifetime risk of endometrial cancer is 2.6 percent in the general population, but in women with PCOS there is a 3-fold increase.<sup>1,7</sup> They also tend to present earlier in life. The increased risk of endometrial carcinoma results from prolonged periods of unopposed estrogen. In women with chronic irregular menses, it is important to rule out endometrial carcinoma by biopsy.<sup>7</sup> Four periods each year are needed to bring the increased risk of cancer into normal range.<sup>1</sup> Oral contraceptives have been the standard treatment for irregular menses for several years and medroxyprogesterone acetate has been shown to decrease the risk of endometrial cancer. Oral contraceptives work by suppressing androgen secretion by the ovaries and correcting unopposed estrogen.<sup>4,7</sup> Oral contraceptives should not be used in women with a history of DVT or in women over 35 years old who smoke. Birth control pills should also be used with caution in women with dyslipidemias, as they can worsen triglyceride levels. Women who are obese should lose weight as this can help to regulate menses.<sup>1,4</sup>

### **Ovulation Restoration in Women Attempting to Conceive**

75 percent of anovulatory infertility is caused by PCOS, and women with PCOS can expect a 30-50 percent first trimester miscarriage rate. Management of infertility can be difficult for the clinician and upsetting to the patient. Infertility management in PCOS is usually a team effort with physicians from endocrinology and obstetrics involved.<sup>1</sup> Lifestyle changes and clomiphene are generally first line treatment. If the first line treatment fails, then gonadotropins, insulin-sensitizers and surgery are the next lines of management options.<sup>4</sup>

Lifestyle changes should be attempted first in any obese women with PCOS wanting to conceive. Weight loss improves insulin resistance which plays a role in menstrual dysfunction.<sup>1</sup> A loss in weight has been proven to restore ovulation in previously anovulatory

women. One study by Kiddy et al. showed that with a weight loss of >5% resulted in about 40% of the studies participants became pregnant.<sup>9</sup> Another study by Clark et al. resulted in a 90% ovulation rate in women with significant weight loss. 77.6% of those women who began ovulating conceived with 67% resulting in live births.<sup>10</sup>

Clomiphene citrate is often used when treating anovulation because of its proven effectiveness in inducing ovulation. However, high doses are generally needed in obese patients and in high doses it can increase the risk of multiple gestations.<sup>1</sup> Metformin and other insulin-sensitizers, like the TZDs have also been proven to induce ovulation by improving insulin resistance<sup>2</sup>, but there has been some controversy as to whether they are as efficacious as clomiphene. In small studies with insulin-sensitizers they have proven as efficacious as clomiphene, but other larger studies contradict these findings.<sup>11</sup> Clomiphene has been studied with metformin at length and TZDs have been studied against placebo. In a large randomized trial, Legro et al. found clomiphene to be superior to metformin or a combination of both in attaining pregnancy and live births as a primary outcome; however, the clomiphene group did result in more pregnancy related adverse events. Also, metformin reduced insulin resistance in those afflicted women and did result in a considerable increase in pregnancy and live births.<sup>11</sup> In a study by Cataldo et al. 55% of the participants reached ovulation while on rosiglitazone and those on the 8mg daily dose had an average 46% drop in insulinemia.<sup>12</sup> Azziz et al. had similar results with troglitazone in a randomized, double-blind, placebo-controlled study.<sup>13</sup> These results are consistent with other studies done with TZDs; however, troglitazone was taken off the market in 2000 due to hepatotoxicity.<sup>1</sup> In those individuals who are clomiphene resistant, pretreatment with insulin-sensitizers improves outcomes of clomiphene and other fertility therapies.<sup>1,13</sup>

When clomiphene and insulin-sensitizers fail, gonadotropins and surgical treatment are often used to induce ovulation. About 20% of women with PCOS are clomiphene-resistant.<sup>14</sup> Laparoscopic ovarian diathermy or drilling is an alternative to gonadotropin therapy. Gonadotropin therapy involves daily injections of synthetic pituitary gland protein hormones, LH and FSH, in order to induce ovulation.<sup>14</sup> The alternative, laparoscopic ovarian diathermy involves resecting portions of the ovaries to induce ovulation. Many studies have shown that gonadotropin use and laparoscopic ovarian diathermy have similar efficacy. Farquhar et al. found similar ovulation rates among women who underwent gonadotropin therapy versus ovarian drilling. He also found that surgical therapy resulted in about one third lower than ovulation rates than gonadotropin therapy. Gonadotropin therapy is also linked with increased risk of ovarian hyperstimulation which can be life threatening when severe and increased risk of multiple gestations. Gonadotropin therapy is also very time consuming because most patients have a treatment course requiring injections nearly every day. Laparoscopic surgery is more invasive, carries the small risk of infection and adhesions, and results in permanent, long-lasting effects on ovarian function.<sup>15</sup> Ovarian surgery can also have beneficial long-term effects that gonadotropin therapy cannot mimic. In a study by Mohiuddin et al. over half of the study's participants had ongoing fertility and regular menstruation after the mean 100 month follow-up period.<sup>14</sup>

