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Early Identification of PCOS in Adolescents and Alternatives in Management

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Table of Contents:

Purpose Statement.....3

Abstract.....4

Introduction/Background Information.....6

Methods/Evidence Acquisition.....9

Results and Discussion/Evidence Synthesis.....10

Conclusion.....24

Student-Created Table.....26

References.....27

Purpose Statement:

Polycystic Ovarian Disorder is a leading cause of female morbidity, including female infertility, insulin resistance, obesity, cardiovascular disease, hirsutism, and acne. In addition, PCOS involves many symptoms that can negatively impact one's quality of life and harm one's confidence. This paper will analyze current literature on the early identification of PCOS in adolescent girls and alternative management of PCOS symptoms so that the disease may be more effectively detected and managed.

Abstract:

Objectives:

This paper aims to research the clinical screening of PCOS in adolescents and alternative management. This will be done by analyzing current medical literature, including randomized clinical trials, systemic reviews, and meta-analyses. In addition, this paper will increase provider awareness of when and how to screen adolescents for PCOS and the best practices to advise patients on managing their symptoms.

Methods (Evidence Acquisition):

Using Web of Science, phrases such as “PCOS Screening” and “Adolescents” were utilized. To analyze PCOS management, the keywords “Alternative Therapy” and “PCOS” were searched. The searches yielded 256 and 255 results, respectively. Other keywords searched included “PCOS Overview,” which revealed 158 papers, and “PCOS and Mental Health” which produced 357 results. Only articles published between 2000 - 2023 were allowed in this literature review resulting in 25 articles utilized in this paper.

Results and Discussion of Evidence (Data) Synthesis:

Studies have shown a correlation between PCOS in adolescents and an increased ovarian volume, number of ovarian follicles, and the ovarian stromal area to total ovarian area (S/A) ratio making ultrasonography a useful diagnostic tool.¹ Research shows a correlation between PCOS in adolescents and an elevation in luteinizing hormone (LH), luteinizing hormone to follicle stimulating hormone ratio (LH/FSH), and fasting insulin level, making these markers a valuable diagnostic tool.² Lipid panel values are correlated to obesity rather than PCOS.² A study of 24 PCOS patients demonstrated a weight reduction of 6.66 kg/m²

when participants followed a ketogenic diet.³ Pharmacological therapy, including Inositol and Quercetin, improved PCOS symptoms but requires future research. Bariatric surgery was found to decrease weight and improve PCOS symptoms drastically.⁴ Forms of laparoscopic ovarian diathermy can improve fertility.⁵

Conclusion:

Overall, the literature supports that an elevated ovarian volume, ovarian follicle count, and S/A ratio are acceptable criteria when screening adolescents for PCOS.¹ Future studies should investigate utilizing ovarian vascularity.¹ In addition, an elevated LH, LH/FSH, and fasting insulin are correlated to PCOS in adolescents and may be used to screen for PCOS.² Lipid values are correlated to obesity rather than PCOS but may be used further to support the diagnosis of PCOS pending future research.²

A ketogenic diet and bariatric surgery resulted in significant weight loss and improved PCOS symptoms.^{4,6} However, a ketogenic diet requires future research before it can be recommended. Studies using acupuncture have many limitations, so they cannot be relied upon.³ Pharmacologic therapy, including Inositol and Quercetin, have plausible mechanisms of action but require extensive trials to confirm their benefits.^{7,8} Lastly, laparoscopic ovarian diathermy and ultrasound-guided transuterine needle drilling improve fertility and may be recommended as surgical alternatives.^{5,9}

Introduction:

Polycystic Ovarian Syndrome, or PCOS, is a common endocrine disorder in women. A retrospective cohort study of over 14,000 women stated that PCOS has an incidence rate of 2.27%, 95% CI [2.23% to 2.31%].¹⁰ PCOS is associated with various symptoms, including hirsutism, acne, psychological disorders, insulin resistance, obesity, cardiovascular disease, and gynecologic cancers.¹¹ PCOS is the leading cause of female infertility, responsible for 90% of ovulatory disorders.¹¹ It must be understood that PCOS is a multifaceted disease with a complex pathophysiology and casual etiology that is not fully understood.¹¹ Theories have been proposed concerning the effects of various phenotypes on symptom presentation.¹² It is established that hormones play a vital role in the pathophysiology of PCOS, and patients are in a hyperandrogenic state.¹¹ One or both ovaries undergo morphologic changes, developing at least ten cysts and enlarging to over 10 milliliters in volume.¹¹

Current Screening Guidelines for PCOS / Challenges in Screening for PCOS in Adolescents

