4-2011

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April 30, 2011

Abstract

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders among adolescent and adult females. Many components are involved in the pathophysiology of the syndrome, especially markers of insulin resistance and hyperandrogenism. Although adult diagnostic criteria have become more refined; adolescent diagnosis remains obscure regardless of Base Metabolic Index (BMI). The aim of this paper is to inquire if there is an underdiagnosis of PCOS in normal weight adolescent females, identify potential underlying reasons and seek out clinical guidelines for practice. A review of the literature was completed and four overall themes emerged: a) hormones and their effects on treatment; b) glucose tolerance and/or insulin resistance; c) treatment options; and d) the need for increased awareness, early recognition, and a multidisciplinary approach to adolescent diagnosis and treatment. Weight as a variable factor was interspersed throughout majority of the studies. Results indicated that medications such as metformin and oral contraceptives are beneficial for treatment of insulin resistance, hyperandrogenism, and menstrual abnormalities. However, the primary treatment is a healthy diet and regular exercise. Implications for practice included; a need for increased awareness, early recognition, comprehensive screening, prompt treatment, and frequent follow-ups for all PCOS adolescents to prevent future morbidities. The final implication was the need for more research involving adolescent females with PCOS.

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Introduction

Polycystic ovarian syndrome (PCOS) is the most common female endocrine disorder, affecting approximately 5%-10% of all females and 4-6% of adolescent girls and young women (Emans, Laufer, & Goldstein, 2005). PCOS is a hormonal disorder that involves multiple organ systems within the body and is believed to be fundamentally caused by insensitivity to the hormone insulin. It can be diagnosed in all phases of life - in girls as young as 8-9 years of age through post-menopausal females. Although PCOS is one of the leading causes of infertility, the reproductive aspects of the disorder are secondary. PCOS is not limited to women of reproductive age or potential. (Polycystic Ovarian Syndrome Association, Inc, 2009).

This topic has had extensive research done over the past five years because of the growing incidence of occurrence among adolescent females, as well as the systemic repercussions that are being discovered with older women who were not managed optimally due to lack of research available to guide treatment. Although there is still much to learn about the topic, treatment guidelines and diagnostic criteria have been developed that allow healthcare providers to confidently manage and treat women with symptoms suggesting PCOS.

PCOS cannot only be on the radar of family and adult healthcare providers. There is growing evidence that PCOS is also a pediatric syndrome. Because some females reach menarche as early as 8-9 years old, PCOS needs to be a topic of concern for health care providers early in a child or adolescent's reproductive health. According to the Centers for Disease Control and Prevention (CDC) (2011), numbers of obese children in the U.S. has tripled since 1980. Many providers are finding increased numbers of obese adolescents having PCOS

when glucose and insulin levels are tested and insulin resistance is revealed. Discovering insulin resistance in obese adolescents plants the idea of PCOS being a differential diagnosis. Upon further clinical evaluation, excess distribution of body hair (hirsutism), acne, or menstrual abnormalities are noticed. The difficulty of diagnosing PCOS in adolescence is the mere awkwardness of the adolescent stage of development. There are many hormonal transitions taking place that could also manifest such as increased acne due to skin oil composition changes or irregular menses for the first year of menarche as the body's hormones are adjusting during puberty. How do pediatric healthcare providers know when to screen for PCOS in adolescent females who are normal weight? Emans et al. (2005) described PCOS as a diagnosis that is correlated to insulin resistance, not being overweight. There are many normal weight female adolescents and adults who have insulin resistance. PCOS would remain unknown in this population unless they volunteer information regarding oligomenorrhea, amenorrhea, and/or excess body hair in places that are not visible with clothing on. The difficulty of diagnosing PCOS reiterates the importance of getting a thorough history and doing a complete clinic exam to reveal key findings and begin interventions sooner. The underdiagnosis of PCOS in this normal weight patient population is the focus of this paper.

Identification of issue

Issue: What are the factors related to the underdiagnosis of polycystic ovarian syndrome in normal weight adolescent females?

PCOS begins in the perimenarcheal period in adolescents and has been characterized as an abnormal and exaggerated transition to puberty involving four key physiological processes: a) the increase in luteinizing hormone (LH) secretion; b) the increase in adrenal androgen

production; c) the increase in body mass; and d) the onset of adult patterns of insulin resistance (IR) (Emans et al., 2005). In 2003, The European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) evaluated the 1990 National Institute of Child Health and Human Disease (NICHD) of the United States National Institutes of Health (NIH) diagnostic criteria. Subsequent recommendations were developed and required at least 2 of the following 3 features for a PCOS diagnosis:

- Oligo-ovulation or anovulation manifested as oligomenorrhea or amenorrhea
- Hyperandrogenism (clinical evidence of androgen excess) or hyperandrogenemia (biochemical evidence of androgen excess)
- Polycystic ovaries (as defined on ultrasonography)
    - Polycystic ovaries are defined as 12 or more follicles in at least 1 ovary measuring 2-9 mm in diameter or a total ovarian volume of >10 cm^3 (Cowan, 2009, Laboratory Studies).

