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Doctoral Manuscript: Fertility Considerations in Prescribing Hormonal Contraceptives in
Individuals with Polycystic Ovary Syndrome

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JOURNAL EXPECTATIONS

Chosen Journal for Submission: Journal of Association

Journal Instructions: This paper will serve as a review article. The guidelines on the JAAPA website for authorship of Review Articles are clear on size, subject, and sources preferred. The article should be between 2,000 and 3,500 words including all headings, references, and content tables. Figures and tables are acceptable, but not necessary. Any subject relevant to PA medical or surgical practice is considered, although subjects relevant to the NCCPA Content Blueprint are preferred if being used as a source of CME credit. Furthermore, the guidelines explicitly state primary sources should be used to share the practice changing conclusions of new research. References should be in AMA format.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a highly prevalent endocrine disorder and the most common cause of infertility among females of reproductive age.¹ While the name “polycystic ovary syndrome” implies people diagnosed with PCOS have numerous cysts on their ovaries, this is not always the case. Clinicians currently use the Rotterdam criteria to diagnose PCOS.² These criteria include: irregular periods/anovulatory cycles, clinical or biochemical signs of androgen excess (acne, hirsutism, androgenic alopecia, etc.), and numerous ovarian cysts seen on imaging.² A diagnosis of PCOS can be made when at least two of three criteria are met.² As this has become a much broader diagnoses, between 4-20% women of reproductive age worldwide are diagnosed with PCOS, with an increase of prevalence in the last 10 years.² This disorder causes a multitude of aesthetic and physiologic changes including weight gain, hair loss, dyslipidemia, and one of the most distressing, infertility.^{1,3} Treatment is symptom management with insulin sensitizing actions (lifestyle changes and metformin) and hormonal contraceptives (oral, intrauterine, or implantable).^{3,4} Systemic insulin resistance is thought to be a large contributing factor in the development of local insulin resistance of the ovaries, commonly believed to be the cause of PCOS and its sequelae. Treatment focuses more on androgen regulation with hormonal contraceptives rather than insulin sensitization. Sadly, focus on regulating androgens only masks some symptoms of PCOS rather than addressing the root cause of insulin resistance.

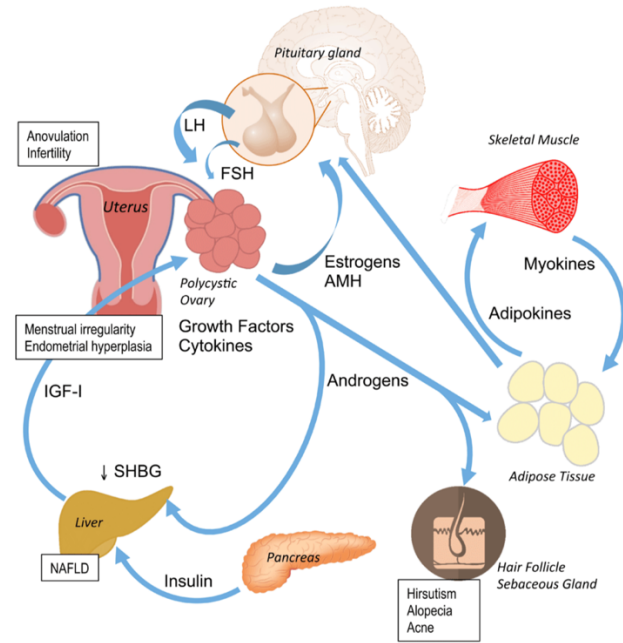


Figure 1: Pathophysiology of PCOS²

It is well understood that improving insulin sensitivity helps to increase fecundity in infertile PCOS women,⁵ but the role prior use of hormonal contraceptives have in improving fertility is less clear. By evaluating the effects of hormonal contraceptives on various aspect of fertility, this review aims to address infertility in women with PCOS with respect to insulin sensitivity.

HORMONAL CONTRACEPTIONS AND THE BRAIN

STRUCTURAL CHANGES

In a recently published cross-sectional study by Chen et al⁶, researchers identified structural changes in the brain associated with OCP use by comparing MRI images of 50 women – 29 natural cycling and 21 OCP users.⁶ The images revealed smaller hypothalamic and pituitary volumes in current OCP users compared to natural cycling women, inferring trophic effects of known central effects of OCPs and insinuating a possible mechanism for a delay in the return of menses.⁶ A systematic review published previous to this cross-sectional study mirrored these

findings.⁷ One consideration these articles fail to address is the long term anatomic and physiologic changes of the brain when hormonal contraceptives are used for greater than a year, nor do they quantify when or if the brain regains its original structure.