Current screening for PCOS is commonly conducted through the Rotterdam Criteria. The Rotterdam Criteria states that the patient must have two out of three: menstrual irregularities, hyperandrogenism, or polycystic ovaries seen on ultrasound.¹¹ However, this criterion may not be appropriate for adolescents because puberty can cause physiologic hyperandrogenemia and irregular menstrual cycles.¹³ This can make it challenging to distinguish PCOS from puberty. Clinical signs of hyperandrogenism, namely hirsutism, and acne, are common physiologic changes during puberty.¹³ This is also true for menstrual irregularities. It can take an adolescent up to two years for their menstrual cycle to become regular after menarche.¹³ This delays the physician from determining if the patient is

experiencing physiologic changes or something more serious such as PCOS. For example, a follow-up study of 136 adolescents with irregular menses found that 36.0% of the girls had PCOS after two years, while 64% did not.¹⁴ This demonstrates the difficulty in distinguishing PCOS from physiologic puberty.¹⁰ Furthermore, it has been found that adolescents without PCOS can demonstrate polycystic ovarian morphology on ultrasonography.⁹ Overall, the natural physiologic changes during puberty make the current PCOS screening guidelines less than ideal for use in the adolescent population.

Current Therapy Guidelines for PCOS

The first-line treatment for PCOS is lifestyle management including weight reduction through diet and exercise.⁷ It has been shown that a 5% decrease in body weight can improve symptoms associated with PCOS.⁷ A decrease in body weight can improve clinical symptoms such as hirsutism and acne, all the way to improving laboratory values, including insulin and testosterone levels.⁷ Oral contraceptive pills are frequently used to treat PCOS as they suppress the hypothalamic-pituitary-ovarian axis, thus improving hyperandrogenism and menstrual irregularities.⁷ Metformin is commonly prescribed because it increases peripheral insulin sensitivity and decreases hepatic glucose production.⁷ While these treatments may be appropriate for adolescents, this paper will review alternative therapies to provide thorough information so providers can best treat their patients.

Although PCOS occurs in up to 26% of adolescent females, it is mainly studied in adult populations.⁷ This creates a knowledge gap in best screening and managing adolescent PCOS. Up to 75% of PCOS patients were not diagnosed until after their first appointment.¹⁵ Studies have shown that adolescents diagnosed with PCOS are unsatisfied with the lack of information provided about lifestyle management of PCOS, long-term complications, and

lastly with emotional support services.¹⁵ This literature review focusing on adolescents, can better advise when to screen patients and how to manage their symptoms best. Doing so early in the disease will lead to higher patient satisfaction and may decrease the progression of associated comorbidities in the future.

Methods:

Web of Science was searched with a PICO question of “female adolescents with PCOS” as the population, “alternatives in screening” as the intervention, “traditional screening” as the comparison, and “positive outcomes” as the outcomes. Unfortunately, this PICO search did not generate results due to its specificity. Likewise, the following PICO question was searched with “female adolescents with PCOS” as the population, “alternative therapy” as the intervention, “traditional therapy” as the comparison, and “hyperandrogenism” as the outcome; no results were produced.

Web of Science was then searched with broader topics using the keywords “PCOS Screening” and “Adolescents.” This generated 256 results. The results were narrowed down to 251 results by implementing a time frame of 2000-2023. From this result, only six papers were used for analysis. The keywords “PCOS” and “Alternative Therapy” were then searched, resulting in 255 results published in 2000-2023. Papers and studies that only included information based on animal studies alone were excluded. Of the 255 articles, nine pieces were included in this literature review. Other keywords searched included “PCOS Overview,” which yielded 158 results in which only one paper was selected. “PCOS” and “Mental Health” were additionally searched and produced 357 pieces. The results were further narrowed by applying a time frame of 2015-2023 and later refined to only clinical trials. A total of 23 current literature papers were analyzed.

Evidence Synthesis:

This section will discuss employing 2D and 3D pelvic ultrasonography and hormonal and biochemical markers to diagnose adolescent PCOS. This section will also discuss alternatives in lifestyle, pharmacological, and surgical therapies to manage PCOS.