A PCOS diagnosis requires exclusion of all other disorders that can result in menstrual irregularity and hyperandrogenism through laboratory testing prior to making a definitive conclusion. Biochemical and/or imaging studies must be done to rule out these possible disorders. Even though diagnosis appears obscure, one thing is certain: PCOS has lifelong implications of increased risk of diabetes mellitus, obesity, insulin resistance, infertility, impaired quality of life, and secondarily, cardiovascular disease (Emans et al., 2005).

PCOS is a syndrome of hormone dysregulation. Knowledge of normal hormone regulation is necessary to better understand where abnormalities occur. The endocrine process starts in the hypothalamus where corticotrophin releasing hormone is released and stimulates the anterior pituitary gland to secrete luteinizing hormone (LH) and adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal glands to secrete androgens, while LH stimulates the ovaries to secrete testosterone, 5-dehydroepiandrosterone (DHEA), and androstenedione; all of which are androgens. Other body areas where androgens are produced include the skin, fat, liver,

and urogenital systems. Androstenedione and DHEA are converted to testosterone in the skin. Testosterone and dihydrotestosterone (DHT), the biologic active metabolite of testosterone, are the only circulating androgens able to activate androgen receptors. Dehydroepiandrosterone sulfate (DHEAS), DHEA, and androstenedione are all precursors of testosterone. The other two androgens, androstenedione and androstenediol, contain androgenic and estrogenic activity. In reproductive aged women, 25% of the circulating testosterone comes from the adrenals; the ovaries contribute with another 25%; and the remaining testosterone is produced by the peripheral conversion of androstenedione to testosterone in adipose tissue (Abdel-Rahman & Hurd, 2010).

Free testosterone has a high affinity to bind to sex hormone binding globulin (SHBG), a glycoprotein produced in the liver that binds to sex hormones testosterone and estrogen. Eighty percent of testosterone is bound to SHBG in healthy women. A lesser amount of testosterone is bound to albumin. About 1% of testosterone circulates freely in the bloodstream. The androgenicity of one's body depends upon the amount of free testosterone that is not bound to SHBG. Elevated free testosterone is one of the sensitivity markers for the diagnosis of PCOS and may be correlated to a decreased level of SHBG in the body. Low levels of SHBG occur because of obesity, insulin resistance, and androgen excess (Abdel-Rahman & Hurd, 2010).

The belief of PCOS being caused by insulin resistance may come from the fact that many women with significant ovarian androgen excess have insulin resistance and hyperinsulinemia. Insulin and insulin-like growth factor-1 (IGF-1) work with LH to directly increase androgen production from the ovaries, even in nonobese women. High levels of insulin increase IGF-1, decrease the insulin growth factor binding protein-1 (IGFBP1), and stimulate activity of the ovarian enzyme P-450c17alphaCYP17; which is crucial to the production of androgens by the

ovary. Women with PCOS appear to have dysregulation of this enzyme. Insulin also decreases hepatic SHBG production, thereby increasing free testosterone levels (Emans et al., 2005). In addition, insulin resistance in PCOS has been associated with adiponectin, a hormone secreted by adipocytes that regulates lipid metabolism and glucose levels. Both lean and obese women with PCOS have lower adiponectin levels than women without PCOS. Slower lipid metabolism and increased glucose levels result in a lower amount of adiponectin (Cowan, 2009).

In conjunction with increased insulin resistance and androgen excess, LH levels are elevated and the LH/FSH (follicle stimulating hormone) ratio may be elevated. The high LH levels stimulate the ovary to secret increased amounts of androgen from the tissue; the androgens, in turn, are converted in the peripheral tissues to estrogens. Under chronic LH stimulation, the polycystic ovaries secrete less androstenedione and testosterone. In contrast to high LH levels, FSH levels are often low to normal in patients with PCOS. The low levels can be caused from a multitude of factors including: a) suppression of the feedback mechanism of estrogen on FSH, b) relative insensitivity of FSH secretion to gonadotropin-releasing hormone (GnRH), and c) production of inhibin from the polycystic ovaries that could in turn stimulate androgen production and inhibit the release of FSH (Emans et al., 2005). In the ovary, a relative aromatase defect (a defect in the enzyme that converts androgens to estrogens) along with FSH deficiency and high intraovarian androgen levels impairs maturation of the follicle. (Farlex, Inc., 2011; Emans et al., 2005). Cyclic production of estrogen induces follicular degeneration and absorption, causing anovulation. Estrogen increases SHBG; low levels of SHBG facilitate the rapid uptake of free androgens and their peripheral conversion to estrogen. This causes free estrogen levels to be higher than those in normal women in the midfollicular phase of the cycle. The constant acyclic levels of estrogen result in continuous stimulation of the endometrium; thus

placing the woman with PCOS at higher risk of developing endometrial uterine cancer (Emans et al., 2005).

Based on diagnostic criteria stated earlier, diagnostic testing for PCOS includes laboratory and imaging studies in addition to a thorough history and physical exam. Laboratory tests should be done early in the morning, with the patient in a fasting state, and, in women with regular menses, samples should be taken between days 5-9 of their cycle. (Cowan, 2009). Hormonal contraceptives must be discontinued for at least 3 months to allow hormone levels to return to baseline by the time laboratory testing is done (Emans et al., 2005).

