POLYCYSTIC OVARY SYNDROME METABOLIC COMORBIDITIES: A CRITICAL APPRAISAL OF THE EVIDENCE WITH PRACTICE RECOMMENDATIONS

A

PROJECT

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POLYCYSTIC OVARY SYNDROME METABOLIC COMORBIDITIES

Abstract

Polycystic ovary syndrome (PCOS) is a complex metabolic and reproductive disorder that affects an extensive number of women of reproductive aged. The purpose of this project was to critically appraise current evidence regarding the metabolic comorbidities associated and their impacts on women with PCOS with goals of identifying what evidence based assessment, evaluation, and treatment options are available to health care providers treating women with PCOS. The results of this critical appraisal and consensus statements from The Endocrine Society and the American Society of Reproductive Medicine [ASRM] concluded that women with PCOS have an increased risk of developing type 2 diabetes, cardiovascular disease, and metabolic syndrome (Akbarzadeh et al., 2012; ASRM, 2012; Legro et al., 2013; Moran, Misso, Wild, & Norman, 2010; Tao, Shengxian, Zhao, Mao, & Liu, 2012; & Yilmaz, Isaoglu, Delibas, & Kadanali, 2011). An evidence based practice algorithm was developed from the results of this critical appraisal and consensus between both The Endocrine Society and ASRM on the diagnosis and treatment of PCOS. The results of this critical appraisal and evidence-based algorithm will assist Advanced Practice Nurses (ANPs) in continued health promotion and the prevention of the comorbidities associated with PCOS.

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Polycystic ovary syndrome affects 5-10% of women of reproductive age (ASRM, 2014). Common PCOS signs and symptoms include anovulation or irregular menses, infertility, obesity, hirsutism, acne, and polycystic ovaries. According to the American College of Obstetricians and Gynecologist ([ACOG], 2015) the cause of PCOS is multifactorial, including insulin resistance, increased levels of androgen hormones, and an irregular menstrual cycle. Furthermore, insulin resistance associated with PCOS increases the risk of type 2 diabetes, cardiovascular disease, and metabolic syndrome (Moran et al., 2010).

Polycystic ovary syndrome is a metabolic and reproductive disorder seen in women that persistently puzzles health care providers. This disorder has a broad variety of phenotype presentation. PCOS exhibits risk factors for cardio-metabolic disorders, women frequently presenting overweight or obese. Affected women often have marked insulin resistance, independent of obesity (Diamanti-Kandarakis and Dunaif, 2012). Although insulin resistance is a contributing factor to the complications of PCOS, the current clinical diagnostic criteria do not address the endocrine pathology of the disorder. Insulin resistance is a central characteristic in the majority of affected women, driving both hyperandrogenism and clinical features (Stepto et al., 2013). Androgen excess may correlate with metabolic risk and contribute at least in part to the adverse metabolic phenotype (O'Reilly et al., 2014).

Polycystic Ovary Syndrome Diagnostic Criteria

In 1935, Stein and Leventhal published a case series of seven women with amenorrhea, hirsutism, and bilateral polycystic ovaries, a condition, which later became known as polycystic ovary syndrome (Roe & Dokras, 2011; Stein & Leventhal, 1935). Since the original description in 1935, the definition of PCOS has undergone several revisions (Roe & Dokras, 2011). At the National Institute of Health (NIH) consensus conference held in 1990, PCOS was defined as; chronic anovulation with clinical and/or biochemical hyperandrogenism, with exclusion of other mimicking etiologies, such as thyroid or adrenal dysfunction (Appendix A) (Roe & Dokras, 2011; Zawadski & Dunaif, 2001).

Diagnostic Criteria Reformations

Guidelines were re-examined by the Rotterdam Consensus Workshop in 2003 and revised to include polycystic ovaries by ultrasound (as defined by enlarged ovaries with at least 12 follicles) (Rotterdam, 2004). At least two of the three clinical manifestations, anovulation, hyperandrogenism and/or polycystic ovaries, must be present to confirm the medical diagnosis of PCOS. Some have argued that the expanded Rotterdam criteria can result in over diagnosis or misdiagnosis of PCOS; different phenotypes may not have similar risks of long-term metabolic morbidities (Roe & Dokras, 2011). It may be perplexing to providers diagnosing women with PCOS who do not present with polycystic ovaries, causing a dubious meaning to the name of the diagnosis. Most recently, the Androgen Excess Society (AES) developed diagnostic criteria for PCOS in 2006 requiring inclusion of all three of the following: hyperandrogenism clinical and/or

biochemical, ovarian dysfunction (oligomenorrhea or anovulation and/or polycystic ovarian morphology), and exclusion of other androgen excess or related disorders (Appendix A). The AES diagnostic criteria could cause concern again for misdiagnosis or underdiagnose of PCOS. In 2008, the AES become the Androgen Excess and Polycystic Ovary Syndrome Society, and narrowed the diagnostic criteria further requiring the inclusion of the following, hyperandrogenism (hirsutism and/or hyperandrogenemia), and ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), and exclusion of other androgen excess related disorders (Appendix A) (Azziz et al., 2009). In December 2012, the NIH endorsed the acceptance of the Rotterdam criteria stating the Rotterdam criteria encompasses the broad spectrum of phenotypes representing PCOS (Trikudanathan, 2015). The Endocrine Society also endorses the Rotterdam criteria for diagnosing PCOS (Legro et al., 2013). Agreement amongst professional organizations that have focused on the perplexities of PCOS should provide confidence in utilizing the Rotterdam criteria for diagnosis of PCOS.

Purpose and Question

The purpose of this project is twofold: to critically appraise current evidence regarding the metabolic comorbidities associated and their impacts on women with PCOS, and to identify evidence based assessment, evaluation, and treatment options available to health care providers treating women with PCOS. The question this project aims to answer is; what is the relationship between PCOS and metabolic comorbidities and what evidence based assessment, evaluation, and treatment options are recommended for health care providers treating women with PCOS?

Ethical Considerations

The Provost established the institutional review board (IRB) and Office of Academic Affairs to protect the interests of research subjects (University of Alaska Anchorage, [UAA], 2012). The main role of the IRB is the review of all human subjects research conducted at UAA to ensure that the research fulfills the requirements of the federal regulations (UAA, 2012). An IRB application for this critical appraisal research project was completed and submitted for review. (Appendix B). The UAA compliance office determined that this critical appraisal research project did not meet the definition of human subjects research, as there would be no interaction or intervention with people.

Study Design and Methods

PICOT Format

The framework presented by Melnyk, Fineout-Overholt, and Williamson (2010), Seven Steps of Evidence Based Practice, guided the critical appraisal of the literature. The clinician poses a clinical question in step zero. Step one, involves further development of the clinical questions using a format known as PICOT. The PICOT helps to narrow and define the literature search. Inquiries in this format take into account the patient population of interest (P), the intervention or area of interest (I), the comparison intervention or group (C), the outcome (O), and the time (T).

The PICOT developed for this project includes the following: Population (P). The population of interest for this study is women with PCOS. Issue of Interest (I). The issue of interest is metabolic comorbidities in women with a diagnosis of PCOS according to Rotterdam criteria. Comparison (C). There will be no comparison in this

project. Outcome (O). The outcomes of this project are to update health care providers of current evidence regarding metabolic comorbidities associated with PCOS and provide an evidence-based algorithm for assessment, evaluation, and treatment of women with PCOS and their comorbidities. Timeframe (T). Six months.

Literature Search and Inclusion Criteria

Step two, consists of a thorough literature search. The search for evidence to inform clinical practice is tremendously streamlined when questions are asked in PICOT format (Melnyk et al., 2010). Search terms were driven by the PICOT format developed in Step 1. Databases utilized for searches included PubMed and the Cochrane Library. These databases were chosen based on recommendations from the UAA Consortium Librarian. Keywords and search terms utilized in PubMed included: Polycystic Ovary Syndrome/diagnosis AND Insulin Resistance AND diagnostic criteria; Polycystic Ovary Syndrome/diagnosis AND Insulin Resistance; Polycystic Ovary Syndrome AND Metabolic Syndrome; Metabolic Syndrome AND Polycystic Ovary Syndrome.; Polycystic Ovary Syndrome/diagnosis"[Major]) AND "Metabolic Syndrome X"[Major]) AND "Insulin Resistance"[Major] AND ("last 5 years"[Publishing Date] AND Humans[Mesh] AND English[language]).