Screening for PCOS in Adolescents Using 2D and 3D Pelvic Ultrasonography

There is debate about whether ultrasonography should be used as a criterion to diagnose PCOS in adolescents. This largely stems from the fact that puberty can simulate polycystic ovarian morphology. Despite this, many studies have demonstrated ultrasonography to be beneficial in aiding in diagnosing PCOS in adolescents¹. Senaldi et al. examined seven studies.¹ Five of those studies consisted of 262 adolescents diagnosed with PCOS who were concerned with 2D ultrasonography (Group A).¹ Another study group consisted of 157 adolescents and young women diagnosed with PCOS who were examined using 3D ultrasonography (Group B).¹ Both study groups were analyzed for their results regarding ovarian morphology.¹ Studies using 2D sonography revealed a clinically significant difference in ovarian volume.¹ The adolescents with PCOS had a mean ovarian volume of 9.29 +/- 4.62 milliliters, while the control group had a volume of 4.77 +/- 2.30 milliliters ($p < 0.001$), indicating that adolescents with PCOS have a significantly larger ovarian volume compared to their counterparts.¹ The 3D ultrasound showed similar results with a mean ovarian volume of 13.3 +/- 3.2 milliliters in PCOS patients and a volume of 6.3 +/- 1.6 milliliters in the control group ($p < 0.0001$), indicating patients with PCOS have a significantly larger ovarian volume than their counterparts.¹ These findings of ovarian volume are consistent with the perspective correlation study by Jain et al. that found that within their population of 50 adolescents with PCOS features, the mean ovarian volume was

11.08 +/- 5.82 compared to the control group with 4.23 +/- 0.89.² Further indicating that ovarian volume in adolescents with PCOS is significantly greater than their age-matched counterparts.² The strength of the association between adolescents with PCOS and a high mean ovarian volume contributes to the reliability of the studies. For this reason, ultrasonography is a valuable tool to help distinguish whether adolescents have PCOS.

Equally important, ultrasound also can distinguish other aspects of ovarian morphology, such as the number of follicles, the stromal area to ovarian area ratio, and ovarian vascularity. The prospective correlation study conducted by Jain et al., consisting of 50 PCOS adolescents, determined that, like PCOS adults, adolescents also have an increase in ovarian follicles.² 16% of adolescents with PCOS were found to have five to eleven follicles, and 72% had over twelve follicles.² Their age-matched counterparts, without PCOS, demonstrated only 0-4 follicles per ovary.² This demonstrates that adolescents with PCOS have more follicles than adolescents without PCOS.² A limitation of this study is the small sample size. However, these findings are consistent with other studies. For example, a study by Silfen et al. showed that 100% of obese PCOS adolescents and 75% of non-obese PCOS adolescents had multiple ovarian follicles compared to only 31% of controls.¹ This indicates that PCOS adolescents have a statistically significant more number of ovarian follicles than adolescents without PCOS ($p < 0.001$).¹ It also indicates a potential confounding correlation between obesity and the number of ovarian follicles.¹ A limitation of the study is that it is not described how many follicles are considered “multiple follicles.” These findings are supported by Senaldi et al., who discusses a study that further concludes obese PCOS adolescents have over ten ovarian follicles.¹ These studies show a correlation between PCOS in adolescents and an increase in the number of follicles.¹ They additionally

show a potential confounding correlation between obesity and the number of follicles in a PCOS patient, meaning that obesity may be a confounding factor in the relationship between adolescents and the number of ovarian follicles, e.g. the number of follicles may be influenced by the presence of obesity in addition to the presence of PCOS alone.¹ The link between obesity and the number of follicles needs to be further explored in the future.

The Rotterdam Criteria does not specify that a PCOS patient needs an increased S/A ratio. An S/A ratio is the comparison between the ovarian stromal area to the total ovarian area. Yet, recent studies have shown a correlation between an increased S/A ratio and PCOS in both adults and adolescents.¹ For example, a paper analyzing two studies with 264 PCOS adolescents identified an increase in the S/A ratio.¹ The study implies PCOS patients have an elevated S/A ratio; therefore, it can be used as a criterion to screen patients.¹ This is supported by a study on 75 adolescent to young adult PCOS patients and 25 controls.¹⁶ The study found that adolescents with PCOS had a mean S/A ratio of 0.513 +/- 0.12 compared to their controls, who had a mean S/A ratio of 0.27 +/- 0.07 ($p < 0.01$).¹⁶ This indicates that adolescent to young adult PCOS patients have an elevated S/A ratio that is statistically significantly increased as compared to non-PCOS patients.¹⁶ Similarly, another paper stated that a S/A ratio greater than 0.34 is suggestive of PCOS in adolescents, further indicating a S/A ratio can be used to screen for PCOS as it is higher in PCOS patients than in patients without PCOS.¹⁷ The studies consistently show a strong and plausible correlation between PCOS and an elevated S/A ratio; therefore, an elevated S/A ratio can help diagnose adolescents with PCOS.

Using ovarian vascularization as a determining factor to diagnose PCOS is a new development. It is accepted that PCOS patients have an increase in ovarian blood flow

because they have a surge in LH, which affects different mechanisms, such as increasing vascular endothelial growth factor.¹ Because of recent developments in 3D ultrasound, it is now possible to use Doppler signals to detect an increase in ovarian vascularization and diagnose PCOS.¹ This theory is plausible but lacks research and needs further study.