Various laboratory studies are helpful to diagnose PCOS. Laboratory studies include measuring total and free testosterone levels or a free androgen index that expresses the ratio of testosterone to SHBG and can be used to summarize the activity of free testosterone (Vankrieken, 1997). An elevated free testosterone level is a sensitive indicator of androgen excess. Another androgen, DHEA-S, may be normal or slightly elevated in patients with PCOS. Levels of SHBG are usually low in patients with PCOS due to many hormonal and insulin resistance influences. A serum human chorionic gonadotropin (hCG) level should be drawn to rule out pregnancy in women with amenorrhea or oligomenorrhea (Cowan, 2009). A fasting serum prolactin level should be drawn to rule out hyperprolactinemia; thyroid-stimulating hormone (TSH) should be measured to rule out hypothyroidism; and LH and FSH levels should be checked if amenorrhea, oligomenorrhea, or anovulation are present. Serum FSH is important to rule out ovarian failure. LH levels, if elevated, may help reinforce the clinical presentation of PCOS in the adolescent (Emans et al., 2005). A 17-hydroxyprogesterone (17-OHP) level should be drawn to rule out late onset congenital adrenal hyperplasia (CAH) and should be drawn between 7 and 8am in the follicular phase of the female's menstrual cycle (Emans et al., 2005).

Because of the metabolic abnormalities associated with PCOS, a 75g oral glucose-tolerance test (OGTT) is suggested to evaluate for insulin resistance (IR) and diabetes mellitus (DM) (Cowan, 2009). It is recommended to obtain a baseline fasting glucose level followed by a 2-hour glucose level (Emans et al., 2005). A 2-hour post-load glucose value of less than 140 mg/dL indicates normal glucose tolerance, 140-199 mg/dL indicates impaired glucose tolerance, and a value greater than or equal to 200 mg/dL indicated diabetes mellitus (Cowan, 2009). A lipid panel is recommended to check for cholesterol, LDL, HDL, and triglycerides if glucose tolerance results indicate diabetes mellitus. (Snyder, 2005). Elevated levels of LDL are in important abnormality in women with PCOS independent of obesity. Triglyceride levels are also typically elevated and HDL levels are reduced (Emans et al., 2005).

Ovarian ultrasonography is obtained selectively in adolescents with concern for PCOS. It is not necessary if history, physical exam, and laboratory tests provide enough data to confidently make the diagnosis. Transvaginal ultrasound is preferred for diagnosis; however, most adolescents prefer the transabdominal method. Ovarian morphology in PCOS is variable on ultrasound and ranges from normal ovaries to enlarged ovaries with a thickened glistening, avascular capsule, multiple small peripheral cysts, and increased stroma or hyperplasia of the ovarian theca stromal cells surrounding the follicle, often referred to as a “string of pearls” appearance. When polycystic ovaries are transected, subcapsular follicles in various stages of degeneration are seen in the periphery of the ovary as well as luteinized theca cells. The degree of total ovarian enlargement or stromal volume does not appear to be correlated with the testosterone levels circulating in the body (Emans et al., 2005).

Follow up requirements for adolescents diagnosed with PCOS depend on management techniques used for treatment and are dependent on treatment of symptoms. Diet and exercise

modification is the primary therapy being used in overweight and obese women with PCOS along with cessation of smoking. A clinic visit should be made to develop a plan between the provider and the patient to reduce weight through exercise and healthy eating. Follow up care can be done on an as needed basis or as the provider feels comfortable; there is no formal follow up guideline recommended. (Snyder, 2005).

Metformin can be used to improve insulin resistance, decrease hyperinsulinemia, improve hyperandrogenemia, and in some cases, improve anovulation in patients with PCOS. A clinic visit should be made with the patient to discuss the medication, including its side effects, intended use, proper administration, when to stop the medication and when to contact the primary care provider. Blood glucose should be checked annually as well as monitor risk for diabetes mellitus. Prior to prescribing metformin, liver and renal function should be assessed because metformin should not be prescribed if creatinine is elevated. Annual follow up should include a creatinine level and complete blood count (CBC) drawn to detect changes in renal function and a rare B12 deficiency. Patients should be counseled about avoiding significant alcohol use and discontinuing metformin prior to surgery or radiologic procedures that require patients to restrict their fluid intake. Metformin should be discontinued if the patient has a gastrointestinal illness or vomiting with potential dehydration. Like any medication, follow up with the patient and the primary care provider is dependent on the comfort level and reliability of the patient (Emans et al., 2005).

Another medication management strategy for treating PCOS is oral contraceptives (OCP). Contraceptives are used for management of oligomenorrhea or amenorrhea, hirsutism, and acne by altering the body's hormones. A clinic visit should be made to discuss information in regard to taking oral contraceptives including how to take them, intended use, what to do

when pills are missed, side effects, indications to stop taking the medication, and situations needing a call to a primary care provider. A history should be taken to assure there is not substantial cardiac history prior to prescription as oral contraceptives can increase risk for blood clots. Follow up care for oral contraceptives is a clinic visit one month after initial prescription. If no concerns are presented, 3 month supply of pills can be dispensed at a time or as the primary care provider feels comfortable (Cowan, 2009).