### **Control of Hyperandrogenism Symptoms**

The hyperandrogen symptoms can be very disconcerting to women with PCOS and can present a challenge for clinicians when trying to reverse the effects. Unfortunately, the treatments for hyperandrogenism are generally palliative instead of curative.<sup>4</sup> The increase in androgens is likely due to an elevation in ovarian androgen secretion. This results from an increase in insulin

stimulation of ovarian steroid-secreting cells, and also insulin-stimulated growth factors. Most women present with hirsutism, acne, seborrhea or dandruff, and male pattern baldness.

Hirsutism generally is the most common of these symptoms with about 60-83% of women with PCOS having some variety of the disease.<sup>6</sup> The mainstay of treatment should be aimed at suppressing testosterone levels in the body or treating the source of the symptoms, as well as, treating the patients symptoms palliatively.<sup>3,4</sup>

Medical management of hyperandrogenism is aimed at reducing the amount of androgen systemically. This is generally done with oral contraceptives and anti-androgens which include spironolactone, flutamide and finasteride.<sup>4</sup> The anti-androgens all work in slightly different ways, but they all block the action of testosterone. Oral contraceptives are often used in conjunction with an anti-androgen to produce a synergistic effect of androgen inhibition. The anti-androgen drugs are contraindicated in pregnancy due to possible teratogenic effects.<sup>3</sup>

Hirsutism is generally treated with mechanical therapy. Mechanical methods involve shaving, plucking, electrolysis, laser and hair removal creams. Shaving is commonly used by women with little side effects, but can be undesirable for some women. Plucking can lead to infections such as folliculitis and can be very difficult to pluck large areas of hair. Electrolysis involves electrocoagulation of the hair follicle and is generally safe. However, it may not be a permanent solution and can be unrealistic when dealing with a large area of hair.<sup>1,4</sup> Laser therapy is aimed at damaging the hair follicle by thermal means. Side effects include edema, erythema, blistering and temporary hyper-/hypopigmentation. Laser treatment is more practical for large areas of hair removal.<sup>1</sup> Lastly, Eflornithine hydrochloride 13.9% cream or Vaniqa is FDA approved for the treatment of hirsutism.<sup>4</sup> Vaniqa slows, but does not stop the growth of hair. Side effects are generally limited to skin irritation. Unfortunately, Vaniqa is expensive and

not readily covered by most insurances, so its use is not wide spread.<sup>1</sup> Metformin has also been proven efficacious when treating moderate to severe Hirsutism. In a study by Harborne et al. women with PCOS and hirsutism were randomized to receive either metformin or dianette, an anti-androgen. The study found that metformin was as effective as dianette at reducing hair at multiple anatomical sites. However, compared with the dianette, metformin produced insignificant change in reducing androgen levels, but reduced insulin resistance significantly.<sup>6</sup>

The other symptoms of hyperandrogenism include acne, seborrhea and male pattern baldness. Acne and seborrhea are generally treated as they would in individuals without PCOS with topical and oral antibiotics, and steroid creams, respectively. Male pattern baldness can be treated with minoxidil or rogain. Rogaine is a vasodilator and has been proven to slow or stop hair loss while promoting hair growth. Unfortunately, any measurable progress is generally lost within a few months of discontinuation of the drug. In addition, women attempting to conceive should not use rogain because it is a pregnancy category C drug. It has been found to pass from mother to baby via breastmilk.<sup>16</sup>