Screening for PCOS in Adolescents Using Hormonal and Biochemical Markers

Based on the Rotterdam Criteria, physicians can examine luteinizing hormones and circulating levels of testosterone or androstenedione to help diagnose PCOS.⁷ This review analyzes if there are similar laboratory value findings in adolescents and if other markers may apply to screening. Hormones play a crucial role in PCOS. A prospective correlation study analyzed 50 adults and 50 adolescents with PCOS.² The 50 PCOS adolescents had an elevated mean LH level of 7.75 ± 4.6 m IU/ml and an elevated mean LH/FSH ratio of 2.08 ± 1.27 . Both adults and adolescents with PCOS have significantly higher ($p < 0.01$) LH and LH/FSH ratios than the controls.² This indicates PCOS adolescents, like adults with PCOS, have an elevated LH and LH/FSH ratio than their non-PCOS counterparts.² These findings are consistent with others. For example, Salmi et al. suggest that an LH/FSH ratio above 3 helps diagnose PCOS in adolescents with a BMI under 27.¹⁴ These findings are plausible because PCOS patients have increased gonadotropin-releasing hormone pulsations, increasing LH, and decreasing FSH.⁵ The prospective correlation study found LH ($r=0.30$, $p=0.003$) and testosterone ($r=0.34$, $p=0.001$) levels are correlated to the ovarian stromal area as both stimulate ovarian enlargement.² As discussed previously, PCOS is associated with ovarian enlargement.¹ The studies are reliable due to their strength, plausibility, and consistency with one another.

Other biochemical markers that may be able to screen for PCOS in adolescents are those found in a lipid panel. This includes cholesterol, triglycerides, VLDL, LDL, and HDL levels. Women with PCOS have a 70% risk of developing metabolic syndrome.¹⁸ A observational study of 120 adolescents with PCOS concluded that one's phenotype could affect their lipid values.⁸ More specifically, patients with hirsutism and oligomenorrhea are more likely to experience severe lipid abnormalities.¹² By screening adolescents early for lipid abnormalities, we can identify PCOS earlier and potentially decrease the risk of adverse outcomes.² However, by stratifying the participants' BMI, it is suggested that lipid abnormalities are due to obesity rather than PCOS.² The prospective correlation study by Jain et al. found there were no statistically significant differences in lipid profiles when PCOS patients were compared to their BMI-matched control, suggesting that lipid values should not be used to screen for PCOS ($p > 0.05$).² The study's limitations include a small sample size and would benefit from further research on the pathophysiologic method of the correlation between obesity and PCOS. A systematic review by Dokras et report that up to 36% of PCOS women have an eating disorder.¹⁹ When psychiatric comorbidities were accounted for, the odds ratio of developing an eating disorder when [...diagnosed with] PCOS was statistically significant at 1.21, 95% CI [1.03, 1.41].¹⁹ This suggests that developing PCOS will increase one's risk of developing an eating disorder.¹⁹ The study's findings were unlikely due to chance, as the confidence interval is narrow and does not cross zero.¹⁹ Smaller studies have been conducted that produced similar results. Eating disorders may contribute to and exacerbate obesity in PCOS patients.¹⁹ Given this information, providers are not recommended to use a lipid panel to diagnose PCOS solely. Instead, providers should be educated that obesity is associated with PCOS and may be used to

support the diagnosis if in conjunction with more definitive screening methods. Providers should also screen known PCOS patients for eating disorders.

Lastly, because hyperinsulinemia or insulin resistance is associated with 85% of PCOS patients, it is proposed that using biomarkers of insulin resistance can help diagnose PCOS.¹¹ While there has yet to be a clear consensus on what specific type of biomarker should be used, a reasonable amount of studies have proposed using a fasting insulin level or fasting glucose.¹¹ A PCOS screening program in California recommends using a fasting insulin of over 20 mIU/ml and a fasting glucose of around 95 mg/dl to aid as diagnostic criteria to diagnose PCOS.¹⁷ Salmi et al. state that while a potential disadvantage to this is that there is a transient state of hyperinsulinemia physiologic to puberty, those with PCOS will still have higher insulin levels than their counterparts.¹⁷ This is seen in the perspective correlation study by Jain et al.² The mean fasting insulin levels within their 50 PCOS adolescent population were elevated at $25.83 + 4.75 \mu\text{U/ml}$.² The calculated mean difference between the adolescent PCOS population and their controls was 14.19.² It was deemed statistically significant ($p < 0.001$), indicating that adolescents with PCOS have a significantly higher mean fasting insulin than adolescents without PCOS.² In contrast, the same study found a mean fasting glucose of $91.55 + 6.45 \text{ mg/dl}$ within the PCOS adolescent population.² The calculated mean difference of fasting glucose between the PCOS adolescents versus their controls was 1.82 mg/dl and was not statistically significant.² This indicates that the fasting glucose between adolescents with PCOS versus adolescents without PCOS is relatively the same and cannot be used to screen for PCOS.² The value of fasting insulin levels is consistent between the studies, while conversely, the use of fasting glucose levels is not.² Therefore, the study recommends that a fasting insulin level be used