Several other treatments for PCOS are available. Short-term or long-term hair removal can be used to treat of hirsutism. Spironolactone oral medication and/or eflornithine cream can be used to treat hirsutism as well but are not as commonly used. Surgery is another option to restore ovulation but would involve extensive follow-up with an endocrinologist and/or gynecologist pre- and post-operatively. The surgical option is most often used in adult females. Finally, consultations to an endocrinologist are helpful. Endocrine follow-up evaluations consist of measuring and treating any biochemical and metabolic dysfunction. A reproductive endocrinologist referral for infertile women desiring pregnancy should be made on a case sensitive basis (Cowan, 2009).

Literature review

A search of the literature was completed with the goal to focus on PCOS in normal weight adolescent females. Academic databases searched include Academic Search Premier, Alt Health Watch, AMED, CINAHL Plus with Full Text, EBSCO MegaFILE, Health and Psychosocial Instruments, Health Source-Consumer Edition, Health Source: Nursing/Academic Edition, MasterFILE Premier, MEDLINE, Professional Development Collection, and Science Reference Center. All databases were searched through the St. Catherine University online

academic library. Search terms “PCOS”, “adolescent”, and “weight” yielded 202 results. Cross-referencing “PCOS”, “adolescent”, and “normal weight” yielded 42 results. Finally, “Polycystic ovary”, “adolescent”, and “normal weight” yielded 61 results. Articles were determined of value if they had research directly pertaining to the issue identified; search criteria were modified to include articles from 2006-2011 in search results. After initial review of 19 articles, 13 articles were deemed pertinent for further review. A couple articles chosen were published prior to the specified time range; however, their content was deemed pertinent for this review.

Six articles incorporated weight and/or BMI into the studies. Pinhas-Hamiel, Singer, Pilpel, Koren, Boyko, Hemis, Parientes, and Kanetys (2009) found that insulin levels were markedly higher in obese adolescents with PCOS ($P < 0.05$) as compared with normal weight adolescents or those of normal weight and PCOS. The findings demonstrated that adiponectin levels are inversely related to the degree of obesity in adolescent girls with PCOS. Whereas, leptin levels in adolescents with PCOS correlated with the degree of obesity ($P < 0.05$), having normal weight girls with PCOS as the controls. The degree of obesity predominantly determines serum adiponectin levels. Nester and Jakubowicz (1997) detected that nonobese women who took metformin had a significant reduction in serum free testosterone ($P<0.001$), and increase in serum SHBG ($P=0.002$), and that nonobese women who take metformin can have increased insulin sensitivity and decrease hyperandrogenism. Guido, Romualdi, Campagna, Ricciardi, Bompiani, and Lanzone (2010) observed that normal weight women who took estrogen and progestin combination pills containing chlormadinone had a decrease in varying androgen levels ($P < 0.03$ by sixth cycle vs. baseline) and significant increase in SHBG levels by the third cycle ($P < 0.01$). Because of the decrease in androgen levels and increase in SHBG, there was a significant decline in free androgen index after 6 cycles ($P < 0.05$).

Bhattacharya (April 2008) noticed abnormal glucose tolerance (AGT) in obese or normal weight adolescents and women with PCOS after completing a fasting plasma glucose level and 2-hour plasma glucose test. Women with abnormal glucose tolerance had a higher BMI than those with normal glucose tolerance. However, BMI alone was an insignificant contributing factor causing the deterioration of glucose tolerance in women with PCOS. Marcondes, Yamashita, Gustavo, Maciel, Baracat, and Halpern (2007) discovered that normal weight women with PCOS and normal insulin sensitivity had a significant decrease ($P < 0.05$) in LH, testosterone, fasting insulin, and insulin-resistance homeostasis model assessment (HOMA-IR); and a significant increase in FSH after taking metformin for 4 months. Finally, Trent, Austin, Rich, and Gordon (2005) determined that adolescent females with PCOS and a high BMI scored lower on the health-related quality of life (HRQL) indicators test that was reviewed from a previous study.

Four articles discussed varying aspects of PCOS diagnosis. Khan (2007) restated the lack of and need for established diagnostic criteria for diagnosis of PCOS in adolescents. Both NIH (1990) and ESHRE/ASRM Rotterham (2003) criteria are used in practice but there are caveats to both when used for adolescent diagnosis. Diamanti-Kandarakis (2010) added that the common features of normal puberty in adolescents, mainly menstrual irregularities and insulin resistance, obscure PCOS diagnosis in addition to lack of defined diagnostic criteria for PCOS in this age group. Bhattacharya (February 2008) concluded that discovering one risk factor for PCOS in women should prompt the clinician to search for other risk factors to trigger early diagnosis. Bronstein, Tawdekar, Liu, Pawelczak, David, and Shah (2011) found that PCOS diagnosis is occurring at an earlier age in the pediatric population, with PCOS preadolescents having had a significantly earlier onset of pubarche and thelarche than adolescents with PCOS ($P = 0.018$). In

addition to earlier puberty, PCOS diagnosis occurred 2 years sooner after thelarche in preadolescents than in adolescents.