### **Management of Insulin Resistance**

Insulin resistance is perhaps the most important aspect of PCOS to manage because of the long-term health risks that it poses, and the fact that it is either directly or indirectly related to the causes of many of the PCOS signs and symptoms.<sup>17</sup> Most women with PCOS are also affected by some severity of insulin resistance, which puts them at an increased risk of cardiovascular events and underlying metabolic syndrome, and type 2 diabetes. In women with PCOS and insulin resistance, most of them generally progress to type 2 diabetes. The risk of type 2 diabetes is increased 4- to 7-fold compared with women in the general population, and they generally develop the disease earlier in life. In addition, Dorkas et al. found that there was an 11-fold

increase in the risk of syndrome X (figure II).<sup>17, 18, 19</sup> Women with PCOS have a 4-fold greater risk of being obese or morbidly obese. They generally have lower HDL-C and higher triglycerides independent of BMI.<sup>19</sup> All of these factors significantly increases the risk of morbidity and mortality from cardiovascular and diabetic complications for women with PCOS. Specifically, each factor is an independent risk for greater atherosclerosis leading to elevated cardiovascular risk.<sup>18</sup>

Women with PCOS generally have elevations in predictors of future vascular disease including carotid wall thickness, CRP, homocysteine levels, and echocardiogram findings.<sup>19</sup> In a case control study with 30, nonobese women, Orio et al found that carotid flow was significantly impeded in PCOS compared to controls. The carotid wall thickness was measured by ultrasound and by flow-mediated dilation of brachial arteries.<sup>20</sup> In another case control study, Orio et al. found increased cardiac size, left ventricular posterior wall thickness and greater end-systolic volume in PCOS patients.<sup>21</sup> As mentioned above inflammatory markers like CRP and homocysteine have been recognized as vascular disease predictors. In a study done by Boulman, 36% of the PCOS women had a CRP of greater than 5 mg/L. CRP levels greater than 2 mg/L are linked to increased risk for cardiovascular events.<sup>22</sup> Schachter et al. found that women with PCOS had significantly higher levels of homocysteine in both obese and nonobese women.<sup>23</sup> Women with insulin resistance should be treated to not only decrease current symptoms, but in order to prevent degeneration to cardiovascular and diabetic complications.

When treating insulin resistance in women with PCOS, lifestyle changes should be first line therapy. As mentioned before, weight loss can improve insulin resistance and is a very important factor in improving all PCOS symptoms.<sup>1</sup> In a randomized study by Weinstock et al. 3 groups of women either performed a trial of diet, diet and aerobic exercise, or diet and strength

training. All groups had behavioral therapy. All groups lost an average of 13.8 kg and had about a 61.8% drop in hyperinsulinemia. There were no significant differences between diet and diet and exercise groups.<sup>24</sup> Another study by Knowler et al compared metformin to moderate lifestyle changes in reducing the development of type 2 diabetes from insulin resistance. During the 2.8 year follow-up period, metformin decreased the risk of developing type 2 diabetes by 31% and the lifestyle change resulted in a risk reduction of 58%.<sup>25</sup> Clearly, lifestyle modification is a very powerful and efficacious tool for clinicians to begin their PCOS therapy.

As mentioned before, metformin and TZDs also result in a reduction in insulin resistance and can be used to treat insulin resistance.<sup>3</sup> Other prevention therapy should be targeted at specific symptoms of Syndrome X and should be treated with the same regimen as those individuals without PCOS. Elevated blood pressure should be treated with diuretics, beta-blockers, calcium channel blockers, ACE-inhibitors and ARBs. Dyslipidemias should be treated with statins, fibrates and other medications used to regulate lipids.<sup>19</sup>

## **Discussion**

Polycystic Ovary Syndrome is a common disorder affecting women, but can be very difficult to diagnose and treat due to vague presenting symptoms and a lack of standardization in treatment. PCOS is defined as having oligo- or anovulation and hyperandrogenism in the absence of other disorders that may cause these symptoms. Disorders that need to be ruled out include: pregnancy, hypothyroidism, hyperprolactinemia, late onset congenital adrenal hyperplasia, androgen secreting tumors, hyperthecosis, adrenal or pituitary tumor, Cushing's syndrome, acromegaly, primary ovarian failure and an insulinoma.<sup>1,3,4</sup>