Inclusion criteria focused on articles published between 2010-2015, the population of interest, articles written in the English language, and human subject research. The initial search on PubMed produced 28 articles, 25 of which met the inclusion criteria. Of the 25 publications, 23 articles were chosen for rapid critical appraisal for full text review. Of the publications rapidly reviewed, 11 were excluded and 12 were chosen for full text review based on their significance to the project topic

and level of evidence presented in each study (Appendix C). Studies included in the full text review were assessed using the standard level I-V hierarchy of evidence (Ebling Library, 2016). Systematic reviews of randomized control trials, meta-analysis of randomized control trials, and experimental/randomized control trials or evidence based reviews of randomized control trials were assigned a level I. Non-Randomized controlled trials, quasi-experimental, were assigned a level II. Level III was assigned to well-designed control and cohort studies. Systematic reviews of descriptive and qualitative studies were assigned a level IV, and level V was assigned to opinions of authorities and/or reports of expert committees.

Studies selected for inclusion and full text review consisted of three systematic reviews and meta-analysis, seven cross-sectional studies, one case-control study, and one retrospective cohort study, levels I, II, and III evidence, respectively. Additionally, sentinel works, such as the 2003 Rotterdam diagnostic criteria of PCOS, The Endocrine Society PCOS Clinical Practice Guideline, and the American Society of Reproductive Medicine Consensus on Women's Health Aspects of PCOS were included due to their applicability to practice.

Critical Appraisal. Critically appraising the evidence is conducted in step three of the guiding framework. Once articles were selected for review, they were rapidly appraised to determine which were most relevant, valid, reliable, and applicable to the clinical question (Appendix D). Rapid critical appraisal uses three important questions to evaluate a study's worth: 1) Are the results of the study valid; 2) What are the results and are they important; and 3) Will the results help me care for my patients? (Melnyk et al., 2010).

An evaluation template was developed guided by Fineout-Overholt, Melnyk, Stillwell, and Williamson (2010) and was utilized to record data extracted from the studies utilized for this critical appraisal (Appendix E). Studies were divided into categories according to the design of the study, study objectives, sample size, relevant findings, and presented in order of latest to oldest dates of publication.

Synthesizing Evidence Findings and Algorithm Development. The goal of step four, is integrating the evidence with clinical expertise and patient preferences and values. For this critical appraisal, the focus of step four was to synthesize the evidence findings. Focus was directed on metabolic comorbidities associated with PCOS and recommendations for treatment from The Endocrine Society and ASRM. Findings from this analysis were utilized to develop a treatment-based algorithm based upon the Rotterdam criteria, including recommendations of The Endocrine Society, and the American Society of Reproductive Medicine. Evaluation methods for metabolic comorbidities in women with PCOS will also be included. Step five of the guided framework for this critical appraisal consisted of the development of a treatment based algorithm (Appendix F).

Dissemination. Finally, step six, will be to disseminate the results of the critical appraisal. Dissemination will include findings from the evidence and the developed treatment based algorithm in the form of a poster presentation and journal manuscript. The goal of the poster presentation will be to present at the annual Alaska Nurse Practitioner Association conference in 2016. These goals for dissemination will provide an opportunity to share evidence based knowledge to ANPs and promote improved PCOS population outcomes. An abstract for poster presentation was submitted to the Alaska

Nurse Practitioner Association (Appendix G). An additional abstract was submitted to *Women's Healthcare: A Clinical Journal for NPs* for manuscript publication consideration. This request for publication was declined due to the journal only accepting doctoral nursing research projects for publication (Appendix H).

Literature Review

Polycystic ovary syndrome is a common hormone disorder that affects approximately five million women of reproductive age in the United States (Johnson, Kaplan, Ouyang, & Rizza, 2012). Several populations of women are at greater risk for PCOS. These include reproductive-aged women with clinical evidence of hyperandrogenism, menstrual and/or ovulatory dysfunction, polycystic ovaries, and/or with insulin resistance or metabolic abnormalities (Moran et al., 2010). In addition to its effects on reproductive health, it is now well recognized that PCOS is a metabolic disorder characterized by decreased insulin sensitivity which leads to an excess lifetime risk of type 2 diabetes and cardiovascular disease (Studen, Sever, & Pfeifer, 2013). Women with PCOS are often resistant to the biological effects of insulin and, consequently, may have higher levels of circulating insulin (Johnson et al., 2012). Women and particularly obese women with insulin resistance and polycystic ovary syndrome have an increased risk of developing gestational diabetes, type 2 diabetes, and cardiovascular disease later in life (Bhathena, 2011).

PCOS Related Insulin Resistance

Polycystic ovary syndrome is recognized as an important metabolic and reproductive disorder conferring substantially increased risk for type 2 diabetes (Diamanti-Kandarakis & Dunaif, 2012). Insulin resistance occurs in up to 20% of lean

women with PCOS, while the incidence is significantly higher (>40%) in obese women with the syndrome (Azziz et al., 2004; Balen, 2004; Bhathena, 2011; Dunaif, 1997; Dunaif, Segal, Futterweit, & Dobrjansky, 1989; Ehrmann, Barnes, Rosenfiled, & Cavaghan, 1999; Falcone, Finegood, Fautus, & Morris, 1990; Mather, Kwan, & Corenblum, 2000; Pasquali & Gambineri, 2006; RCOG, 2008; Tsilchorozidou, Overton, & Conway, 2004; & Wild, 2002).

Insulin resistance results in a compensatory increase in insulin secretion by the islet cells of the pancreas to maintain normal glucose homeostasis (Azziz et al., 2009). Affected women have marked insulin resistance, independent of obesity (Diamanti-Kandarakis & Dunaif, 2012). As many as 70% of PCOS women are insulin resistant and 10% have type 2 diabetes mellitus (Freeman, Pollack, & Rosenbloom, 2010; Azziz et al., 2009). Consequently, women with PCOS have a significantly higher rate of impaired glucose tolerance than those without the disorder (Dokras, 2013; Moran et al., 2010). The secondary hyperinsulinemia drives many of the phenotypic features of the disorder including the associated ovarian hyperandrogenism and acanthosis nigricans (Azziz et al., 2009).

Insulin Resistance PCOS Research

A meta-analysis of 11 studies including 935 women with PCOS and 568 controls. Results from this meta-analysis showed an increased prevalence of impaired glucose tolerance (IGT) as defined by either the World Health Organization (WHO) or American Diabetes Association (ADA) definitions for IGT (Odds Ratio (OR) 2.48, 95% CI 1.62-3.77) (Dokras, 2013; Moran et al., 2010). The same authors performed a meta-analysis of 12 studies reporting that 12,102 women with PCOS compared to controls of 56,959

women had an increased prevalence for type 2 diabetes, with an OR of 4.43 (95% CI 4.06-4.82) (Dokras, 2013; Moran et al., 2010).

Moran et al. (2010) conducted a systematic review and meta-analysis, 2,192 studies were reviewed and 35 were selected for final analysis. This study focused on the prevalence of impaired glucose tolerance, type 2 diabetes, and metabolic syndrome in women with PCOS compared to women without PCOS. Articles were included in the study based on the NIH and Rotterdam diagnostic criteria of PCOS. The findings from this study concluded that women with PCOS had an increased prevalence of impaired glucose tolerance (OR 2.48, 95% CI 1.63, 3.77), diabetes type 2 (OR 4.43, 95% CI 4.06, 4.82), and metabolic syndrome (OR 2.88, 95% CI 2.40, 3.45) compared to women without PCOS (Moran et al., 2010). The prevalence of impaired glucose tolerance, diabetes type 2, and metabolic syndrome was found in both PCOS body mass index (BMI) matched and non-BMI matched studies. No studies reported metabolic syndrome incidence (Moran et al., 2010).

Akbarzadeh et al. (2012) conducted a cross-sectional control study in women with PCOS diagnosed from the Rotterdam criteria investigating whether omentin and vaspin, secretory adipokines that are produced by the visceral adipose tissue, change in non-obese women with PCOS. This study included 39 women diagnosed with PCOS using the Rotterdam diagnostic criteria, and a control group consisting of 39 women with normal pelvic sonographic reports having regular menstruation and no signs of infertility (Akbarzadeh et al., 2012). Significant findings from this study reported insulin and fasting glucose levels demonstrating a noteworthy increase in insulin resistance in PCOS subjects ($p = 0.007$) (Akbarzadeh et al., 2012). Akbarzadeh et al. concluded that if

hyperandrogenism and insulin resistance are early warning signs of increasing risk of PCOS, these patients are prime candidates for preventative medicine.