Four articles focused on glucose tolerance or insulin resistance as a main research topic. Marcondes et al. (2007) discussed their findings on the positive effect metformin had normal weight, normal insulin sensitive women with PCOS. Metformin significantly decreased ($P < 0.05$) fasting insulin, carbohydrate tolerance and the area under the curve for insulin, and insulin resistance-homeostasis model assessment (HOMA-IR) in these women. Bhattacharya (April 2008) found out that AGT was increased in women with PCOS and increased BMI; however, other parameters of obesity need to be considered besides glucose tolerance tests for PCOS diagnosis. Nestler and Jakubowicz (1997) revealed that the mean area under the serum insulin curve after oral glucose administration decreased after taking metformin for normal weight or thin women diagnosed with PCOS ($P = 0.003$). Finally, Pinhas-Hamiel et al. (2009) determined insulin levels were substantially higher in obese adolescents with PCOS compared with those of normal weight adolescents ($P < 0.05$) and normal weight PCOS adolescents. Insulin levels did not statistically differ between normal weight adolescents and normal weight PCOS adolescents. Assessment of correlation between adiponectin levels and insulin levels was also completed; adiponectin concentrations correlated inversely with insulin ($P = 0.02$).

Three articles concentrated on the role of hormones and their effect on PCOS diagnosis and treatment. Nestler and Jakubowicz (1997) found that GnRH-stimulated peak serum 17alpha-hydroxyprogesterone (a steroid hormone) decreased after normal weight or thin PCOS women took metformin ($P = 0.005$). Serum free testosterone decreased by 70% ($P < 0.001$) and serum SHBG increased ($P = 0.002$) with the intake of metformin for the same study sample. Marcondes et al. (2007) noticed a significant decrease in LH and testosterone ($P < 0.05$) and significant

increase in FSH ($P < 0.05$) on normal weight women with PCOS and normal insulin sensitivity after taking metformin for 4 months. Guido et al. (2010) ascertained that plasma levels of SHBG significantly increased ($P < 0.01$) in hirsute women with PCOS after taking ethninylestradiol-chlormadinone acetate combination oral contraceptive for 6 weeks. Free androgen index, androstenedione, and 17-hydroxyprogesterone significantly decreased ($P < 0.03$) after the same study sample took the combination oral contraceptive pill for 6 weeks. Hirsutism significantly improved by the end of treatment ($P = 0.04$).

Five articles aimed at increasing awareness, early recognition, and prompt treatment that includes comprehensive screening for PCOS. Bronstein et al. (2011) found that PCOS is being diagnosed earlier in a female's life; often times in preadolescence more often than adolescence based on a literature review of 28 studies published within the last three years. Due to earlier onset and diagnosis of PCOS, increased awareness of PCOS in preadolescence and adolescence is needed, especially those who develop early pubarche and thelarche. Workup for PCOS should also be considered in this population. Bhattacharya (February 2008) observed that metabolic syndrome and dyslipidemia were more common than fasting glucose abnormalities in adolescent and adult females with PCOS. In light of this data, finding one risk factor for dyslipidemia should prompt the clinician to search for other factors. In addition, all females should undergo periodic screening for metabolic syndrome. Khan (2007) revealed that regular follow-ups with a provider, annual screening for diabetes and hyperlipidemias, and counseling about weight loss and fertility are vital treatment components for adolescents with PCOS to obtain progress and prevent future health complications. Mastorakos, Lambrinoudaki, and Creatsas (2006) agreed with others that diagnosis is occurring earlier in life, as early as the first decade of life, so timely recognition and screening need to take place to intervene promptly for prevention of long-term

sequelae. Finally, Warren-Ulanch and Arslanian (2006) reinforced the need for a high index of suspicion due to the difficulty of PCOS diagnosis in adolescents. Timely and comprehensive screening and treatment are crucial to prevent future diseases from developing. Because treatment options are unclear due to lack of research, long term follow-up needs to take place to effectively monitor improvement.

Three articles stated the importance of collaborative management of care through a multi-disciplinary approach to improve perceived quality of life in adolescents with PCOS. Mastorakos, Lambrinoudaki, and Creatsas (2006) established that reduction of body weight in adolescents with PCOS, the primary therapeutic goal, may require the teamwork of the primary care provider, dietician, and psychotherapist; hinting at the benefit of a multi-disciplinary approach. Wiksten-Almstromer, Hirschenberg, and Hagenfeldt (2007) noticed that different types of eating disorders were significantly higher in amenorrheic and oligomenorrheic adolescent girls ($P < 0.001$). Many of the girls also had coexisting psychiatric diagnoses and family problems ($P < 0.01$). This reiterated the need for collaborative care and using a multi-disciplinary approach to treat the whole person rather than only their medical condition. Often times, other psychosocial and/or medical components are occurring alongside those of PCOS. Trent et al. (2005) discovered the importance of perceived quality of life related to BMI in adolescent girls diagnosed with PCOS. Data evaluated from a previous adolescent PCOS quality of life survey revealed girls with PCOS scored significantly lower on scales pertaining to general health perceptions ($P < 0.001$), physical functioning ($P = 0.001$), family activities ($P < 0.03$), behavior ($P < 0.04$), and mental health; which was statistically insignificant. Differences in perceived quality of life were connected to increased BMI in adolescents with PCOS.