in conjunction with other screening methods to confirm the diagnosis of PCOS in adolescents.² However, the pathophysiologic method of why fasting insulin levels are consistent while fasting glucose levels are not, should be further explored to increase the study's plausibility.

Alternative Lifestyle Management of PCOS

After being diagnosed with PCOS, patients are concerned with how to manage their symptoms. While there are current guidelines to follow, this section will discuss alternatives in therapy so providers can offer patients a personalized, holistic treatment plan. Like other health concerns, lifestyle modification is the first step to managing PCOS symptoms.

Acupuncture has been rising in popularity as a treatment for various medical concerns. Some believe acupuncture can even be used to help treat PCOS symptoms. The proposed reasoning is that acupuncture increases beta-endorphins, so it can also affect the gonadotropin-releasing hormone, helping to restore ovulation and one's menstrual cycle.²⁰ A better understanding of the mechanism of action of acupuncture and how it affects ovulation is needed in the future. Despite the uncertainty behind its mechanism of action, numerous randomized control trials have claimed acupuncture increases the pregnancy and ovulation rates in women diagnosed with PCOS.³ For instance, a randomized control trial with 60 people compared the effects of acupuncture with Letrozole versus control with Letrozole alone.³ In the observational group, the trial found a statistically significant elevation in pregnancy rate of 60.53% ($p < 0.05$) and an elevated ovulation rate of 89.47% ($p < 0.05$) compared to the control group.³ This indicates that acupuncture may synergize with Letrozole and improve fertility in PCOS patients.³ These results are supported by a randomized control trial of 60 PCOS patients.²¹ The trial found that the patients treated with

acupuncture experienced a mean decrease in their LH/FSH ratio of 0.39 ($p = 0.043$) and a mean increase in menstruation frequency of 0.33 ($p = 0.047$).³ These results indicate that acupuncture can result in hormonal and menstruation benefits; however, the results were like that of the pharmacologically treated group.³ This means that while acupuncture may benefit PCOS patients, it has no superiority over other pharmacologic treatments.³ We cannot confidently recommend acupuncture to PCOS patients yet. Many trials have small populations, do not have appropriate controls to compare acupuncture effects and include different therapies and acupuncture in the observational group.²⁰ In the future, acupuncture studies must incorporate larger populations, have stricter control groups, and restrict the number of drugs tested simultaneously.²⁰

Due to their increased levels of androgens, up to 71% of women with PCOS will develop obesity.¹¹ It is well-accepted that obesity can exacerbate the metabolic symptoms of PCOS and lead to detrimental health concerns.¹¹ It is, therefore, imperative that every provider encourage overweight PCOS patients to lose weight, maintain a healthy diet, and encourage exercise for all patients. The importance of weight loss is further emphasized when considering that a decrease of only 5% in body weight can regulate a woman's cycle, promote fertility, decrease insulin levels, and improve hirsutism.¹¹ While recommending a healthy diet and exercise is currently the first-line therapy for all patients with PCOS, there is no widely accepted consensus on the "healthy diet."¹¹ A possible diet for providers to recommend is the ketogenic diet which involves eating a diet low in carbohydrates and high in vegetables and proteins.³ A study on 24 overweight PCOS women showed a significant mean decrease of 6.66 kg in body weight after 12 weeks of following the ketogenic diet, indicating that a ketogenic diet results in weight loss.³ The study did not disclose if the

participants followed a calorie-restricted ketogenic diet or if they engaged in exercise-all are variables that affect weight loss. However, these results are supported by a randomized controlled pilot trial.⁶ The trial found that participants BMI decreased significantly from 32.81 +/-3.75 kg/m² to 28.33 +/- 2.62 kg/m².⁶ Like the previous study, this indicates that a ketogenic diet can result in significant weight loss.⁶ A limitation of this study is the small population size of only 20 participants, making the results questionable.⁶ It is plausible that a low-carbohydrate diet would lead to a decline in insulin levels and regulate endocrine function.³ Salmi et al. agrees, stating that a diet low in carbohydrates and high in protein would improve the endocrine status in PCOS patients.¹⁷ A ketogenic diet is a promising alternative therapy for PCOS patients. But to confidently recommend a ketogenic diet to patients, future studies must be conducted with larger sample populations and stricter controls.