Women with PCOS may have varying symptoms and signs, as well as, different priorities placed on reversing certain symptoms. Therapy should be appropriate for each patient taking



into consideration her fertility, health and cosmetic desires. Generally, there are three main groups to identify and treat when managing an individual with PCOS: management of anovulation and infertility, controlling symptoms of hyperandrogenism and treating insulin resistance and any related problems. All groups should first be treated with lifestyle changes as this can yield improvement in all areas. Diet, exercise and weight loss has proved efficacious in restoring ovulation, improving hyperandrogenism and decreasing insulin resistance. Management of anovulation and infertility will depend on whether or not the patient is attempting to conceive. If not, then oral contraceptives to decrease the risk of endometrial carcinoma will be the appropriate choice.<sup>1</sup> If the individual is trying to conceive, then clomiphene citrate is considered first line in order to restore ovulation and promote fertility. If the patient is clomiphene resistant then, metformin should be tried as it has shown to improve ovulation although not as well as clomiphene.<sup>11</sup> The next options include laparoscopic ovarian diathermy or gonadotropin therapy. Both options come with their risks and benefits and a decision will be based on the clinician's recommendations and the patient's choice.

When treating symptoms of hyperandrogenism such as: hirsutism, acne, seborrhea and male pattern baldness, anti-androgens should be used in all patients not attempting to conceive in order to reduce the amount of systemic testosterone causing the symptoms. Specifically, hirsutism is generally treated with mechanical methods like: shaving, plucking, laser, electrolysis and Vaniqa. Metformin has also shown to help improve hirsutism.<sup>6</sup> Acne can be treated with topical and oral antibiotics and seborrhea can be managed with steroid creams. Rogaine should be used in women with male pattern baldness; however, must be avoided in women who are pregnant, breastfeeding or attempting to conceive.

Finally, and most importantly, women with PCOS should always be screened and treated for insulin resistance and syndrome X to prevent and slow the progression of diabetic and cardiovascular complications. If insulin resistance is found, patients should be put on metformin or TZDs to increase insulin sensitization. Also, if other disorders associated with metabolic syndrome are present, such as hyperlipidemia or hypertension, they should be treated appropriately.<sup>18</sup> Figure III gives an overview of PCOS management.

Future study ideas include more studies on the affect of lifestyle changes on all symptoms of PCOS and whether or not treating insulin resistance early results in a significant change in future morbidity and mortality. In addition, further research to establish standard diagnostic criteria and treatment should be addressed. PCOS is a treatable condition that warrants proper workup in women in whom it is suspected. If women with this disorder are diagnosed and managed properly with lifestyle changes and other pharmacological and surgical therapy, most distressing symptoms can be alleviated and future complications of diabetes and cardiovascular events can be slowed or prevented.

<b>Table I: Etiology Hypotheses of Polycystic Ovarian Syndrome</b>
Hypothalamic-pituitary communication abnormalities cause abnormal secretion of gonadotropin releasing hormone and luteinizing hormone, causing increased ovarian androgen production.
Enzymatic defect of ovarian steroidogenesis favoring excess androgen production.
Insulin resistance leads to metabolic and reproductive abnormalities in PCOS.
<i>Information for Table I derived from reference 5</i>