The final theme extracted from the literature was that of treatment options discussed in four articles. Mastorakos, Lambrinoudaki, and Creatsas (2006), Khan (2007), Warren-Ulanch and Arslanian (2006), and Diamanti-Kandarakis (2010) all mentioned similar treatment options effective in adolescents diagnosed with PCOS. Adoption of balanced, healthy dietary habits and regular exercise is the primary therapeutic choice with pharmaceutical modalities implemented on an as-needed basis and as an adjunct to lifestyle modification. Metformin and oral contraceptives, estrogen, progestin, or combination, have proven to be the most effective multi-symptom treatment. Shaving, waxing, or laser hair removal are treatment options for hirsutism along with one of the above medications and/or anti-androgens depending on presenting symptoms. All authors agree that follow-up needs to occur early and often to efficiently adjust the plan of care.

Discussion of findings

Many themes have emerged from the literature; however, four general themes seemed to resurface one way or another in each study. These themes are displayed in Table 1 along with which articles support each theme. All studies recommended the need for more research to be done.

Table 1. Summarization of themes from pertinent literature

Themes	Citations
Hormones and its effects for treatment	Nestler & Jakubowicz (1997); Guido et al. (2010).
Glucose tolerance/insulin resistance/weight	Bhattacharya (April 2008); Pinhas-Hamiel et al. (2009); Marcondes et al. (2007); Bhattacharya (Feb. 2008).
Treatment options and recommendations	Warren-Ulanch & Arslanian (2006); Khan (2007); Mastorakos, Lambrinoudaki, & Creatsas (2006).

Increased awareness, early recognition, multidisciplinary approach	Bronstein et al. (2011); Wiksten-Almstromer, Hirschenberg, & Hagenfeldt (2007); Trent et al. (2005); Diamanti-Kandarakis (2010).

Four studies reviewed were descriptive informative studies relaying knowledge to the general public regarding the pathophysiology of PCOS, diagnostic criteria, and the most effective treatment plans based on limited research with adolescents and adult females with PCOS. Many of the remaining studies were conducted in international settings that has some benefit for research; but could be argued as a limitation for applying research to the U.S. with a similar cultural population providers are going to be managing on a daily basis. Furthermore, specific diagnostic criteria for adolescents with PCOS do not exist. Many practicing providers use the 2003 ESHRE/ASRM criteria, more commonly known as the Rotterham criteria, for diagnosis guidelines. These criteria are not ideal for adolescent female PCOS diagnosis as the mere stage of adolescence can cause oligomenorrhea and/or menstrual irregularity. In addition, some teenagers might have the presence of bad acne due to alteration in the composition of sebaceous glands during the pubertal period (Emans et al., 2005). The 1990 NICHD/NIH criteria are also used but are more stringent than that of the 2003 Rotterham criteria, needing to meet all 3 criterions to confirm diagnosis. Lastly, some studies had fairly small sample sizes (n =10-44), leading their validity and applicability to numerous settings to be questionable.

Data has shown that a PCOS diagnosis is occurring earlier in adolescence and into preadolescence (Bronstein et al., 2011). Metformin is a positive adjunct for lifestyle modification even with PCOS adolescents who are normal weight and who have normal insulin sensitivity. Metformin is shown to improve LH and FSH levels. Obesity is found to have strong correlation with PCOS in adolescents but is not always present and should not be the only indicator for

screening. Providers have to be superior detectives to gather data that could contribute to a diagnosis. Negative findings from the literature review included perceived lower quality of life related to increased BMI in PCOS adolescents and general lack of concrete information for providers to access when attempting to diagnose and treat.

The findings of this literature review impact counseling needs by emphasizing follow-up care that is catered to the adolescent and family. Psychosocial ramifications involved with the PCOS diagnosis need to be taken into consideration and how they are related to peers' appearance and acceptance during this difficult developmental period. A multi-disciplinary approach to treatment and counseling for this population is important because endocrine disorders in adolescents seem to be of multifactoral origin: eating disorders, family, academic and social stress, and lifestyle choices can all be contributing factors (Wiksten-Almstromer et al., 2007). Trent et al. (2005) described the influence that BMI in adolescents with PCOS had on perceived overall health-related quality of life. The adolescent's weight loss strategies need to be investigated while maintaining an enthusiastic mentality for the female during this transition phase. Most adolescent females are already sensitive about their weight and very aware if they are overweight: thus, a negative approach to obtain improvement is not effective (Trent et al., 2005). Overall, counseling should include: a) regular follow-ups with a provider to monitor menses and decrease the chance of developing diabetes and other problems; b) annual screening for diabetes and hyperlipidemias; and c) guidance and education on weight loss and fertility should the adolescent want children later in life (Khan, 2007).