FUNCTIONAL CHANGES

As the structures of the brain are altered, so are the functions. Menting-Henry et al⁸ described changes in emotional recognition with patients on oral contraceptives. They noted altered ability to interpret emotions via changes in the amygdala in those taking androgenic and anti-androgenic contraceptives.⁸ With altered interpretation of emotions intimate relationships are likely to be impaired, leading to potential decrease in sexual activity.

Oral contraceptive use has also been associated with risk for mental health concerns. Anderl et al⁹ demonstrated how OCP use potentiates the future risk for major depressive disorder (MDD). This was a prospective study which tracked of MDD in young women aged 13-19 for 6 years after use of OCPs.⁹ They discovered use of OCPs in adolescences increases the risk for MDD up to 6 years after use, particularly in those with no prior concerns of MDD.⁹ This study sheds light on the risk OCPs have on the developing brain and body.⁹ It is important to recognize patients with PCOS are up to eight times more likely to be diagnosed with depression than the general population.²

In addition to depression, it is known that female sexual dysfunction has a higher prevalence in women diagnosed with PCOS which also impacts fertility.³ Addressing an alternative aspect of fertility and behavior, a study by Weiss et al³ compared the effects of lifestyle modifications, hormonal contraceptives, and a combination of both on sexual dysfunction. In 114 women with PCOS, they determined the Female Sexual Function Index (FSFI) and Female Sexual Distress Scale-Revised (FSDS-R) before and after 16 weeks of either

a combined oral contraceptive, weight loss inducing lifestyle changes, or a combination.³ 30% of those evaluated had sexual dysfunction based on their scores and of those, use of OCPs and lifestyle changes improved FSFI similarly.³ Combined treatment improved FSFI more than each alone, but it was not a completely additive effect.³ Additionally, FSDS-R was found to be decreased when using OCPs, but not as significantly as lifestyle alone or when coupled with lifestyle modifications.³ These results could be due to the well-known improvements in mental health related problems with physical exercise and healthy eating, but increased insulin sensitization as a contributing factor should not be excluded.

RETURN TO FERTILITY AFTER HORMONAL CONTRACEPTIVE USE

A prospective cohort study done by Yland et al¹⁰ in 2020 sought to quantify the return of fertility after using various contraceptives. Using data from 17,954 women and 9 methods of contraceptives, fecundity was measured through menstruation recovery and number of cycles needed for pregnancy.¹⁰ Data of the different methods were compared to barrier method, as there are no physiologic changes associated with use of barriers as with longer acting methods.¹⁰ Through this investigation, it was determined that resumption of normal cycles varies by type of contraceptive.¹⁰ Long-acting injectables yielded the longest time for cycle resumption, while hormonal intrauterine devices (IUDs) demonstrated the shortest period of time.¹⁰ Oral contraceptives (OCPs) had a short recovery period, but IUDs were still shown to be superior in the fastest recovery of normal menstruation and pregnancy.¹⁰ Data were separated by various qualifiers, such as BMI, parity, and cycle regularity history.¹⁰ In the comparison of those with a history of regular versus irregular menstrual cycles previous to using contraceptives, hormonal and copper IUDs were still shown to be superior to other methods in those with irregular

cycles.¹⁰ In individuals with previously regular cycles, the patch and hormonal IUDs were the most successful in return of fertility.¹⁰ OCPs were seen to need a small recovery period in both groups, consistent with the overall data.¹⁰ As most individuals with PCOS have irregular cycles, these data are relevant. This study seems to demonstrate minimal adverse effects OCPs have on fecundity. Landersoe et al¹¹ found similar results when measuring anti-Mullerian hormone and antral follicle count in women after discontinuation of combine oral contraceptives (COCs). In women with greater than 3 years use of COCs and no known conditions causing infertility, hormonal markers of fertility returned to baseline within 2 months of discontinuation.¹¹

Patients with a history of PCOS have a different response to OCP use than those without infertility at baseline. In a retrospective cross-sectional study Kulshreshtha et al¹² looked at the return to regular menstruation following withdrawal of OCPs in patients with PCOS. Researchers looked at 48 patients with PCOS who had been on OCPs for at least four months to identify if they were able to regain their menstrual cycle.¹² They found only seven women were able to regain menses without alternative intervention and 36 obtained menses using either spironolactone or metformin.¹² It was determined the longer a patient had been on OCPs prior to discontinuation, the longer it took for resumption of menses indicating a correlation between reduced fertility and prior OCP use in those with PCOS.¹²

