

## PCOS and Infertility

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### Abstract

Polycystic Ovary Syndrome (PCOS) is a hormonal disorder in which individuals have small cysts that develop on their ovaries, sometimes inhibiting menstruation and ovulation. Individuals with PCOS have excessive levels of androgens, which can cause hormonal imbalances, irregular menstruation, and symptoms of hyperandrogenism. PCOS can also cause infertility since this hormonal imbalance inhibits ovulation in the body. One way to treat infertility is In Vitro Fertilization (IVF), in which the ovaries are stimulated to create multiple egg-containing follicles from which eggs are retrieved, fertilized outside of the body, then inserted into the uterus. Individuals with PCOS are also more likely to develop type 2 diabetes, cardiovascular complications, and endometrial cancer. Some ways of treating PCOS include oral contraceptives to balance hormones, and drugs like metformin to decrease insulin and androgen production. Infertility-specific medications, like clomiphene and follistim, stimulate the production of estrogen and FSH, which thereby increases fertility.

### Introduction

Polycystic Ovary Syndrome (PCOS) is a condition in which women develop multiple unruptured cysts on their ovaries due to hormonal imbalances (Rasquin and Mayrin). This is a disorder that is commonly diagnosed in women of reproductive age. PCOS is often characterized by irregular menstruation, hyperandrogenism, and infertility. People with PCOS may also have issues with regulating their weight, and they can grow hair in a “male” pattern (hirsutism). PCOS also causes elevated levels of insulin in the blood, which causes blood glucose levels to rise. In turn, as cells produce more insulin, insulin resistance is formed (Rasquin and Mayrin). Individuals with PCOS also have higher levels of androgens (mainly testosterone), as well as decreased levels of estrogen and progesterone. This results in menstrual irregularities that prevent regular ovulation and can lead to infertility.

### Diagnosis

PCOS is diagnosed through different criteria. First, to receive a diagnosis of PCOS, one must be presenting two of the three following symptoms: irregular ovulation/irregular menstrual cycles, increased androgen levels (through blood work that indicates high levels), and multiple small cysts on the ovaries, which an ultrasound would detect (“Diagnosing Polycystic Ovary Syndrome”). To diagnose this condition, a physician would conduct a physical exam checking for these symptoms; they would also obtain a detailed history on the patient. They would usually then order blood tests to measure levels of a panel of hormones including testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). A doctor can also recommend a pelvic ultrasound in order to look for ovarian cysts (Peter and Adashi).

### Hormone Imbalance

Individuals with PCOS have higher levels of androgens and lower levels of female reproductive hormones. This imbalance produces cysts that form on the ovaries of people with PCOS. Their ovaries do not release eggs; instead, the egg remains in the follicle and is not released after every menstrual cycle. Over time, these eggs present as multiple small cysts (4-9mm) that accumulate in the ovaries (NHS, 2022). The imbalance that results tends to affect levels of

estrogen and progesterone, as well as LH and FSH. LH is a hormone produced in the female body which triggers ovulation. FSH refers to a hormone that recruits follicles and increases the number of LH receptors in the body. FSH and LH are responsible for regulating the production of estrogen and progesterone, which is required in order to have regular menstruation cycles (Sterling). The ideal ratio of LH to FSH in a healthy woman is 1:2. Many women with PCOS still have LH and FSH levels within 5-20 mIU/ml, with the normal range being 1.4-15.4 mIU/mL (University of Rochester Medical Center). However, their LH level is often 2-3 times that of the FSH level, leading to an elevated LH to FSH ratio equal to or higher than 2:1; this change in the LH to FSH ratio is enough to disrupt ovulation (Mikhael et al.). Ovarian theca cells are responsible for producing androgens, and signaling androgen receptors throughout the ovary. The imbalance in LH: FSH also causes a rapid increase in the number of ovarian theca cells, which in turn leads to hyperandrogenism (Ashraf et al). Hyperandrogenism manifests as excess hair growth on the face and neck (hirsutism) and acne, amongst other symptoms.

### **Further Complications**

PCOS can lead to many different health problems in the future if left untreated. Individuals with PCOS are far more likely to develop type 2 diabetes, high blood pressure, problems with the heart and blood vessels, and uterine cancer (Rasquin and Mayrin).