The impact of findings on educational needs includes early and frequent education with the patient and family. Many adolescents and their families will be caught off guard with a diagnosis of PCOS due to lack of public awareness of the condition. Teenagers may find it

difficult to conceptualize how insulin and glucose can affect their menstruation. Due to the complexity of the issue and ramifications involved, education needs to occur in steps with frequent follow-up for reinforcement and understanding. The adolescent will need to be educated about PCOS; what the diagnosis means for them now and in the future; the importance of a healthy diet and regular exercise as primary treatment; and pharmaceutical treatment options as adjuncts to lifestyle modification. If medication is prescribed, education regarding the medication will be necessary as well. The provider should expect understanding to be a slow process with frequent clarification as questions surface in relation to new information presented. Early recognition and regular follow-up, as mentioned in the literature review, are key indicators to successful treatment as well as a positive relationship between the primary care provider and adolescent.

As knowledge is gained from more research, results may impact health care policy by uncovering the need for updated PCOS diagnostic criteria specifically for adolescents. The criteria could change protocol and guidelines for diagnosis and treatment in the clinic setting, as well as education for providers and what the primary care provider can manage. If providers have increased awareness of the syndrome, the health issue can be discovered sooner and early interventions can begin immediately. Early identification of PCOS could increase management in the primary care clinic, decrease the need for referral to subspecialties and help contain costs for health care.

Implications for practice & recommendations

Analysis of the reviewed literature demonstrate that more research needs to occur to gain a better understanding of the intricacies involved in adolescents with PCOS. Specifically, more

studies need to emerge with larger sample sizes in non-randomized clinical trials, and to create more validity, reliability and applicability of the research results. Longitudinal studies that follow adolescents over at least 5 years from time of diagnosis through the beginning of adulthood would be helpful to create a comprehensive picture of lifestyle and the most effective modifications that were made. Lastly, additional studies conducted in the U.S. would be beneficial for providers practicing in that location to gain a better understanding of how PCOS affects adolescents of such cultures and backgrounds.

Implications and recommendations for practice among all articles are similar: a) importance of early recognition and prompt treatment; b) adoption of balanced dietary habits and regular exercise as primary treatment; c) pharmaceutical modalities implemented on an as-needed basis and as an adjunct to lifestyle modification with metformin and oral contraceptives proven to be the most effective; and d) further research needing to be done with adolescents diagnosed with PCOS. Regular follow-up is recommended to lessen the chance of developing other morbidities later in life. Metformin tends to be a great pharmaceutical adjunct for reducing insulin resistance, increasing glucose sensitivity, improving ovulation, and secondarily reducing hirsutism due to the effect metformin has on androgenic activity and insulin resistance (Emans et al., 2005). Oral contraceptives have been proven to be useful in altering the hormonal dysregulation of females with PCOS to return the body to ovulation, improve acne, and slightly improve hirsutism (Emans et al., 2005). The difficulty with diagnosis of PCOS in normal weight women, and to a greater degree, adolescence was reinforced in every article. Many of the females who present with PCOS are overweight and those who are normal weight tend to have more subtle clinical symptoms that are frequently missed. The only presenting complaint may be amenorrhea or oligomenorrhea. Lack of distinct clinical symptoms reiterates the importance for

increased awareness by the pediatric primary care provider to have PCOS in the differential diagnosis when clinical factors present in the early stages of puberty.

Implications for pediatric nurse practitioner practice include an increased awareness of PCOS in the adolescent females being seen in clinic whether they are overweight or normal weight. Follow-up should occur as mentioned earlier or more often if the adolescent is at risk for other diseases (diabetes, hyperlipidemia, cardiovascular disease, and hypertension). The provider needs to remember that adolescents can be emotionally fragile and are living a difficult part of their life as they transition to adulthood. Incorporating all the elements of holistic care is important for these patients. Primary care providers should expect some parents to be resistant to their adolescent taking medication, especially oral contraceptives. Education and reinforcement may need to occur more often before parents fully understand the benefits of medications being prescribed. Treatment may progress slower and with greater struggles due to parents' lack of awareness and education regarding the condition. Patience is vital in these circumstances. For those adolescents who are nonobese, pharmacological measures such as metformin have been shown to improve insulin sensitivity, improve menstrual cycle abnormalities, and decrease ovarian androgen production (Nestler & Jakubowicz, 1997; Marcondes et al., 2007). Lastly, comprehensive screening is recommended for adolescents to facilitate early diagnosis and treatment (Bhattacharya, 2008; Bronstein et al., 2011).

Recommended internet resources

Living in the internet era provides patients and families with access to a plethora of information at their fingertips. A list of internet resources for health professionals, patients, or

both is enclosed in appendix A with a brief critique of their reliability and recommendations for use.