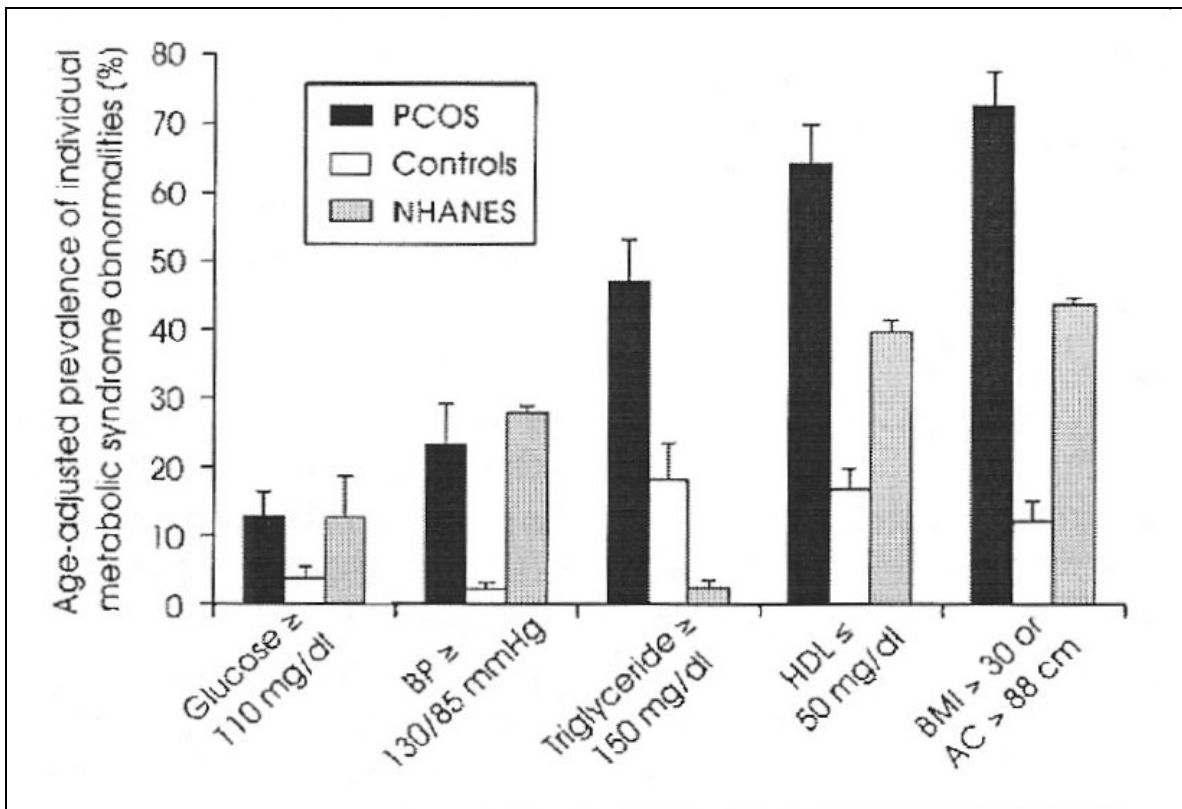
<b>Table II: Symptoms and Signs of Polycystic Ovarian Syndrome</b>	
Oligomenorrhea/Amenorrhea	Hirsutism
Oligo-/Anovulation and Infertility	Acne
Chronic First Trimester Miscarriage	Acanthosis Nigricans
Obesity with high rate of centripetal fat distribution	Male Pattern Baldness
Sleep Apnea	Enlarged Ovaries
<i>Information for Table II derived from reference 1 and 4</i>	

<b>Table III: Differential Diagnosis for PCOS and Associated Laboratory Tests and Values</b>		
<b>Diagnosis</b>	<b>Laboratory Test</b>	<b>Normal Value</b>
Pregnancy	Urine or Blood HCG	Positive
Hypothyroidism	TSH	0.4-4 microunits/ml
Hyperprolactinemia	Prolactin	<20ng/ml
Late onset congenital adrenal hyperplasia	17-hydroxyprogesterone	<200 ng/dl in follicular phase
Ovarian or other androgen secreting tumor	Total Testosterone	24-47ng/dl
Hyperthecosis	Total testosterone	24-47ng/dl
Adrenal Tumor	DHEA-S	12-535 mcg/dl
Cushings Syndrome	24-hr urine free cortisol	23-195 mcg/24 hr
Acromegaly	IGF1	10-1000 ng/ml
Pituitary Tumor	LH/FSH ratio	< 2.0
Primary Ovarian Failure	LH/FSH ratio	< 2.0
Insulinoma	Insulin C-Peptide Proinsulin	5-20 microunits/ml <3.3-5ng/ml, age dependent <0.8 ng/ml
<i>Information for Table III derived from reference 1, 3, and 4</i>		