First, individuals with this condition usually have insulin resistance. Normally, pancreatic beta cells produce insulin in order to allow glucose to enter the cell. In insulin resistance, cells are not as responsive to insulin, and glucose cannot easily be taken from the blood to the cell for metabolism (National Institute of Diabetes and Digestive and Kidney Diseases, 2018). Due to the lack of glucose, patients tend to eat more, making the beta cells create insulin to accommodate the increase in blood sugar. Insulin resistance tends to get worse over time; these pancreatic beta cells eventually can die due to being constantly stimulated by high blood glucose. This then causes the pancreas to no longer produce enough insulin to overcome the cells' resistance. The result of this is higher blood glucose levels, ultimately leading to prediabetes and or type 2 diabetes (Rasquin and Mayrin).

Additionally, PCOS patients are more susceptible to developing cardiovascular disease, including hypertension and atherosclerosis. An increased level of androgens can elevate blood pressure; since patients with PCOS have excess androgen levels, they may have elevated blood pressure levels. PCOS patients also often have metabolic disturbances, such as obesity and insulin resistance. These metabolic complications in turn create an increased risk of atherosclerosis, which is a buildup of fats and cholesterol in the blood vessels of the body (Shuster et al.). This thereby significantly increases the risk of cardiovascular disease in patients with PCOS.

Lastly, another possible complication that may result from PCOS is malignancy. PCOS raises the chances of getting endometrial cancer due to the unregulated thickening of the uterine walls. In women with PCOS, irregular menstruation causes the endometrium to become thick and build up without regulation (Rasquin and Mayrin). This process is unregulated because the endometrium alters progesterone-regulated genes, leading to the endometrial lining proliferating without bounds (MacLean and Hayashi). This unregulated thickening of the uterine lining is known as endometrial hyperplasia, and it is a precancerous condition that may turn malignant and develop into endometrial cancer ("Endometrial Hyperplasia").

### **Treatment for PCOS**

While there is not a cure for Polycystic Ovary Syndrome, people can use hormonal birth control to help reduce their symptoms. Combination birth control pills that contain both estrogen and progesterone would help the body lower testosterone levels and raise estrogen, helping the hormonal imbalance in the individual (Planned Parenthood). Birth control works by inhibiting the release of gonadotropin-releasing hormone (GnRH). The GnRH hormone stops the secretion of LH and FSH, thereby inhibiting ovulation. The hormones that one receives from taking birth control can regulate menstruation, reduce excessive acne and hair growth, and even reduce the risk of endometrial cancer (“How Can Birth Control Treat PCOS?: Westmed Family Healthcare: Family Physicians”).

Another popular way of managing PCOS symptoms is through metformin. Metformin is a medicine used to treat type 2 diabetes. It is also used as a drug for individuals who are highly susceptible to develop diabetes. Metformin can be used to manage PCOS because, in addition to treating insulin resistance, it can restore ovulation by reducing androgen production, weight, and the risk of associated cardiovascular health complications - mainly diabetes and cardiovascular disease (Barbieri).

### **Infertility**

PCOS causes ovulation problems due to the hormonal imbalances of LH and FSH, and the most prominent problem is infertility. In general, female infertility can be defined as the failure to conceive after one year of unprotected sex. Infertility in women is caused by a variety of reasons, including anatomical complications, disorders of the ovaries, or disorders of the endocrine system (“Female Infertility”).

The hormonal imbalance associated with this condition leads to reduced levels of both estrogen and progesterone. Progesterone plays a crucial role in maintaining the endometrial lining in preparation for pregnancy. Without this process or a sufficient increase in progesterone levels following egg implantation, maintaining a pregnancy becomes challenging. Estrogen is responsible for the buildup of the uterine lining, while progesterone aids in the shedding of this lining. In individuals with PCOS, estrogen production occurs, but progesterone production is deficient. This thereby causes a thickened uterus lining, preventing spontaneous ovulation (MacLean and Hayashi).

### **Solutions for Infertility**

Although infertility is an extremely common side effect of PCOS, individuals with this hormonal disorder may still conceive a child in many different ways. One example of a hormonal solution to PCOS-driven infertility is medication to aid ovulation such as Clomiphene, Follistim, Gonal-F, or Bravelle. Clomiphene Citrate (CC) is a selective estrogen receptor modulator; it acts as a competitive inhibitor of estrogen receptors in the hypothalamus. Thus, the brain perceives a low level of estrogen, and it triggers the pituitary gland to secrete an increased amount of both FSH and LH. This in turn stimulates the growth of the ovarian follicle, and initiates ovulation. Follistim, Gonal-F, and Bravelle are artificial forms of the hormone FSH. These pills serve to increase FSH levels and re-balance the healthy ratio of LH to FSH (1:2) mentioned previously (Sawant and Bhide).