A nonrandomized comparison trial conducted by Yilmaz et al. (2011) compared all phenotypes of PCOS for anthropometrical, hormonal, and metabolic difference according to Rotterdam criteria. This study was conducted on 127 patients with PCOS and 44 control subjects without PCOS. The four phenotypes of PCOS included patients with polycystic ovaries on ultrasound (PCO), oligo or anovulation (O) and biochemical and/or clinical hyperandrogenism (HA); 29/127 were HA and O, 24/127 were PCO and O, 18/127 were HA and PCO, and 42/127 represented the new phenotype PCO, O, HA, and PCO. Glucose-insulin ratio which is important for insulin resistance was lower in phenotypes HA with O and PCO with HA and O than the other phenotypes and the control group (Yilmaz et al., 2011). The highest values of insulin resistance were found to be in the phenotypes HA with O and PCO with HA and O phenotypes and the lowest values were in the HA with PCO, PCO with O phenotypes and the control group (Yilmaz et al., 2011). Numbers of patients with insulin resistance according to phenotypes were as follows: PCO with HA and O (27/56; 48.21%), HA with O (12/29; 41.37%), HA with PCO (6/18; 33.33%), PCO with O (7/24; 29.16%) and the control group (13/44; 29.54%). Diagnosis of PCOS is independent to each individual and often binds women to continuous health care throughout their lifespan. Accuracy of diagnosis is important and at times challenging with the features presented in PCOS.

Additionally, Tao et al. (2012) conducted a cross-sectional study involving 137 Chinese women with PCOS diagnosed from the Rotterdam criteria and 123 normal women as the control. Each participant underwent anthropometry, lipid profile, sex

hormone, high-sensitivity C reactive protein, oral glucose tolerance tests and insulin tolerance tests. The aim of this study was to evaluate the levels of insulin sensitivity and beta cell function in Chinese women with PCOS. Tao et al. (2012) concluded that early impaired beta cell function was detected in both lean and obese Chinese women with PCOS; however more serious primary defect in insulin action was detected in lean Chinese women with PCOS compared to obese Chinese women with PCOS. These findings imply early screening and intervention as therapeutic for Chinese women with PCOS (Tao et al., 2012).

PCOS Related Androgen Excess

Hyperandrogenism is one of three diagnostic criteria measures presented in the Rotterdam criteria. Hyperandrogenism is clinically manifested by hirsutism, acne, and androgenic alopecia. Hirsutism is defined as increased terminal (coarse, pigmented) hair in a male pattern distribution around the upper lip, chin, shoulders, chest, periareolar areas, along the linea alba of the abdomen, inner aspects of the thighs, and midline lower back (Trikudanathan, 2015). Women affected by androgen excess and/or PCOS often report unwanted hair growth, acne, and/or loss or thinning of hair.

The pathophysiology of hyperandrogenism results from ovarian theca cells increase ovarian androgen production under the stimulatory activity of the elevated luteinizing hormone (LH) levels, and in many cases, elevated insulin levels (Abdel-Rahman, 2015). Hyperinsulinemia due to peripheral insulin resistance is often present in women with PCOS which promotes hyperandrogenemia through the binding of insulin to the insulin-like growth factor-1 (IGF-1) receptor. Insulin mimics the action of IGF-1, which augments androgen production by the theca cell in response to LH, ultimately

stimulating an increase in circulating levels of free testosterone (Abdel-Rahman, 2015). The complexities of hyperinsulinemia in PCOS precipitate hyperandrogenemia and its presenting symptoms.

Androgen Research

A study conducted by O'Reilly et al. (2014) evaluated insulin resistance in 86 PCOS patients fulfilling Rotterdam diagnostic consensus criteria. Forty-three age and BMI matched controls underwent measurement of serum androgens by tandem mass spectrometry and an oral glucose tolerance test with homeostatic model assessment of insulin resistance and insulin sensitivity index calculation. O'Reilly et al. (2014) analyzed urine androgen excretion by gas chromatography/mass spectrometry. PCOS patients had higher levels of serum androgens and urinary androgen metabolites than controls ($P < .001$).

Wang, Kao, Huddleston, and Cedars (2011) conducted an additional study focusing on the effects of androgen excess. This cross-sectional study consisted of 200 women ages 18 to 44 years diagnosed with PCOS from the Rotterdam criteria. The women where split into two groups, one with documented androgen excess the other documented without androgen excess. Wang et al. concluded that the women with androgen excess trended toward higher fasting glucose and lower HDL cholesterol than those without androgen excess. A similar cross-sectional study conducted by Huang et al. (2015) examined 460 women diagnosed with PCOS from the Rotterdam criteria with a goal of identifying potential endocrine characteristics related to risk and severity of metabolic disturbances. Huang et al. concluded that the highest risk for metabolic syndrome were the women with PCOS and those with higher free androgen index, the

fasting free androgen index correlated with more severe metabolic abnormal findings in this study. Similarly, Yilmaz et al. (2011) also found higher free androgen index amongst women diagnosed with PCOS from the Rotterdam criteria than the women without PCOS in the control group.

PCOS Associated Obesity

Since the original description in 1935 by Stein and Leventhal, obesity is described as a common feature of PCOS (Sam, 2007). Obesity has been linked to abnormal function of the hypothalamic-pituitary-ovarian (HPO) axis through multiple mechanisms that contribute to a development of PCOS (Legro, 2012). A meta-analysis of 35 studies, including 15,129 women, demonstrated that women with PCOS had increased prevalence of being overweight or obese, with central obesity, compared with women without PCOS (Dokras, 2013; Lim, Davies, Norman, & Moran, 2012). A similar meta-analysis of 30 studies demonstrated that obese women with PCOS have decreased sex hormone binding globulin, increased testosterone, increased fasting glucose, increased fasting insulin, and abnormal lipid profile (Yildiz, 2013). Obesity affects women with PCOS and is associated with insulin resistance. The prevalence of insulin resistance is greater in obese than non-obese patients (Azziz et al., 2009). Similarly, in the nonrandomized comparison study conducted by Yilmaz et al. (2011) the mean BMI was higher in phenotypes PCO with HA and O in addition to phenotype HA with PCO. Waist to hip ratios were higher in women with PCO with HA and O, HA with PCO, and HA with O compared to PCO with O and controls.

Obesity affects a vast number of women in the United States. The National Health and Nutritional Examination Survey from 2011-2012 documented data showing

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36.6% of women ages 20 years and older in the United States were obese (Fryar, Carroll, & Ogden, 2014). According to the WHO (2015), in 2014, more than 1.9 billion adults were overweight, over one third of those were obese. The WHO (2015) defines obesity as a BMI $\geq$ 30 kg/m^2. The association between obesity and alterations in female reproductive functions was recognized long ago (Rogers & Mitchell, 1952), and has been confirmed more recently. The Practice Committee of the American Society of Reproductive Medicine [PCASRM] (2012) lists obesity as one of the most common causes of ovulatory dysfunction and anovulation infertility, although it may not affect all obese women. Additionally, research by Wilkes and Murdoch (2009) found that obese women have a higher prevalence of infertility, maternal morbidity, mortality, and fetal anomalies.

PCOS Associated Risk for Dyslipidemia

Women with PCOS have a high prevalence of several traditional risk factors for cardiovascular disease (Dokras, 2013). These include controllable risk factors such as dyslipidemia, diabetes, hypertension, and obesity (Wild et al., 2010). Increased risk of dyslipidemia including elevated low density lipoprotein (LDL), elevated triglycerides (TG) and low high density lipoprotein (HDL) has been shown in PCOS (Dokras, 2013). In a meta-analysis by Wilde et al. (2010), TG levels were significantly lower in control women, HDL levels were significantly higher in control women and LDL levels were significantly lower compared to women with PCOS. Insulin resistance is a key factor in the pathophysiology of PCOS, thus dyslipidemia in women with PCOS may be consistent with those found in an insulin resistance state (Kim & Choi, 2013). In a recent meta-analysis, triglycerides and LDL cholesterol levels were 26 mg/dL and 12 mg/dL higher,

and HDL cholesterol concentration was 6 mg/dL lower in women with PCOS versus those of controls (Kim & Choi, 2013). Wild (2012) concluded that on average, women with PCOS were found to have 26 mg/dl higher triglyceride [26.39 95%CI (17.24, 35.54)], lower HDL cholesterol [6.41 95%CI (3.69, 9.14)], and higher non-HDL cholesterol levels [18.82 95% CI (15.53, 22.11)] than their non-PCOS counterparts. A meta-analysis conducted by Wild (2012) confirmed in weight matched studies that women with PCOS have lower HDL cholesterol, higher non-HDL cholesterol, and higher LDL cholesterol concentrations in addition to higher triglycerides levels than age matched non PCOS women.