Another study, by Legro et al¹, evaluated the efficacy of OCPs, lifestyle changes, or a combination of both as methods for attaining regular ovulation and improving fertility in women between 18-40 with a BMI of 27-42 kg/m² and PCOS. It was a randomized controlled trial with 149 participants that were carefully screened for confounding variables impacting fertility.¹ Some of the inclusion criteria used to screen for participants included oligomenorrhea, hyperandrogenemia, and no other major medical conditions.¹ The participants were randomly

and equally placed in each of the three preconception intervention groups and for 16 weeks participants either used OCPs, followed specific lifestyle changes, or both.¹ They then underwent four cycles of ovulation induction and attempted pregnancy with each ovulation.¹ Legro et al¹ concluded a lifestyle change is the most effective preconception intervention compared to OCPs, likely due to the benefits on cardiovascular and metabolic health.¹ OCPs were shown to have some improvement in ovulation rate when not associated with weight gain. This study¹ helps tie together important pathophysiology of PCOS with two different treatment methods to identify how to best support future fertility.¹ One major limitation to this study is its short duration which impacts clinical relevance. Many women with PCOS are treated for years before desiring fertility and this study fails to answer if long term treatment leads to successful pregnancy similarly to short term interventions.¹

HORMONAL CONTRACEPTIVES AND INSULIN

There are two studies published within the past 3 years which evaluate the role hormonal contraceptives have on insulin resistance and hyperglycemia. Both are animal studies using either mice or rats as models, however both demonstrate concerning connection between hormonal contraceptive use and hyperinsulinemia contributing to insulin resistance.

In 2019, Brazilian researchers Roso de Oliveira et al¹³, identified hyperinsulinemia in both fasting and fed mice receiving continuous combined OCPs compared to control mice. They saw enhanced insulin secretion to glucose loading and reduced insulin degradation through a lower plasma C-peptide/insulin ratio.¹³ These results suggest increased risk of insulin resistance with long term use of OCPs as seen with greater HOMA-IR scores in the mice receiving continuous combined OCPs.¹³ Adeyanju et al¹⁴ later proposed a mechanism for the induced

insulin resistance in their 2020 random controlled trial using rats as animal models. Their findings suggest an association between mineralocorticoid receptors and insulin resistance with the use of OCPs.¹⁴ They found mineralocorticoid receptor antagonists help reduce the insulin sensitizing effects of OCPs.¹⁴ While these results cannot be used to modify clinical practice, they do reveal an area for further research.

CONCLUSION

PCOS affects a significant portion of the world's women of reproductive age and when left untreated, causes significant health concerns such as chronic pain, hair loss, cystic acne, metabolic syndrome, and infertility. Management of this condition is largely symptomatic with lifestyle modifications, hormonal contraceptives, and insulin sensitizing agents such as metformin as mainstays of treatment.⁴ Despite these techniques, PCOS remains the most common cause of infertility in women of reproductive age, a staggering 70-80%.⁴ The role of hormonal contraceptives in fertility for those with PCOS has not been well understood. Recent studies suggest that while hormonal contraceptives cause a decrease in fertility, this decrease is likely temporary. However, research also indicate hormonal contraceptive use is less effective than insulin sensitizing efforts in managing symptoms and infertility associated with PCOS and may play a role in propagating insulin resistance, a known mechanism for PCOS.^{1, 6, 10, 13, 14} There continues to be room for researchers to find how these common PCOS treatments are impacting women over a lifespan rather than the course of a few months to a year. It is important to recognize the research on hormonal contraceptives currently available is not sufficient to make broad-stroke decisions regarding the care of specific populations, such as those with PCOS.

KEY TAKEAWAYS:

- Hormonal contraceptive use in adolescence is seen to increase depression rates in early adulthood.⁹
- Hormonal contraceptives temporarily decrease fertility in women.^{1,4,10,11,12}
- Combined oral contraceptives are shown to confer insulin resistance in animal studies.^{13,14}
- In patients with PCOS, hormonal contraceptives are less effective at managing symptoms and supporting fertility than insulin sensitizing efforts.^{1,5}

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