Apart from medication, there are other methods for infertile women to become pregnant. Laparoscopic Ovarian Drilling (LOD) applies heat or a laser to the ovaries with a laparoscope passed through a small cut below the umbilicus. The goal of this procedure is to disrupt the ovarian tissue and decrease the production of androgens in the woman’s body. This leads to



improved ovulation and menstrual regularity, along with a more favorable hormonal environment for fertility. This surgery improves the way that the ovaries produce as well as respond to hormones, thereby increasing the chances of ovulation. LOD is best recommended for patients with CC resistance—that is, if the patient fails to ovulate with 150 mg of CC for at least three cycles. However, this surgery is not very common due to the invasiveness of the procedure. The cost of the surgery can cost between \$2,000 to \$10,000, which is another reason why this procedure is not performed very often (Nayak et al.).

Lastly, the most popular method to achieve fertility is In-Vitro Fertilization (IVF). In this technique, the ovaries are stimulated to produce multiple egg-containing follicles. These eggs are retrieved from the uterus using surgery; they are then fertilized in a lab using a sperm sample. One or more healthy fertilized embryos are then transferred back into the woman's uterus. After a few weeks of the embryos being transferred, a pregnancy test is taken to confirm whether or not the procedure is successful. IVF is extremely common among individuals with PCOS in the US; in fact, 80.5% of women with PCOS end up using IVF to become pregnant (Liu et al.). The advantage of IVF is that it stimulates ovulation and creates conditions in which the ovulatory complications present in PCOS no longer pose a significant challenge to conception.

## Conclusion

Overall, PCOS is a condition characterized by hormonal imbalance, cysts on the ovaries, and irregular menstruation. The hormonal imbalance is a result of excess androgens, and it can cause symptoms of hyperandrogenism in women. It also leads to reduced levels of progesterone, which can cause fertility complications. Individuals with PCOS are also more likely to develop type 2 diabetes, cardiovascular complications, and endometrial cancer. Some ways of treating PCOS include oral contraceptives to balance hormones, and drugs like metformin to decrease insulin and androgen production. Infertility-specific medications, like clomiphene and follistim, stimulate the production of estrogen and FSH, which thereby increases fertility.

Despite the advances in the research and treatment of PCOS, there is still more work that needs to be done. Future research should focus on the genetic and environmental factors that may cause PCOS in women. Oftentimes, genetic correlation and external conditions work together to produce PCOS. Genetic predispositions may interact with environmental triggers to affect the onset and progression of this disorder. Studying the connection between genes and the environment can help pinpoint different causes and contributions to developing PCOS. In turn, this would create new ways to treat PCOS with specialized planning to target the specific phase or step of the syndrome. Scientists and researchers can then work to better alleviate symptoms and help individuals with PCOS manage their health. This can create more effective treatments and increase the quality of life of individuals with PCOS for the future.

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## References

Ashraf, Sairish, et al. "Hyperandrogenism in Polycystic Ovarian Syndrome and Role of CYP Gene Variants: A Review." *Egyptian Journal of Medical Human Genetics*, vol. 20, no. 1, 20 Nov. 2019, [jmhg.springeropen.com/articles/10.1186/s43042-019-0031-4](https://doi.org/10.1186/s43042-019-0031-4), <https://doi.org/10.1186/s43042-019-0031-4>.

Barbieri, Robert L. "Clomiphene Versus Metformin for Ovulation Induction in Polycystic Ovary Syndrome: The Winner Is ...." *The Journal of Clinical Endocrinology & Metabolism*, vol. 92, no. 9, Sept. 2007, pp. 3399–3401, [academic.oup.com/jcem/article/92/9/3399/2597358](https://doi.org/10.1210/jc.2007-1393), <https://doi.org/10.1210/jc.2007-1393>.