Cochrane Systematic Reviews on Treatment Modalities for PCOS

The Cochrane Library is a collection of six databases that contain different types of high-quality, independent evidence to inform healthcare decision-making (Cochrane Library, 2016). Four Cochrane Library reviews that focused on treatment modalities of associated comorbidities of PCOS were examined for recommendations. The reviews were selected based on date of publication between 2010 to 2015 and relevance to the study topic. Recommendations were found for treatment of PCOS with lifestyle modification including diet and exercise, insulin-sensitizing drugs, interventions for hirsutism, oral anti-diabetic agents, and statin therapy.

Moran, Hutchison, Norman, and Teede (2011) conducted a systematic review to assess the effectiveness of lifestyle treatment in improving reproductive, metabolic, anthropometric (weight and body composition), and quality of life factors in PCOS. Six randomized control trials comparing lifestyle treatment (diet, exercise, behavioral or combined treatments) to minimal or no treatment in women with PCOS were included

with 164 participants (Moran et al., 2010). Moran et al. concluded that lifestyle intervention improves body composition (weight P <0.00001, waist circumference (P .006), hyperandrogenism (hirsutism P 0.04), and insulin resistance (P 0.002) in women with PCOS. There was no evidence of effect for lifestyle intervention on improving glucose tolerance or lipid profile and no literature assessing clinical reproductive outcomes, quality of life, and treatment satisfaction.

A systematic review conducted by Tang, Lord, Norman, Yasmin, and Balen (2011) examined the effectiveness of insulin-sensitizing drugs in improving reproductive outcomes and metabolic parameters for women with PCOS. Tang et al. (2011) selected 44 randomized controlled trials of insulin sensitizing drugs compared with either placebo, no treatment, or an ovulation induction agent for women with PCOS, menstrual disturbance, and subfertility for inclusion. Thirty-eight of the studies used metformin and involved 3,495 women. Tang et al. (2011) concluded that there was no evidence that metformin improved live birth rates, whether it was used alone or in combination with clomiphene; however, clinical pregnancy rates were improved with metformin versus placebo and for metformin and clomiphene versus clomiphene alone. In studies that compared metformin and clomiphene alone, there was evidence of an improved live birth rate and clinical pregnancy rate in the group of obese women who took clomiphene (Tang et al., 2011). The role of metformin in improving reproductive outcomes in women with PCOS appears to be limited (Tang et al., 2011).

An additional systematic review conducted by Raval, Hunter, Stuckey, & Hart (2011) conducted a systematic review to assess the efficacy and safety of statin therapy for women with PCOS who are not actively trying to conceive. Of the randomized

control trials comparing a statin versus placebo or statin combination with another drug versus another drug alone in women with PCOS, 244 women with PCOS fulfilled the study inclusion criteria. Raval et al. (2011) concluded that statins improved lipid profiles and reduced testosterone levels in women with PCOS ($P < 0.00001$). In women with PCOS, statins are effective in reducing serum androgen levels and decreasing LDL cholesterol, but did not prove to be effective in reducing fasting insulin or insulin resistance (Raval et al., 2011).

Literature Review Conclusions

There is a clear consensus throughout the literature that women with PCOS have a significantly higher rate of impaired glucose tolerance, type 2 diabetes, dyslipidemias, and metabolic syndrome (Akbarzadeh et al., 2012; Moran et al., 2010; Tao et al., 2012; & Yilmaz et al., 2011). Hyperandrogenism is a main feature of PCOS; evidence suggests that insulin resistance or insulin action play critical roles in its pathophysiology (Huang et al., 2015; O'Reilly et al., 2014; Wang et al., 2011; & Yilmaz et al., 2011). Dyslipidemia in women with PCOS has been linked to insulin resistance. The presence of dyslipidemia, insulin resistance, and obesity in women with PCOS are intricately related as a preventable cause of morbidity.

The current diagnostic criteria for PCOS does not include insulin resistance, obesity, or other cardio-metabolic disorders such as dyslipidemia. The results from this literature review supports that women with PCOS having a higher prevalence of insulin resistance then women without PCOS (Akbarzadeh et al., 2012; Moran et al., 2010; Tao et al., 2012; & Yilmaz et al., 2011). While impaired insulin resistance and obesity are not

included in the current diagnostic criteria for PCOS, the clinical impact associated with these metabolic comorbidities should not be ignored.

Recommendations from Professional Organizations

Recommendations and guidelines from two main professional organizations that focus on the diagnosis and treatment complexities of PCOS were appraised for this project, The Endocrine Society, and the American Society of Reproductive Medicine.

The Endocrine Society

The Endocrine Society is a prestigious professional organization that has been representing professionals in all aspects of endocrinology for 100 years. Founded in 1916, The Endocrine Society is the world's oldest, largest and most active organization devoted to research on hormones and the clinical practice of endocrinology (Lohr & Gingery, 2013). The Endocrine Society issued a Clinical Practice Guideline (CPG) for the diagnosis and treatment of PCOS, the most common hormone disorder in women of reproductive age and a leading cause of infertility (Lohr & Gingery, 2013). The CPG is designed to assist health care providers with the complexities of PCOS diagnosis and treatment.

Endocrine Society PCOS Clinical Practice Guideline. The Endocrine Society suggests using the Rotterdam criteria for diagnosing PCOS, which include two of the following criteria: androgen excess, ovulatory dysfunction, or polycystic ovaries (Legro et al., 2013). In regards to the cardio-metabolic abnormalities associated with PCOS the guidelines developed by The Endocrine Society advise screening women for impaired glucose tolerance and type 2 diabetes with the use of an oral glucose tolerance test and/or a hemoglobin A1c if the individual is unable to complete or refuses an oral glucose

tolerance test. Rescreening is suggested every three to five years, or more frequently if clinical factors such as central adiposity, substantial weight gain, and/or symptoms of diabetes develop (Legro et al., 2013). This guideline recommends providers screen for cardiovascular risk factors associated with PCOS such as obesity, smoking, hypertension, and dyslipidemia.

Hormonal contraceptives (i.e. oral contraceptives, patch, or vaginal ring) are recommended as first-line management for the menstrual abnormalities and hirsutism/acne of PCOS (Legro et al., 2013). Metformin is second-line therapy for menstrual cycle irregularities in women who cannot take or tolerate hormonal contraceptives (Legro et al., 2013). Life style modifications including weight loss is addressed in the guidelines and should be encouraged. Weight loss for obese and overweight women with PCOS beginning with restricted caloric intake is recommended as beneficial for both reproductive and metabolic dysfunctions. Metformin is recommended for women with type 2 diabetes and those with impaired glucose tolerance who fail lifestyle modification (Legro et al., 2013). The Endocrine Society recommends against the use of metformin as first-line treatment for androgen excess associated symptoms of hirsutism and/or acne.

American Society of Reproductive Medicine

The American Society of Reproductive Medicine is a multidisciplinary organization dedicated to the advancement of the science and practice of reproductive medicine (ASRM Board of Directors, 2014). The Society accomplishes its mission through the pursuit of excellence in education and research and through advocacy on behalf of patients, physicians, and affiliated health care providers. Two widely cited

consensus statements developed by the European Society of Human Reproduction and Embryology [ESHRE]/ASRM focused on PCOS diagnosis (2004) and infertility management (2008) (ASRM, 2012). The most resent PCOS consensus report summarizes current knowledge and identifies gaps regarding various women's health aspects of PCOS addressing both the diagnosis and treatment of PCOS (ASRM, 2012). Both The Endocrine Society and American Society of Reproductive Medicine address the diagnosis and treatment of PCOS.

American Society of Reproductive Medicine Consensus on PCOS. Relevant topics addressed PCOS in adolescence, hirsutism and acne, contraception, menstrual cycle abnormalities, quality of life, ethnicity, pregnancy complications, long-term metabolic and cardiovascular health, and cancer risk (ASRM, 2012). Similarly, to the Endocrine Society, the ESHRE/ASRM consensus also recommends utilization of the Rotterdam diagnostic criteria for the diagnosis of PCOS (ASRM, 2012). Agreement on the Rotterdam criteria between both organizations should provide confidence in utilizing the Rotterdam criteria for the diagnosis of PCOS.