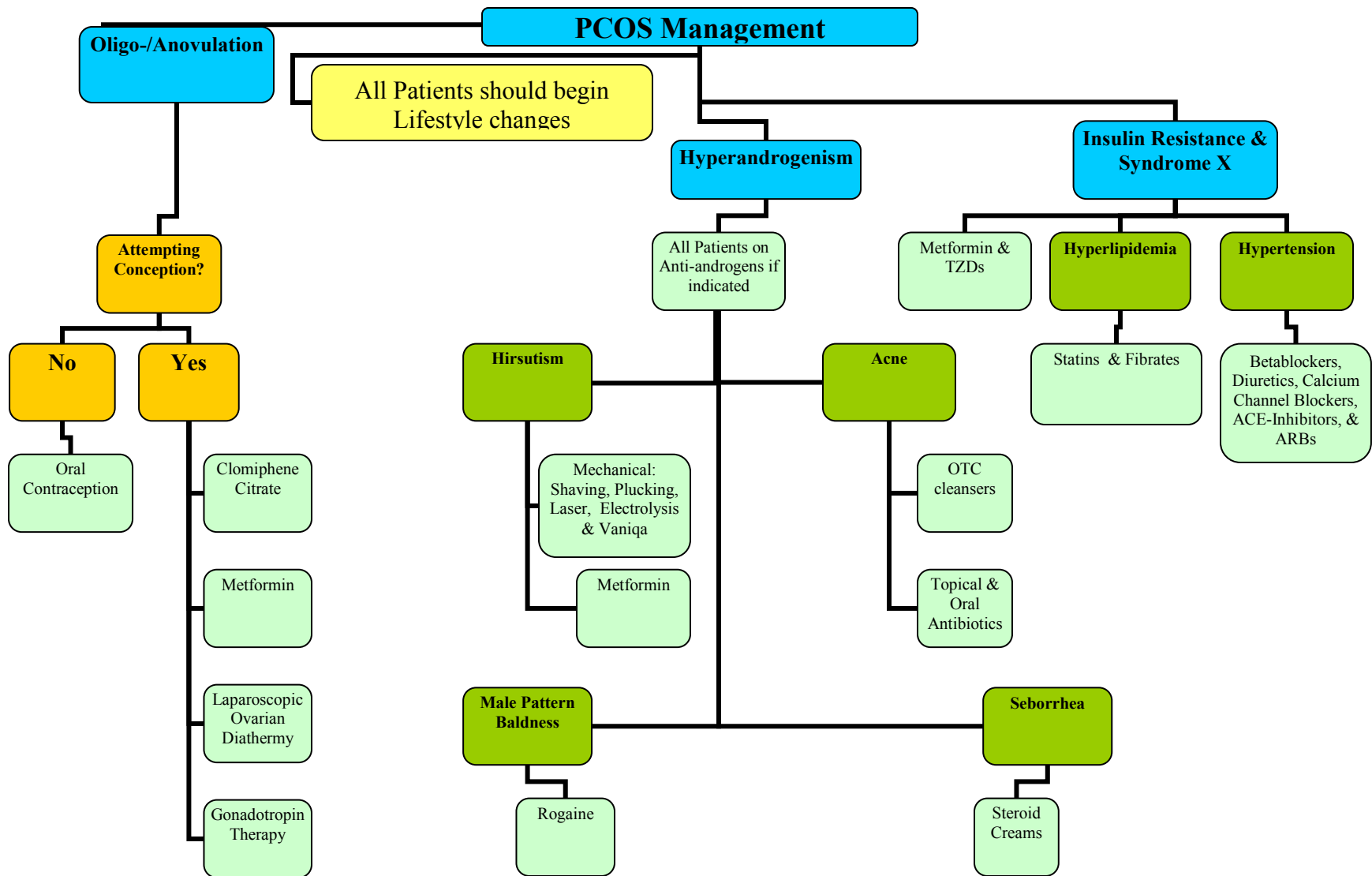
**Figure I:** Examples of Polycystic Ovaries; a) Ultrasound view, b) Gross view