Alternative Pharmacologic Management of PCOS

Metformin is proven to inhibit glucose synthesis and is thus a well-accepted therapy to manage PCOS symptoms.¹⁹ A systemic review and meta-analysis of 24 randomized control trials concluded that metformin decreases glucose and body weight and BMI, total testosterone, androstenedione, and LDL-C, and increases pregnancy rate in PCOS.¹⁸ This large study of 564 participants compiled well-documented evidence to prove that metformin is a valuable treatment for PCOS.¹⁹

While it is proven that metformin is effective as monotherapy for PCOS, research is being done to discover if it has a synergistic response with other medications. In particular, the medication class inositols are being researched. Inositols, such as myo-inositol (MYO) and its metabolite D-chiro-inositol (DCI), are cyclic polyalcohols naturally found in the

human body.⁷ It is known that MYO regulates glucose uptake and plays a role in FSH signaling.⁷ DCI regulates glucose synthesis and is a part of insulin-mediated androgen synthesis.⁷ Studies have shown that PCOS patients have a decreased release of DCI-IPG mediator and an increased urinary excretion of DCI, potentially contributing to hyperinsulinemia common in PCOS patients.⁷ MYO supplementation alone has been associated with improvement in metabolic function along with oocyte and embryo quality.⁷ Because of its action mechanism, it is plausible that MYO and DCI supplementation is synergistic with Metformin.⁷ This is supported by a randomized, double-blind study of 137 women diagnosed with PCOS.²² The study found that after six months, participants treated with MYO or DIC both experienced a statistically significant decrease in their total cholesterol ($p < 0.05$), triglycerides ($p < 0.05$), and basal insulin serum levels ($p < 0.05$).²² This suggests that inositols can be prescribed to women with PCOS to improve their metabolic function.²² The randomized, double-blind study of 137 women also concluded that inositols could restore menstrual cycle regularity.²² The study found that 66% of the women treated with MYO and 64% of those treated with DCI experienced a statistically significant improvement in the regularity of their menstrual cycle ($p < 0.001$).²² This suggests that insitols can restore menstrual cycles in women with PCOS and may improve fertility.²² Further studies should be conducted to confirm if inositols benefit PCOS patients when used as monotherapy or in conjunction with metformin.

A new and emerging medication for PCOS therapy is Quercetin, a natural flavonoid with beneficial properties, including anti-inflammatory, anti-obesity, and anti-oxidative effects.⁸ Two clinical trials were executed over 12 weeks in which an 80-participant group and an 84-participant group were given 1000 mg of Quercetin orally.⁸ Compared to the controls, both

studies found a statistically significant decrease in testosterone, luteinizing hormone, homeostatic assessment of insulin resistance, and insulin.⁸ The findings suggest Quercetin can regulate endocrine and metabolic disruptions in PCOS patients.⁸ One group found a significant decrease in BMI, and the other found a significant increase in sex hormone-binding globulin.⁸ These findings appear robust, but each study was performed on small sample sizes. Similarly, a randomized control study of 72 participants found that Quercetin significantly reduced luteinizing hormone levels from 5.35 ± 1.62 to 3.16 ± 1.43 after three months of use ($p = 0.029$).²³ These findings indicate that Quercetin can significantly lower luteinizing hormone within PCOS.²³ Moreso, 26 of the 31 patients taking Quercetin became pregnant compared to only 4 participants in the control group.²³ This signifies that Quercetin can improve pregnancy rates in PCOS patients.²³ More clinical studies should be conducted concerning Quercetin and its effect on PCOS. Future studies should utilize larger populations so the results of Quercetin can be clinically applicable.

Alternative Surgical Management of PCOS

As previously emphasized, weight loss is a key component of PCOS management, and physicians should encourage lifestyle changes that promote weight loss.^{4,11} A randomized control trial of 183 women with PCOS found that weight loss contributed to a statistically significant improvement in ovulatory disorders (estimate 0.157 SE 0.030, $p < 0.001$) and hyperandrogenism (estimate 0.097 SE 0.027, $p < 0.001$).²⁴ This demonstrates the benefits of weight loss on the ovulatory and biochemical symptoms associated with PCOS.²⁴ When lifestyle changes are ineffective, patients may want to consider bariatric surgery, which has been found to improve symptoms in women with PCOS. Ezzat et al. created a cohort study that examined 36 obese women with PCOS before and after bariatric surgery.⁴⁴ All