Consensus was found between ESHRE and ASRM workshop that obesity is increasing and has an important bearing on the phenotype of PCOS. Obesity (by amplifying insulin resistance) is an exacerbating factor in the development of impaired glucose tolerance and diabetes type 2 in PCOS. ASRM recommends two main treatment modalities for PCOS; lifestyle management and metformin. Lifestyle management with caloric restricted diet and exercise on obesity result in weight loss and improvement in surrogate markers of metabolic disease/syndrome (ASRM, 2012). Diet and exercise are

first choice for improving fertility and prevention of diabetes. Metformin is recommended for impaired glucose tolerance and diabetes type 2.

Metabolic disorders associated with PCOS are major predictors of prediabetes, diabetes, and metabolic syndrome in reproductive-age women. Not all PCOS phenotypes have similar metabolic risk; the combination of hyperandrogenemia and oligomenorrhea signifies the most at-risk (ASRM, 2012). ASRM, conclude that insulin resistance is a prominent feature of PCOS making PCOS a major risk factor for developing impaired glucose intolerance and diabetes type 2. Recommendations from the ESHRE and ASRM consensus directed at the care of diabetes type 2 in PCOS include screening for impaired glucose intolerance and diabetes type 2 by oral glucose tolerance testing. Screening for impaired glucose tolerance was recommended in the following conditions: hyperandrogenism with anovulation, acanthosis nigricans, obesity (BMI >30 kg/m^2, or BMI >25 in Asian populations), and in women with a family history of diabetes type 2 or gestational diabetes (ASRM, 2012).

The metabolic dysfunctions associated with PCOS increase the risk for cardiovascular disease. The ESHRE/ASRM consensus concluded that PCOS at any age is characterized by greater odds for elevated cardiovascular risk markers, elevated markers occurring without obesity and are magnified with obesity. Dyslipidemia, impaired glucose tolerance, and type 2 diabetes, classic risk indicators of atherosclerosis and cardiovascular disease, are more prevalent in women with PCOS, even when weight matched with normal control women (ASRM, 2012). ESHRE and ASRM consensus recommendations including a cardiovascular risk assessment at any age for psychological stress, blood pressure, glucose, lipid profile (cholesterol, triglycerides, HDL, LDL, and

non-HDL cholesterol), waist circumference, physical activity, nutrition, and tobacco use (ASRM, 2012).

In addition to cardio-metabolic risk factors, menstrual cycle irregularities are also an important feature of PCOS and should be addressed. It is unclear to what extent the severity of the menstrual disturbance is associated with the severity of the PCOS phenotype (ASRM, 2012). Menstrual cycle abnormalities can be controlled in woman with PCOS and is usually achieved by using hormonal contraceptive management. Overall, the benefits of hormonal contraceptives outweigh the risks in most patients with PCOS, and are recommended as first line treatment of irregular menstrual cycles in women with PCOS not trying to conceive (ASRM, 2012). Oral contraceptives can address many of the goals of reproductive-aged women with PCOS; ameliorate hyperandrogenic skin manifestations and regulate menstrual cycles. Norethindrone, norgestrel, and levonorgestrel are known to have androgenic activity, whereas desogestrel, norgestimate, and gestodene are less androgenic. The pills containing progestin with antiandrogenic activity, rather than second and third generation oral contraceptives containing progestins with varying androgenic activity, appear to be an appropriate alternative in the treatment of PCOS (ASRM, 2012).

Synthesis of Professional Organization Recommendations

Consensus was found between the ESHRE and ASRM and The Endocrine Society on the treatment and management of PCOS and associated comorbid risk factors. Both the Endocrine Society and the ESHRE and ASRM endorse the use of the Rotterdam criteria as the diagnostic criteria of choice for PCOS. In addition, both organizations

recommend life style modifications including restricted caloric intake and exercise for weight loss management in obese and overweight women with PCOS.

Women with PCOS should be screened for impaired glucose tolerance utilizing an oral glucose tolerance test in addition to screening for other cardio-metabolic risk factors including tobacco use, hypertension, obesity, and dyslipidemia (ASRM, 2012; Legro et al., 2013). First-line treatment for diabetes type 2 in women with PCOS should include metformin (ASRM, 2012; Legro et al., 2013; Tang et al., 2011). In women with impaired glucose tolerance who fails life style modification should be treated with metformin as second line therapy. Recommendations by both organizations for first-line treatment of menstrual cycle irregularities in women with PCOS not trying to conceive includes the use of hormonal contraception, which may also be beneficial in the treatment of hirsutism and acne (ASRM, 2012; Legro et al., 2013). The clear similarities amongst both of these professional organizations will assist health care providers in accurate diagnosis and treatment of women with PCOS.

Results

The results of the critical appraisal and consensus statements from The Endocrine Society and the American Society of Reproductive Medicine conclude that women with PCOS have an increased risk of developing type 2 diabetes, cardiovascular disease, and metabolic syndrome (Akbarzadeh et al., 2012; ASRM, 2012; Legro et al., 2013; Moran et al., 2010; Tao et al., 2012; & Yilmaz et al., 2011). The high prevalence of insulin resistance amongst women with PCOS has been documented in several studies, indicating insulin resistance plays a significant role in PCOS (Akbarzadeh et al., 2012; Moran et al., 2010; Tao et al., 2012; & Yilmaz et al., 2011). The current diagnostic

criteria do not address metabolic comorbidities as one of the criteria in diagnosing PCOS, yet they remain a critical aspect of comprehensive treatment for this complex syndrome.

Given the impact metabolic comorbidities have on women with PCOS, the Endocrine Society and the American Society of Reproductive Medicine agree that screening should be performed for metabolic comorbidities in women with PCOS (Legro et al., 2013; ASRM, 2012). Both professional organizations concluded that metabolic screening for impaired glucose intolerance and diabetes type 2 should be performed by an oral glucose tolerance test. Equally, each also recommends lifestyle modification through diet and exercise as the first-line treatment for weight loss and diabetes prevention. Additionally, both recommend the use of metformin in women with PCOS who have diabetes type 2 and those with impaired glucose tolerance who have failed lifestyle modifications. A consensus between the two organizations was also found utilizing hormonal contraceptives for menstrual cycle irregularities, hirsutism, and acne is indicated.

Theoretical Framework

In 1975 Nola J. Pender developed a conceptual model for preventative health behavior (Pender, 1982). Pender's health-promotion model notes that each person has unique personal characteristics and experiences that affect subsequent actions (Gonzalo, 2011). The set variables for behavior specific knowledge and affect have important motivational significance; these variables can be modified through nursing actions (Gonzalo, 2011). Assumptions of the health promotion model reflect both nursing and behavioral science perspectives. Pender emphasizes the active role the patient embodies

by shaping and maintaining health behaviors and in modifying the environment and context for health behaviors (Masters, 2015).

The health promotion model is useful in practice when the focus of nursing care includes promoting behaviors to enhance health (Masters, 2015). The role of the nurse in Pender's health-promotion model revolves around raising consciousness related to health-promotion behaviors, promoting self-efficacy, enhancing the benefits of changes, controlling the environment to support behavior changes, and managing the barriers to change (Pender, Murdaugh, & Parsons, 2006). There are three major categories to consider in Pender's health promotion model: (1) individual characteristics and experiences, (2) behavior-specific cognitions and affect, and (3) behavioral outcome (Masters, 2015). This analysis will focus on behavioral outcome. Health promoting behavior, which is ultimately directed toward attaining positive health outcomes, is the product of the health promotion model (Masters, 2015). In the context of this analysis, behavioral outcome is defined as identifying metabolic comorbidities in women with PCOS, ultimately promoting health and disease prevention.

Applying the Evidence to Clinical Practice

The development of the evidence-based treatment algorithm was efficiently constructed from the synthesized results determined from the through literature review conducted for this project. Results concluded from the literature review were weighted along side the recommendations for diagnosis and treatment of PCOS presented by both The Endocrine Society and ASRM. Similar and supportive results presented in the literature were highlighted along side those presented in each of the professional organization recommendations. Areas of consensus throughout the literature and

professional recommendations were outlined in a rough draft algorithm, narrowed to provide the best evidence-based recommendations for evaluation, assessment, diagnosis, and treatment of PCOS in the form of a treatment based algorithm.

Impact on Advanced Nursing Practice

Advanced nurse practitioners (ANPs) are primary care providers who are at the forefront of health promotion and disease prevention. ANPs have a comprehensive approach to practice and are able to recognize the different features of PCOS. With the evidence provided from this critical appraisal, ANPs will be able to identify high-risk patients with PCOS and screen them appropriately to prevent additional morbidity and mortality. An evidence-based algorithm will assist ANPs in health promotion and the prevention of the comorbidities associated with PCOS.