In conclusion, PCOS is a common endocrine disorder of female adolescence and adulthood with exact etiology unknown but pathophysiology rooted in insulin resistance, hyperandrogenism, and chronic anovulation. A multitude of clinical factors can present including hirsutism, menstrual irregularities, metabolic abnormalities, acne, and increased BMI. History, physical exam, and laboratory tests are all components of making a diagnosis as some adolescents do not present with all clinical factors. Treatment options include healthy dietary habits and regular exercise accompanied by additional medications, such as metformin or hormone therapy to treat presenting symptoms. Primary care providers should be suspicious of PCOS in adolescent females regardless of their weight. A high level of suspicion will facilitate timely recognition, prompt treatment, and potential reduction or elimination of future morbidities until more information is known.

Appendix A

Recommended internet resources for patients and families

Wikipedia

- Good resource for patients and families for a basic understanding of PCOS with resources stated at the end of the article. Because anyone can submit information to the site for publication it is not recognized as medically reputable.
- http://en.wikipedia.org/wiki/Polycystic_ovary_syndrome

PCOSupport

- Great website for a support network for patients and families after diagnosis. It was started and is operated by women diagnosed with PCOS and is a volunteer, non-profit organization. It provides information in an easy-to-read, understandable manner. Not recommended for medical explanation of PCOS.
- http://www.pcosupport.org/

SoulCysters.com

- Good support for patients and families with a chat area available to interact with others who were diagnosed. Founded by Kathryn Carney, past anchor of *CNN Headline News*. Website is not very child friendly. It is acceptable for PCOS education but better sites are available for accurate medical information.
- http://www.soulcysters.com/

Insulite Laboratories

- Poor website: Has good education for patients and families about PCOS but it tries to manage one's PCOS by selling the "Insulite PCOS system" as opposed to recommending professionally suggested methods or visiting a primary care provider.
- http://pcos.insulitelabs.com/

PCOS Challenge

- Great for support for patients/families. It has a "PCOS Challenge TV show", ability to read others web posts, and chat room for support. Has limited educational information; other sites are better for that purpose.
- http://www.pcoschallenge.com/

Center for Young Women's Health

- Good for support/guidance for adolescent patients and families. The website is catered appropriately to teens and information is easy to read and understand. Accurate medical information is well-rounded; addressing all concerns for adolescents and families. Written by Center for Young Women's Health at Children's Hospital Boston; has HON code for trustworthy health information.
- http://www.youngwomenshealth.org/pcos_parent.html

Kids Health/Teens Health

- Good education for teens and families but not as reliable or beneficial as Center for Young Women's Health. Website appears to be catered more to the preadolescent. Site is operated by the Nemours Foundation, an organization dedicated to improving children's health through research, media, and hospital support. Disclaimer at the bottom of the site states it is for educational purposes only. For specific medical advice, diagnoses, and treatment, consult your doctor.
- http://kidshealth.org/teen/sexual_health/girls/pcos.html

Girls Health.gov

- Good for teens, parents, and education referral resource for professionals. Similar benefits as Center for Young Women's Health website. Owned and maintained by Office on Women's Health in the Office of the Assistant Secretary for Health at the U.S. Dept of Health and Human Services.
- http://www.girlshealth.gov/parents/parentsbody/pcos_educators.cfm

Recommended internet resources for professionals

Lab Tests Online:

- Great for professionals in education and explanation of labs to order and what results to expect for a PCOS diagnosis. Operated by the American Association for Clinical Chemistry; has HON code standard for trustworthy health information.
- http://www.labtestsonline.org/understanding/conditions/pcos-3.html

Medscape Reference

- Good for professionals with in-depth medical information and explanation of all avenues of PCOS for adolescents. Disclaimer at the bottom: "The site is designed primarily for use by qualified physicians and other medical professionals but should not be replacement for a visit to a health care provider if concerned about health." For

educational purposes only. The editing board with credentials is attached to each article and available for readers to view.

- http://emedicine.medscape.com/article/256806-overview#showall

Medscape Nurses: News

- Similar to Medscape Reference; PCOS article is a little older (2005) with professional journal publication citation and information available about the author's credentials.
- http://www.medscape.com/viewarticle/515682_3

Both

WomensHealth.gov through the Mayo Clinic

- Good for patients and families: great for explaining accurate medical information in an easy-to-understand language. Operated by the Mayo Foundation for Medical Education and Research. Has a HON code standard for trustworthy health information.
- http://www.mayoclinic.com/health/polycystic-ovary-syndrome/DS00423

WebMD for Women's Health

- Good for patients, families, and professionals at explaining the syndrome; probably more beneficial for professionals due to medical language used. Reputable site with URAC accredited health website seal, HON certified code, and TrustE certified privacy seal.
- http://women.webmd.com/tc/polycystic-ovary-syndrome-pcos-topic-overview

PubMed Health

- Good for professionals, patients, and families for medical information about PCOS with language that is easy to understand. Operated by the National Center for Biotechnology Information (NCBI) and the U.S. National Library of Medicine (NLM). Has partnership with American Society of Health System Pharmacists (ASHP), Agency for Health Research Quality (AHRQ), and Institute for Quality and Efficiency in Healthcare (IQWIG). Has seals for NLM, National Institutes of Health (NIH), U.S. Dept of Health and Human Services, and USA.gov.
- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001408/

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