participants had been infertile for at least one year, and women 40 or older were excluded from the study.⁴ The cohort study found that BMI dropped from 34.6 +/- 1.76 kg/m² pre-operatively to 29.1 +/- 1.17 kg/m² one year post-operatively.⁴ This demonstrates that bariatric surgery causes a significant decrease in body weight.⁴ All participants are now under the 35 kg/m² BMI limit to start fertility treatment.⁴ The study also found statistically significant changes in serum androgen levels.⁴ The mean serum-free testosterone decreased from 51.5 +/- 16.5 pg/ml pre-operatively to 28.6 +/- 9.2 pg/ml with a $p < 0.001$ one year post-operatively.⁴ This demonstrates that bariatric surgery can improve endocrine dysregulation in PCOS patients.⁴ There was a measurable increase in the mean sex hormone binding globulin level from 16.3 +/- 2.31 nmol/L to 29.3 +/- 4.21 nmol/L one year after the surgery, indicating an improvement in metabolic function.⁴ Lastly, the study investigated bariatric surgery's effect on ovarian morphology. After bariatric surgery, the mean ovarian volume significantly decreased from 14.7 +/- 1.79 ml to 8.15 +/- 0.99 ml with a $p < 0.001$, indicating that bariatric surgery significantly decreased ovarian volume.⁴ The ovarian volume decreased to be within the normal range for all the participants.⁴ These results are similar to those found in systemic reviews and meta-analyses that involved larger populations.⁴ Bariatric surgery demonstrates robust results in obese women diagnosed with PCOS. Bariatric surgery should be considered in obese PCOS patients who do not respond to traditional lifestyle changes and are considered eligible surgical candidates.

Surgery may be considered a last resort for those with pharmacologic-resistant PCOS. Laparoscopic ovarian diathermy is one potential surgery PCOS patients can undergo.⁵ This procedure utilizes electrocautery or a laser to traumatize ovarian tissue.⁵ The pathophysiology behind why ovarian trauma improves PCOS is not fully understood.

Several concepts propose that a decrease in ovarian size or a decrease in ovarian blood flow leads to PCOS improvement.⁵ The trauma to ovarian tissue is believed to decrease androgen production.⁵ Despite what tool is being used, 80% of ovarian diathermies restore ovulation in women with PCOS.⁵ This is supported by Table 1, which shows improvements in aspects of infertility. Furthermore, a 252-participant study showed that laparoscopic surgery that

Table 1: Data Abstracted from "Advances in polycystic ovary syndrome treatment: metformin and ovarian diathermy."

Type of Ovarian Diathermy	Ovulation Rate, % (Confidence Interval)	Spontaneous Pregnancy Rate, % (Confidence Interval)	Cumulative Pregnancy Rate, % (Confidence Interval)
Laparotomy (n= 679)	81.6 (58-93)	50 (32-67)	55.3 (39-67)
Laparoscopy			
Laser (n= 322)	71.5 (68-80)	43.7 (N/A)	53.1 (35-59)
Cautery (n= 720)	79.7 (78-87)	51.5 (37-53)	63.6 (44-62)

Source: LeClair C. "Advances in Polycystic Ovarian Syndrome Treatment: Metformin and Ovarian Diathermy" *Current Women's Health Report 2.5* (2002) 333-337. Web of Science. Web 5 February 2023

used electrocautery resulted in 92% ovulation success, and 84% of the participants became pregnant.²⁵ The study demonstrates that laparoscopic surgery can significantly improve fertility in PCOS patients.²⁵ The effects of the laparoscopic surgery were persistent, with two-thirds of those women ovulating up to twenty years post-surgery.²⁵ An adverse effect of laparoscopic ovarian diathermy is ovarian adhesions, with one study reporting up to 90% of patients developing postoperative adhesions.²⁵ However, the methods used during the surgery affect the rate of adhesions, with electrocautery only causing adhesions in 30% of patients.²⁵ This indicates that while all forms of laparoscopic diathermy have similar benefits, the provider needs to consider the risks associated with specific methods and discuss those with the patient.²⁵ Laparoscopic ovarian diathermy should not be recommended as a first-line therapy for PCOS patients, but it may be used in patients who

have failed other management strategies.²⁵ Unlike laparoscopic ovarian diathermy, ultrasound-guided transvaginal ovarian needle drilling (UTND) can be used as a first-line treatment if the patient resists clomiphene citrate treatment.⁹ A randomized control trial found that UTND has similar efficacy as laparoscopic ovarian diathermy.⁹ However, the trial found that UTND is more time efficient, with a 15.3 +/- 5.61 minutes duration compared to 25.6 +/- 8.2 minutes for laparoscopic ovarian diathermy (p-value < 0.05).⁹ This statistically significant difference indicates that UTND is equally as efficient as laparoscopic ovarian diathermy with the added benefit of being a shorter procedure.⁹ Both laparoscopic ovarian drilling and UTND are effective surgical alternatives to manage PCOS symptoms.^{9,25}