Conclusion

The aim of this project was two fold: 1) to evaluate the evidence about the associated metabolic comorbidities in women with PCOS and 2) educate providers with current evidence based critical appraisal findings. The development of a treatment based algorithm for assessment, evaluation, and treatment of women with PCOS and the metabolic comorbidities was developed based upon synthesis of this critical appraisal. Treatment and diagnostic recommendations from The Endocrine Society and the ASRM were developed (Appendix F). The clinical practice algorithm will assist health care providers in the treatment of women with PCOS. Utilizing current evidence-based recommendations ultimately increases health promotion, disease prevention, and improved health outcomes.

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Appendix A

Diagnostic Criteria for Polycystic Ovary Syndrome

POLYCYSTIC OVARY SYNDROME METABOLIC COMORBIDITIES

NIH Criteria (1990)

All three of the following:

- Clinical or biochemical evidence of hyperandrogenism
- Oligomenorrhea and/or anovulation
- Exclusion of other disorders

Rotterdam Criteria (2003)

At least two of the following:

- Oligomenorrhea and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries

PCOS can be diagnosed only after the exclusion of related disorders (e.g., severe insulin resistance, androgen-secreting neoplasms, Cushing's syndrome, hyperprolactinemia and thyroid abnormalities)

Androgen Excess Society Criteria (2006)

All three of the following:

- Chemical or biochemical hyperandrogenism
- Ovarian dysfunction (oligomenorrhea or anovulation or polycystic ovarian morphology)
- Exclusion of other androgen excess related disorders

PCOS is predominantly a disorder of androgen excess.

Androgen Excess and PCOS Society Criteria (2008)

All three of the following:

- Hyperandrogenism: hirsutism and/or hyperandrogenemia
- Ovarian Dysfunction: oligo-anovulation and/or polycystic ovaries
- Exclusion of other androgen excess or related disorders

Adapted from the NIH, Rotterdam, AES, & AE-PCOS Society diagnostic criteria of PCOS by Azziz, Carmina, Dewailly, Diamanti-Kandarakis, Escobar-Morreale, Futterweit, et al., 2009; Rotterdam ESHRE/ASRM, 2003; Roe et al., 2011, Zawadski & Dunaif, 2001.

Appendix B

UAA UNIVERSITY of ALASKA ANCHORAGE

INSTITUTIONAL REVIEW BOARD

REQUEST FOR DETERMINATION OF HUMAN SUBJECTS RESEARCH

All research conducted by University of Alaska Anchorage faculty, staff, or students, which involves human subjects must be reviewed by the Institutional Review Board (IRB). To determine if your project involves human subjects or is research under UAA IRB definitions, complete this form and send it to the UAA Research Compliance Officer, simumaw@uaa.alaska.edu.

For help, contact the Office of Research Integrity & Compliance (ORIC): (907) 786-1099.

Consider your activity (research project, thesis, study, task, assignment) and the data (information) you, a member of your research team, or a collaborator, plan to collect, when responding to these questions.

Activity Examples: surveys, questionnaires, focus groups, interviews • passive observation of public behavior (in physical or online environments, including social media) • experiments using electronic equipment or gaming techniques • the use of instruments or devices, including phones, to collect or monitor or influence behavior • diet, nutrition studies, or taste tests • physical or biomedical procedures, such as imaging, scanning, blood collection, anthropomorphic procedures • studies examining individuals' responses to manipulation of their physical or online environment • studies examining effectiveness of educational tools or curricula • pilot studies and other preliminary studies • any other activity that involves observation of, or interaction with, individuals to gather information for research.

Enter a response for each question, complete Section B on Page 2 and send to simumaw@uaa.alaska.edu	Yes/No Not sure
Is all of the data (information) being obtained about deceased people? (If No, skip the next question and go to RD1)	No
In addition to information about the deceased people, are you also collecting information from living persons about their recollections of the deceased people? (If No, stop here and go to RD **2**)	
RD1) Does your project only involve existing data, information, documents, or samples that you will obtain from a publicly available source that does not require permission to access the data? (If Yes, stop here and go to RD**2**.)	Yes
Does a funding source (federal, state, or local), either directly (direct funder) or indirectly (secondary, or pass-through funder) require IRB review? (If Yes, stop here and go to RD**3**)	
Is any of the data (information) being obtained about individuals who are, or could be, living now?	
Is any of the data (information) being obtained, directly or indirectly, from living individuals?	
Are you observing people, directly or indirectly, to collect your information?	
Are you interacting (face-to-face, through telephone, electronic media or documents) with people?	
Is the data collected by intervening (taking measurements, samples, images) with people, or observing an intervention carried out by another person?	
Does the data/information you are collecting only center on things, quantities, or other questions about what item, process, or procedure is used? (If Yes, stop here and go to RD**2**)	
Does the data/information you are collecting include the opinions, characteristics, or behavior of individuals?	
Does the data/information you are collecting include any information that could identify the individuals?	
Does the data/information you are using to recruit people for your project include any information that could identify the individual?	
During the process of collecting data, will you or any research team member, be able to identify the individuals?	
Will the data or information you are collecting examine, for example, the function of culture, expression of gender, or political views of members of the population in the study?	
Could the results of this evaluation be used to make a general conclusion about the data/information you will collect?	
Is this evaluation connected to individual or group outcomes?	
Could the results of this evaluation impact the future use of similar programs, services, or public policy?	
Can this evaluation affect the development or implementation of other programs of a similar nature?	

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If you answered Not Sure for any question, briefly explain why you are uncertain. Briefly explain here.
RD2 – Your work is most likely not human subject research and you do not need to complete the rest of the first section. Complete Section B and return the Request for IRB Determination form for a final confirmation.
RD3 – Your work must be reviewed by the IRB. Go to IRBNet and complete a UAA IRB Proposal and all additional documents for IRB review.

Section B – Instructions, tab to each box and complete the information.

Name: Rhianne Christopherson Today's Date: 12/28/2015

Affiliation with UAA (If this project will be used for class credit, complete the next two lines. If not, skip to Faculty/Staff):

Student Level: MSN-FNP Course Number: NS 696 32399

Faculty Advisor: Lisa Jackson Department: School of Nursing

Faculty or Staff College or School: Department:

Project Title: Polycystic Ovary Syndrome Expanded Diagnostic Criteria: A Critical Appraisal of the Evidence with Diagnostic Criteria Recommendations

Project Description: Briefly (< 100 words) describe the project. The purpose of this project is to critically appraise current literature to clarify the diagnostic criteria of women with polycystic ovary syndrome
Population: Briefly describe the population of interest. Women with Polycystic Ovary Syndrome
Plan: Briefly describe how you will interact or intervene with the population and the information you will collect. Data will be gathered from the literature.

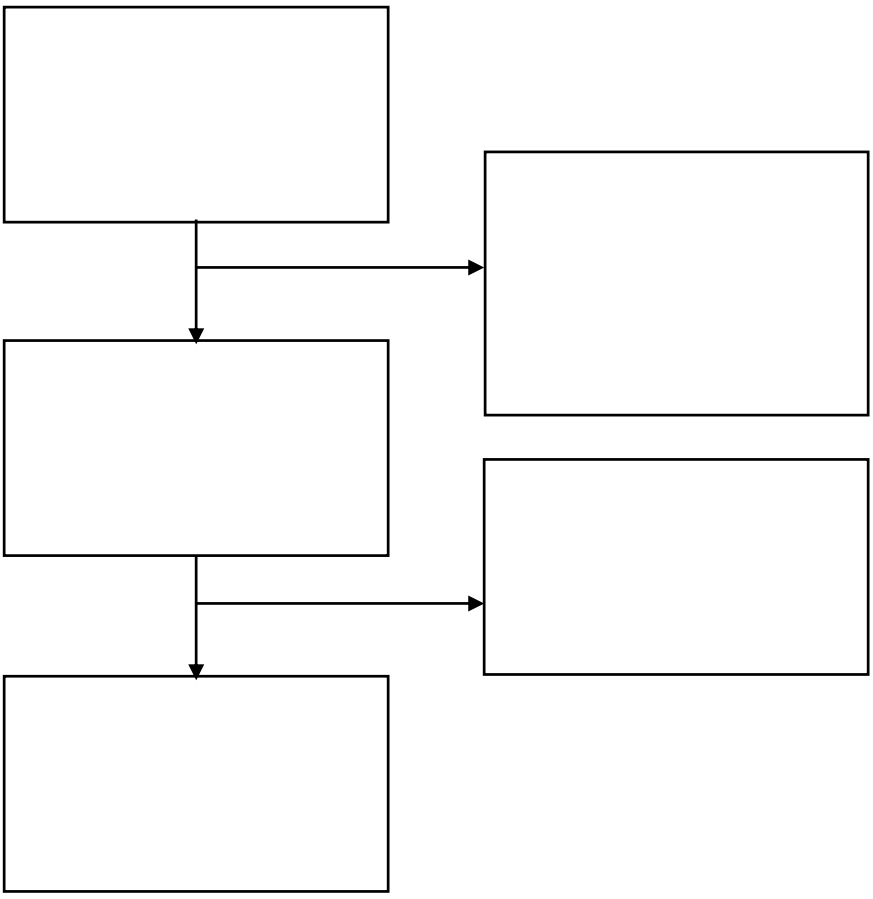
For Office of Research Integrity & Compliance Use Only

Final Determination: HSR Not HSR

Statement of Findings: No interaction or intervention with people, description of literature search which does not meet definition of HSR.