*Figure I: a) picture from reference 8, b) picture from reference 9*



**Figure II:** Age-adjusted prevalence of metabolic syndrome criteria in women with PCOS

*From reference 18*



**Figure III: An Overview of PCOS Management**  
*Information from references 1, 3, 14, 16, 18*

## Bibliography

1. Sheehan MT. Polycystic Ovarian Syndrome: Diagnosis and Management. *Clinical Research and medicine*. 2004; 2:13-27.
2. Seli E, Duleba AJ. Should Patients with Polycystic Ovarian Syndrome be treated with Metformin? *Human Reproduction*. 2002; 17:2230-2236.
3. Setji TL, Brown AJ. Polycystic Ovary Syndrome: Diagnosis and Treatment. *American Journal of Medicine*. 2007; 120:128-132.
4. Schroeder BM. ACOG Releases Guidelines on Diagnosis and Management of Polycystic Ovary Syndrome. *American Family Physician*. 2003; 67:1619-1622.
5. Polycystic Ovarian Syndrome Writing Committee. American Association of Clinical Endocrinologists Position Statement on Metabolic and Cardiovascular Consequences of Polycystic Ovary Syndrome. *Endocrine Practice*. 2005; 11:126-134.
6. Harborne L, Fleming R, Lyall H, Sattar N, Norman J. Metformin or Antiandrogen in the Treatment of Hirsutism in Polycystic Ovary Syndrome. *Clinical Endocrinology and Metabolism*. 2003; 88:4116-4123.
7. Johnson A, Brannian J, Hansen K. Current Diagnosis and Treatment of Polycystic Ovary Syndrome. *South Dakota Journal of Medicine*. 2008; 61:129-137.
8. Virtual Medicine Centre. Polycystic Ovary Syndrome. Available at <http://www.virtualendocrinecentre.com/diseases.asp?did=851>. Accessed July 22, 2008.
9. Rebar RW. Chapter 3d Evaluation of Amenorrhea, Anovulation and Abnormal Bleeding. Available at: <http://www.endotext.org/female/female4/index.html>. Accessed July 22, 2008.
10. Diddy DS, Hamilton-Failey D, Bush A, Short F, Anyaoku V, Reed MJ. Improvement in Endocrine and Ovarian Function during Dietary Treatment of Obese Women with Polycystic Ovary Syndrome. *Clinical Endocrinology*. 1992; 36:1876-1880.
11. Legro RS, Barnhart HX, Schlaff WD, et al. Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome. *New England Journal of Medicine*. 2007; 356:551-566.
12. Cataldo NA, Abbasi F, McLaughlin TL, et al. Metabolic and Ovarian Effects of Rosiglitazone Treatment for 12 weeks in Insulin-Resistant Women with Polycystic Ovary Syndrome. *Human Reproduction*. 2005; 21:109-120.
13. Azziz R, Ehrmann D, Legro RS, et al. Troglitazone Improves Ovulation and Hirsutism in the Polycystic Ovary Syndrome: A Multicenter, Double Blind, Placebo-Controlled Trial. *Clinical Endocrinology and Metabolism*. 2001; 86:1626-1632.
14. Mohiudinn S, Bessellink D, Farquhar C. Long-term Follow Up of Women with Laparoscopic Ovarian Diathermy for Women with Clomiphene Resistant Polycystic Ovarian Syndrome. *Australian and New Zealand Journal of Obstetrics and Gynaecology*. 2007; 47:508-511.
15. Farquhar CM, Williamson K, Brown PM, Garland J. An Economic Evaluation of Laparoscopic Ovarian Diathermy versus Gonadotropin Therapy for Women with Clomiphene Citrate Resistant Polycystic Ovary Syndrome. *Human Reproduction*. 2004; 19:1110-1115.
16. Scow DT, Nolte RS, Shaughnessy AF. Medical Treatments for Balding in Men. *American Family Physician*. 1999; 59:1294-1298.
17. Meyer C, McGrath BP, Teede HJ. Effects of Medical Therapy on Insulin Resistance and the Cardiovascular System in Polycystic Ovary Syndrome. *Diabetes Care*. 2007; 30:471-478

18. Dokras A, Bochner M, Hollinrake E, Markham S, VanVorrhis B, Jagasia DH. Screening Women with Polycystic Ovary Syndrome for Metabolic Syndrome. *Obstetrics and Gynecology*. 2005; 106:131-137.
19. Lorenz LB, Wild RA. Polycystic Ovarian Syndrome: An Evidence-based Approach to Evaluation and Management of Diabetes and Cardiovascular Risks for Today's Clinician. *Clinical Obstetrics and Gynecology*. 2007; 50:226-242.
20. Orio F Jr, Palomba S, Cascella T, et al. Early Impairment of Endothelial Structure and Function in Young Normal-weight Women with Polycystic Ovary Syndrome. *Clinical Endocrinology and Metabolism*. 2004; 89:4588-4593.
21. Orio F Jr, Palmoba S, Spinelli L, et al. The Cardiovascular Risk of Young Women with Polycystic Ovary Syndrome: An Observational, Analytical, Prospective Case-Control Study. *Clinical Endocrinology and Metabolism*. 2004; 89:3696-3701.
22. Boulman N, Levy Y, Leiba R, et al. Increased C-reactive Protein Levels in the Polycystic Ovary Syndrome: A Marker of Cardiovascular Disease. *Clinical Endocrinology and Metabolism*. 2004; 89:2160-2165.
23. Schachter M, Raziel A, Friedler S, et al. Insulin Resistance in Patients with Polycystic Ovary Syndrome is Associated with Elevated Plasma Homocysteine. *Human Reproduction*. 2003; 18:721-727.
24. Weinstock RS, Dai H, Wadden TA. Diet and Exercise in the Treatment of Obesity. *Archives of Internal Medicine*. 1998; 158:2477-2483.
25. Knowler WC, Barrett-Conner E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. *New England Journal of Medicine*. 2002; 346:393-403.