Conclusion:

After an in-depth review of the current literature, it can be concluded that a clear correlation exists between adolescents with PCOS, and findings seen on 2D and 3D ultrasonography and with biochemical markers. There is sufficient evidence to confirm that the ultrasonography elements within the current Rotterdam Criteria, such as having an enlarged ovarian volume, a high number of ovarian follicles, and an elevated S/A ratio apply to adolescents with PCOS.¹ Additional elements like ovarian vascularity may be added to PCOS criteria, pending further randomized control trials to test their efficacy.¹ In addition, hormonal and biochemical markers may be added to the requirements to screen adolescents for PCOS. The luteinizing hormone, luteinizing hormones to follicle-stimulating hormone ratio, and fasting insulin levels are statistically elevated in adolescents with PCOS compared to their age-matched controls.² As such, using these hormonal and biochemical markers as diagnostic criteria to diagnose adolescent PCOS is appropriate. Lipid panel values are correlated to obesity rather than PCOS.² Because obesity is linked to PCOS, high lipid panel values may be used to confirm the diagnosis but cannot be relied upon solely.² Findings from ultrasonography and laboratory values should be used together and with other screening guidelines. This will allow for a holistic approach to diagnosing adolescents with PCOS.

This study analyzed alternative therapies to manage PCOS. It is plausible that the ketogenic diet can improve the features of PCOS.³ However, this review needed more studies to confirm its effectiveness. Because of this, the ketogenic diet should be studied in the future with larger sample populations so it can be recommended over other diets to manage PCOS. Likewise, we cannot yet recommend working PCOS symptoms with

acupuncture. Studies on acupuncture were conducted with small sample sizes, did not have consistent control groups, and included other therapies combined with acupuncture inside their observational group.³ Because of these limitations, the effects of acupuncture currently need to be more reliable. Medications found to be beneficial for PCOS include Metformin with Inositols like MYO or DCI.⁷ These were found to have a synergistic effect with one another. The mechanism of action behind inositol and its impact on PCOS is plausible but has yet to be thoroughly researched.⁷ The combination of Metformin and inositol requires more extensive randomized control trials in the future. Quercetin shows promise in treating PCOS symptoms, including normalizing hormonal and biochemical levels and decreasing BMI.⁸ However, the Quercetin studies used a small sample population, prompting the need for more extensive studies in the future.

Lastly, bariatric surgery was found to significantly decrease patients' BMI, normalize their hormonal and biochemical levels, and reduce their ovarian volume.⁴ While effective in treating PCOS symptoms, bariatric surgery is aggressive and should only be used as a last-line treatment.⁴ The same is true for laparoscopic ovarian diathermy, which is effective at restoring ovulation and promoting pregnancy but is an aggressive treatment.²⁵ Another equally effective yet quicker surgical alternative would be ultrasound-guided transvaginal ovarian needle drilling.⁹

Student-Created Table 1:

Author	Study Design	Population (n)	Key Findings	Comments
Abdalla M, et al.	Systematic Review and Meta-Analysis of Randomized Control Trials	564 Females Diagnosed with PCOS	Increased pregnancy rate (OR = 3.00), (95% CI: 1.95, 4.59) ¹⁸	Metformin can improve the pregnancy rate in women with PCOS. ¹⁹ Adolescents should be informed of PCOS's impact on fertility and educated about potential treatment options if they want to conceive.
Pena A, et al.	Cross-Sectional Study	77 Female Adolescents Diagnosed with PCOS	40.3% of the participants believe treating fertility/reduced fertility is one of the most critical areas of future PCOS research. ¹² 16.9% of participants believe understanding/preventing pregnancy complications is one of the most critical areas of future PCOS research. ¹²	While small, this study demonstrates concerns patients have about their future fertility. ¹² Because this is a concern for patients, it should also be a concern of ours. Therefore, our future research should be directed at how to prevent the best infertility and how to treat it.
Shi Y et al.	Randomized Control Trial Randomized Control Trial	60 60	Those treated with electroacupuncture experienced an increase in the live birth rate of 50% compared to the control group (treated with sham acupuncture), with a live birth rate of 26.3%. P < 0.005. ³ Those treated with Chinese herbal medicine alone had a pregnancy rate of 18.42%. ³ Those treated with Chinese herbal medicine and manual acupuncture had an increased pregnancy rate of 46.34%. P < 0.05. ³	Both randomized control trials show potential for using acupuncture to treat infertility in PCOS. ³ Future research is required.

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