Appendix C

Data Search Process



Appendix D

Rapid Critical Appraisal (RCA) for Full Text Review

Author (year)	Are the results valid?	What are the results and are they important?	Will the results help me care for my patients?
Baptiste, C.G., Battista, M.C., Trottier, A., & Baillargeon, J.P. (2010)	Review	Yes. The main feature of PCOS is hyperandrogenism and evidence suggest that insulin resistance or insulin action plays in its pathophysiology. Further study needed to confirm.	Yes.
Moran, L.J., Misso, M.L., Wild, A., & Norman, R.J. (2010)	Systematic Review	Women with PCOS had an elevated prevalence of IGT, DM2, and metabolic syndrome in both BMI matched and non-BMI matched studies.	Yes.
Phelan, N. et al., (2010)	Case-control study	Yes. Women with PCOS have potentially important differences in lipid profile with greater LDL levels and increased rates of more atherogenic non-LDL pattern.	Yes. Excluded, diagnosis not based on Rotterdam, NIH.
Yilmaz, M., Isaoglu, U., Delibas, I.B., & Kadanali, S. (2010).	Non-randomized comparison	Decrease risk of metabolic comorbidities in women with only polycystic ovaries and anovulation. Yes.	Yes.

Bhathena, R.K. (2011)	Review	Yes. Women with PCOS have reproductive disturbances and insulin resistance, are at risk for development of cardio-metabolic abnormalities similar to those that lead to metabolic syndrome.	Yes.
Manneras-Holm et al., (2011)	Non-randomized comparison	Yes. Increase in adipose tissue was found to be associated with insulin resistance in PCOS.	Yes. Excluded, diagnosis criteria not identified.
Wild, R.A., Rizzo, M., Clifton, S., & Carmina, E. (2011)	Systematic review/meta-analysis	Yes. Dyslipidemia is common in PCOS.	Yes.
Akbarzadeh, S. et al., (2012)	Cross-sectional case control study	Yes. Results show that PCOS is not a determinant of decreased omentin and vaspin plasma levels and those high androgen level and insulin resistances are warning sings of PCOS.	Yes.
Bonny, A.E. et al., (2012)	Cross-sectional, anonymous, internet survey	No. Heterogeneity between providers initial diagnosing and management of PCOS among members of NASPAG was consistent.	No. Excluded
Lim, S.S., Norman, R.J., Davies, M.J., & Moran, L.J. (2012)	Systematic review/meta-analysis	Yes. Obesity significantly worsened all metabolic & reproductive outcomes measured except for hirsutism when compared to normal weight women with PCOS.	Yes.

Rahmanpour, H., Jamal, L., Mousavinasab, S.N., Esmailzadeh, A., & Azarkhish (2012)	Randomized	Yes. Obesity and insulin resistance are important risk factors for metabolic syndrome in PCOS.	Yes. Excluded, diagnosis criteria not based on Rotterdam criteria, NIH.
Tao, T., Li, S., Shao, A., Mao, X., & Lui, W. (2012).	Cross-sectional	Early impaired beta cell function was detected in lean/obese women with PCOS. Yes.	Yes.
Yildiz, B.O., Bozdag, G., Yapici, Z., Esinler, I., & Yarali, H. (2012)	Cross-sectional study	Higher rate of dx of PCOS with Rotterdam criteria compared to others. Yes.	Yes.
Roe, A.H., Prochaska, E., Smith, M., Sammel, M., & Dokras. (2013)	Retrospective chart review	Adolescents diagnosed with PCOS based on the AE-PCOS criteria are at significantly increased risk of >1 metabolic abnormality. Yes.	Yes. Excluded, diagnostic criteria not based on Rotterdam criteria, NIH.
Yidiz, B. (2013)	Meta-analysis	Yes. Obese women with PCOS have multiple comorbidities associated with obesity.	Yes. Excluded, diagnosis not based on Rotterdam criteria, NIH.
Mani, H. et al., (2013)	20-year retrospective cohort study	Yes. Showed a high incidence of diabetes and cardiovascular events in women with PCOS.	Yes.
Aydogdu, A. et al., (2013)	Non-randomized comparison study	Yes. Increase in subscapular & suprailiac skinfold thickness are increased in women with PCOS with significant relation to impaired insulin resistance.	No. Excluded.

Kim, J.J., & Choi, Y.M. (2013).	Review	Yes. Although the prevalence of obesity in Korean women with PCOS is low, even young and non-obese Korean women with PCOS have substantially increased prevalence of dyslipidemia.	Yes.
Kim, J.J. et al., (2013)	Case-control study	Yes. Non-obese women with PCOS may have no significant quantitative or qualitative changes in LDL-C profiles	Yes.
Dokras, A. (2013)	Review	Yes. Women with PCOS have a higher risk for cardiovascular disease.	Yes.
Livadas, S., Kollias, A., Panidis, D., & Kandarakis, E.D. (2014)	Cross-sectional study	Yes. In PCOS age was negatively and BMI was positively associated with insulin resistance.	Yes
O'Reilly et al. (2014)	Cross-sectional study	Yes. PCOS patients had higher levels of serum androgens and urinary androgen metabolites than controls.	Yes
Huang, C.C., et al. (2015)	Cross-sectional study	Major predictor of metabolic abnormalities was free androgen index and luteinizing hormone. Yes.	Yes.

Appendix E

Evidence Evaluation Table Full Test Reviewed Articles

Author (year)	**Study Objectives**	**Design**	**Sample size Rotterdam criteria**	**Relevant Findings**
Huang, C.C., et al. (2015)	What are the potential endocrine characteristics related to risk and severity of metabolic disturbances in women with PCOS?	Cross-sectional study	460 participants Rotterdam criteria	High rates of metabolic syndrome and free androgen index in participants with PCOS.
Livadas, S., Kollias, A., Panidis, D., & Kandarakis, E.D. (2014)	To evaluate the changes in insulin resistance and its associations with clinical, biochemical, hormonal, and ultrasound findings in a large cohort of women with PCOS and controls, as they are aging.	Cross-sectional study	1345 women with PCOS Rotterdam criteria 302 controls of Caucasian origin and Greek ethnicity comprised the control group	Aging increases insulin resistance in obese but not in lean and over weight women with PCOS.

O'Reilly et al. (2014)	Androgen excess may correlate with metabolic risk and PCOS consensus criteria define androgen excess on the basis of serum testosterone.	Cross-sectional study	86 women with PCOS Rotterdam criteria 43 age and BMI controls.	Measurements of serum testosterone and androstenedione levels represents a useful tool for predicting metabolic risk in PCOS women; high androstenedione levels are a sensitive indicator of PCOS-related androgen excess.
Kim, J.J. et al., (2013)	Is a preponderance of small dense LDL cholesterol observed in non-obese women with PCOS?	Case-control study	64 PCOS patients Rotterdam criteria and 64 age-BMI matched controls	Findings suggest that non-obese women with PCOS may have no significant quantitative or qualitative changes in LDL cholesterol.