"Endometrial Hyperplasia." *Yale Medicine*, [www.yalemedicine.org/conditions/endometrial-hyperplasia#:~:text=Share-](http://www.yalemedicine.org/conditions/endometrial-hyperplasia#:~:text=Share-). (accessed on 2024-3-29)

"Female Infertility." *Pennmedicine.org*, 2023, [www.pennmedicine.org/for-patients-and-visitors/patient-information/conditions-treated-a-to-z/female-infertility#:~:text=Problems%20with%20ovulation%20are%20the](http://www.pennmedicine.org/for-patients-and-visitors/patient-information/conditions-treated-a-to-z/female-infertility#:~:text=Problems%20with%20ovulation%20are%20the). (accessed on 2024-4-12)

"How Can Birth Control Treat PCOS?: Westmed Family Healthcare: Family Physicians." *Www.westmedfamilyhealthcare.com*, [www.westmedfamilyhealthcare.com/blog/how-can-birth-control-treat-pcos](http://www.westmedfamilyhealthcare.com/blog/how-can-birth-control-treat-pcos). (accessed on 2024-3-29)

Knight, P. G., & Glistler, C. (2019). Theca cells and the regulation of ovarian androgen production. *Bioscientifica Proceedings*. <https://doi.org/10.1530/biosciprocs.8.021> (accessed on 2024-8-5)

Liu, Su , et al. "Pregnancy Outcomes of Women with Polycystic Ovary Syndrome for The First in Vitro Fertilization Treatment: A Retrospective Cohort Study with 7678 Patients." *Frontiers in Endocrinology*, vol. 11, 24 Sept. 2020, <https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2020.575337/full>.

MacLean, James A., and Kanako Hayashi. "Progesterone Actions and Resistance in Gynecological Disorders." *Cells*, vol. 11, no. 4, 1 Jan. 2022, p. 647, [www.mdpi.com/2073-4409/11/4/647](https://doi.org/10.3390/cells11040647), <https://doi.org/10.3390/cells11040647>.

Mikhael, Sasha, et al. "Hypothalamic-Pituitary-Ovarian Axis Disorders Impacting Female Fertility." *Biomedicines*, vol. 7, no. 1, 4 Jan. 2019, p. 5, <https://doi.org/10.3390/biomedicines7010005>.

National Institute of Diabetes and Digestive and Kidney Diseases. *Insulin Resistance & Prediabetes* | NIDDK. National Institute of Diabetes and Digestive and Kidney Diseases. <https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/prediabetes-insulin-resistance#:~:text=the%20normal%20range.-> (accessed on 2024-5-1)

NHS. *Polycystic Ovary Syndrome*. NHS.

<https://www.nhs.uk/conditions/polycystic-ovary-syndrome-pcos/> (accessed on 2024-2-1)

Planned Parenthood. "Birth Control Pill." *Planned Parenthood*, 2000,

[www.plannedparenthood.org/learn/birth-control/birth-control-pill](http://www.plannedparenthood.org/learn/birth-control/birth-control-pill). (accessed on 2024-3-29)

Rasquin, Lorena, and Jane V Mayrin. "Polycystic Ovarian Disease (Stein-Leventhal Syndrome)." *Nih.gov*, StatPearls Publishing, 2022, [www.ncbi.nlm.nih.gov/books/NBK459251/](http://www.ncbi.nlm.nih.gov/books/NBK459251/).

Sawant, Shital, and Priya Bhide. "Fertility Treatment Options for Women with Polycystic Ovary Syndrome." *Clinical Medicine Insights: Reproductive Health*, vol. 13, Jan. 2019, p. 117955811989086, [www.ncbi.nlm.nih.gov/pmc/articles/PMC6935873/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6935873/), <https://doi.org/10.1177/1179558119890867>.

Shuster, A, et al. "The Clinical Importance of Visceral Adiposity: A Critical Review of Methods for Visceral Adipose Tissue Analysis." *The British Journal of Radiology*, vol. 85, no. 1009, Jan. 2012, pp. 1–10, [www.ncbi.nlm.nih.gov/pmc/articles/PMC3473928/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3473928/), <https://doi.org/10.1259/bjr/38447238>.

Sterling, E. "Hormone Levels and PCOS." *Contemporary OB/GYN*, 2011, [www.contemporaryobgyn.net/view/hormone-levels-and-pcos](http://www.contemporaryobgyn.net/view/hormone-levels-and-pcos). (accessed 2023-12-4)