Mani, H. et al., (2013)	The incidence and prevalence of cardiovascular events in a cohort of women with PCOS.	(20-year) retrospective cohort study	2301 women Rotterdam criteria	Data showed high incidence and age-group specific prevalence of type 2 diabetes, myocardial infarction, and angina in the women with PCOS. Age, history of hypertension, and smoking had significant correlations with cardiovascular outcomes in the PCOS patients.
Akbarzadeh, S. et al., (2012)	Investigate whether omentin and vaspin levels change in non-obese PCOS subjects.	Cross-sectional case control study	39 women with PCOS Rotterdam criteria 39 women for control group with normal pelvic sonographic reports having regular menses and no signs of infertility	PCOS is not a determinant of decreased omentin and vaspin. High androgen level and insulin resistances are warning signs of PCOS.

Lim, S.S., Norman, R.J., Davies, M.J., & Moran, L.J. (2012)	Assess the effects of overweight, obesity and central obesity on the reproductive, metabolic, and psychological features of PCOS.	Systematic review/meta-analysis	30 eligible studies	Being overweight adversely affects many aspects of PCOS while being obese further worsens these outcomes.
Tao, T., Li, S., Shao, A., Mao, X., & Lui, W. (2012).	Clarify the pathogenic features by evaluating the levels of insulin sensitivity and beta cell function in women with PCOS.	Cross-sectional	137 Chinese women with PCOS Rotterdam criteria & 127 normal women	Early impaired beta cell function was detected in both lean and obese women with PCOS; more serious primary defect in insulin action was detected in lean women compared to obese women.
Yildiz, B.O., Bozdag, G., Yapici, Z., Esinler, I., & Yarali, H. (2012)	What is the prevalence, phenotype, and metabolic features of PCOS in the same population according to three different diagnostic criteria?	Cross-sectional study	392 women with PCOS Rotterdam criteria	Higher rates of women were diagnosed with PCOS under Rotterdam criteria and a higher rate of metabolic syndrome was diagnosed under the NIH criteria.
Wild, R.A., Rizzo, M., Clifton, S., & Carmina, E. (2011)	To quantify the magnitude and pattern of LDL cholesterol and HDL cholesterol levels in women with PCOS versus control women.	Systematic review/meta-analysis	2710 women with PCOS Rotterdam criteria and/or NIH criteria 1657 non-PCOS controls	Dyslipidemia is common in PCOS. Women with PCOS have higher LDL cholesterol and non HDL cholesterol regardless of BMI.

Moran, L.J., Misso, M.L., Wild, R.A., & Norman, R.J. (2010).	PCOS is a common condition in reproductive aged women associated with IGT, DM2, and metabolic syndrome.	Systematic Review	2,192 studies reviewed, 35 selected for final analysis	Women with PCOS had an elevated prevalence of IGT, DM2, and metabolic syndrome in both BMI and non BMI matched studies.
Yilmaz, M., Isaoglu, U., Delibas, I.B., & Kadanali, S. (2010).	To compare all phenotypes of PCOS for anthropometrical, hormonal, and metabolic differences according to Rotterdam criteria.	Cross-sectional study	127 women with PCOS Rotterdam criteria 44 non-PCOS controls	Women with just polycystic ovaries and anovulation (PCO+O) were at decreased risk of development of metabolic syndrome and insulin resistances than other phenotypes.

Running head: POLYCYSTIC OVARY SYNDROME METABOLIC COMORBIDITIES

Appendix F

Primary Care Evaluation of Polycystic Ovary Syndrome (PCOS), diagnosed by Rotterdam criteria

At least two of the following:

- Hyperandrogenism (hirsutism/acne/alopecia)
- Oligomenorrhea and/or anovulation
- Polycystic ovaries (> 12 follicles on ultrasound)
  - ❖ Exclude in all women before making a diagnosis of PCOS: thyroid disease, prolactin excess, non-classical congenital adrenal hyperplasia (TSH, prolactin, 17-hydroxyprogesterone)

History & Physical Exam

Hyperandrogenism; hirsutism/acne/alopecia

- Modified Ferriman-Gallway Score for hirsutism. (upper and lower abdomen, chin)
- First-line treatment: hormonal contraceptives. (desogestral, norgestimate)
- Antiandrogens have equivalent efficacy to hormonal contraceptives. (spironolactone 50-200mg po daily)
- Hormonal contraceptive use >6 months, necessary to document response of hirsutism.
- Antiandrogens should not be used without contraceptives.
- Refer alopecia to dermatology
- Refer acne not responding to hormonal contraceptives to dermatology

Oligomenorrhea/Anovulation
Desires pregnancy

No

- First-line hormonal contraceptives (screen for contraindications)
- Second-line Metformin for those who cannot tolerate hormonal contraceptives.

Yes

Exclude other causes of infertility:

- Pregnancy
- Hypothalamic amenorrhea
- Primary ovarian insufficiency
- Androgen-secreting tumor
- Cushing's syndrome
- Acromegaly

Address:

- Overweight/obesity
- Insulin resistance
- Optimizing health: smoking cessation, folic acid vitamin supplementation, lifestyle, & diet.

Anovulatory infertility

- First-line: Clomiphene citrate or Letrozole
- Referral to reproductive endocrinology infertility specialist.

Polycystic Ovaries (>12 follicles on ultrasound)

Screen all women with PCOS for:

Overweight/obesity (BMI >30 kg/m^2 or BMI >25 kg/m^2 in Asian populations) → Lifestyle modification:

- Restricted caloric intake
- Exercise

Smoking
Hypertension
Dyslipidemia
Obstructive Sleep Apnea
Family History of Cardiovascular disease → Statin therapy for those who meet current indications for statin therapy.

*IGT & *T2DM

- 2-HOUR 75g GTT
- HgbA1c (if unable to tolerate or refuses GTT)

Metformin may be used for patients with T2DM or IGT who fail lifestyle modification.

Developed from the following:

ASRM. (2012). Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-sponsored 3rd PCOS consensus workshop group. *Fertility and Sterility, 97(1), 28-38e.25.*

Legro, R.S. (2013). Diagnosis and treatment of polycystic ovary syndrome: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology Metabolism, 98(12), 4565-4592.*

*IGT: impaired glucose tolerance; T2DM: diabetes type 2

Appendix G

Thank you for your interest in presenting a poster at the Alaska Nurse Practitioner Association's Annual Conference. Poster presentations are valued by the conference attendees and showcase research by fellow nurse practitioners. Please submit the follow for review by the selection committee.

The date for the poster presentation is September 22, 2016 at 4-5pm. The poster presentations need to be attended for the entire hour by the presenter. Please submit the following information below. If you are selected to present, you will be contacted by a member of the selection committee. Additional information will be requested at that time.

Please email submissions to: presidentelectANPA@gmail.com

Name: Rhianne Christopherson (907) 223-9202; rhiannechristopherson@gmail.com
School: University of Alaska Anchorage
Program: MSN-Family Nurse Practitioner

Title of Poster: PCOS Evidence-Based Algorithm

Abstract (Less than 150 words)

Abstract

Polycystic ovary syndrome (PCOS) is a complex metabolic and reproductive disorder that affects an extensive number of women of reproductive aged. The purpose of this project was to critically appraise current evidence regarding the metabolic comorbidities associated and their impacts on women with PCOS with goals of identifying what evidence based assessment, evaluation, and treatment options are available to health care providers treating women with PCOS. The results of this critical appraisal and consensus statements from The Endocrine Society and the American Society of Reproductive Medicine [ASRM] concluded that women with PCOS have an increased risk of developing type 2 diabetes, cardiovascular disease, and metabolic syndrome (Akbarzadeh et al., 2012; ASRM, 2012; Legro et al., 2013; Moran, Misso, Wild, & Norman, 2010; Tao, Shengxian, Zhao, Mao, & Liu, 2012; & Yilmaz, Isaoglu, Delibas, & Kadanali, 2011). An evidence based practice algorithm was developed from the results of this critical appraisal and consensus between both The Endocrine Society and ASRM on the diagnosis and treatment of PCOS. The results of this critical appraisal and evidence-based algorithm will assist Advanced Practice Nurses (ANPs) in continued health promotion and the prevention of the comorbidities associated with PCOS.

Appendix H

Hi Rhianne,

Thanks for sending us your letter of inquiry.

With respect to publishing research projects in Women's Healthcare: A Clinical Journal for NPs, we consider only those completed for a DNP degree, not a master's degree. Also, even if we were to consider a master's degree project, we've published an article on PCOS in the recent past and have more on this topic in the pipeline.

If you have a doctoral research project for us to review in a few years, please do send it our way!

Sincerely,
Dory

Dory Greene, Managing Editor
Women's Healthcare: A Clinical Journal for NPs
Work: 908-903-0230
Fax: 908-903-0231
Mobile: 908-347-4592