

# Ovulation Induction In Polycystic Ovary Syndrome

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## Abstract

**Background** Infertility is often caused by ovulation disorders, among which polycystic ovarian syndrome (PCOS) is clearly the most frequent. Based on the phenotype, ethnicity, and categorization system employed, the incidence of PCOS in the general population ranges from 5% to 15%. **Summary** Elevated concentrations of androgen, inconsistent menstruation, and/or little cysts on one or both ovaries are all symptoms of PCOS, a complex condition. Therefore, the goal of conventional therapies for PCOS-linked anovulatory infertility is to shift the equilibrium of intraovarian steroid production away from an elevated androgen synthesis caused by LH-insulin-leptin that results in follicular atresia and toward an FSH-driven final advancement of a dominant follicle. There are several therapy possibilities.

**Keywords:** Ovulation, Induction, Polycystic Ovary Syndrome

## INTRODUCTION

Enhanced androgen concentrations, inconsistent menstruation, and/or little cysts on one or both ovaries are symptoms of the complex condition called polycystic ovarian syndrome (PCOS). (1).

A physical or predominantly biochemical symptom of the condition is polycystic ovary (hyperandrogenemia). Hyperandrogenism, a clinical trait of PCOS, has the potential to cause anovulation, microcysts in the ovary, follicular growth retardation, and irregular menstruation. (2).

As per investigations, PCOS is the most common endocrine disorder among American women of fertility age, affecting 5% to 10% of females within the ages of 18 and 44. Women who seek treatment for obesity, amenorrhea, acne, excessive hair growth, and infertility are often found to have PCOS. Women with PCOS have higher rates of endometrial cancer, dyslipidemia, cardiovascular diseases, and type 2 diabetes (T2DM). (3).

The majority of scientific associations and health authorities today recognize the Rotterdam definition as the most prevalent PCOS categorization. (4).

According to the definition, PCOS may be identified in any woman who exhibits at least two of the following three symptoms: Ovulatory malfunction, clinical and/or biochemical hyperandrogenism, and PCOM (5).

The National Institute of Child Health and Human Development also maintains an earlier definition that excludes ovarian morphology in favor of requiring the existence of both hyperandrogenism and ovulatory disruption. (6).

According to the NIH 2012 workshop report, the number of reproductive-aged females in the United States who have PCOS is calculated to be around 5 million. The cost of detecting and treating PCOS for the healthcare system is approximately \$4 billion annually, not counting the cost of severe comorbidities related to PCOS. (7).

Infertility, DM-2, metabolic syndrome, OSA, obesity, poor glucose tolerance, cardiovascular consequences, depression, endometrial cancer, and NAFLD/NASH are only a few of the disorders linked to PCOS. Additionally, studies have revealed that Mexican Americans are more likely to experience it than non-Hispanic whites and African Americans. (8)

Obesity increases the severity of these disorders. Peripheral insulin resistance and hyperinsulinemia are also connected to PCOS. Increased insulin concentrations may have gonadotropin-enhancing impacts on ovarian functions and may be a secondary cause of insulin resistance in PCOS due to postbinding defects in insulin receptor signal transduction. (9).

Additionally, hyperinsulinemia may prevent the liver from producing sex hormone-binding globulin (SHBG), which might enhance androgenicity. (9).

The genetic contributions to PCOS, a genetically diverse condition, are still not well understood. The outcomes of published candidate gene investigations on PCOS have been dismal, and several published genetics research in this area have been underpowered. (10).

According to research, a first-degree relative with a history of type 2 diabetes is linked to an elevated risk of metabolic abnormalities, impaired glucose tolerance, and T2DM in a large group of PCOS-positive women. (11).

## **Pathophysiology**

The pathophysiology of PCOS involves fundamental anomalies in the hypothalamic-pituitary axis, insulin discharge and activation, and ovarian performance. (12).

Although the exact etiology is unclear, overweight and insulin resistance have been linked to PCOS. The connection with insulin functioning is to be expected given that too much insulin triggers the release of androgens from the ovaries, which may prevent ovulation. Ovarian function is regulated by insulin. Follicular maturity arrest is usually a sign of an ovarian irregularity. (12).

Teenage girls who are approaching puberty and have a genetic history of PCOS are prone to the disorder, according to many studies. Elevated concentrations of prolactin were seen in 25% of PCOS patients. (13).

Further testing for suspected PCOS has two objectives: to rule out other disorders that may be treated that resemble PCOS, and to identify and address long-term metabolic problems. It is prudent to hold off on checking for PCOS in teenagers until they have been oligomenorrheic for minimum two years since anovulation is often seen following menarche. (14).

## **Treatment**

### **Non pharmacological Techniques**

The symptoms of PCOS are treated since the underlying cause is unclear. Despite the existence of symptoms, the patient may choose not to get therapy because she wants to become pregnant despite the fact that few treatment options address all features of the illness. (15). Correcting anovulation, preventing androgens from acting on specific tissues, and lowering insulin resistance should all be treatment objectives. (15).

For PCOS individuals who are obese, losing weight has several advantages. Reduced insulin, testosterone, and luteinizing hormone (LH) levels are benefits of weight reduction. Additionally, by assisting with ovulation control, it increases the likelihood of becoming pregnant. (16).

Multiple holes are made in the ovarian surface and stroma during laparoscopic ovarian drilling (LOD), an outpatient surgical procedure. (17). This treatment is believed to damage androgen-producing tissue, which should result in lower levels of androgen. Without raising the likelihood of multiple pregnancies, it has been demonstrated to be just as successful as medical procedures. (17).

### **Pharmacological Techniques**

#### **Antiandrogens**

Antiandrogens include flutamide (Schering/Merck, Eulexin), spironolactone (Pfizer, Aldactone), and finasteride (Merck, Propecia) reduce androgen levels in PCOS, which lessens the symptoms of hirsutism and acne. These antiandrogens could also lower people with PCOS's increased cholesterol levels. (18).

The most widely used antiandrogen is spironolactone, which may be taken in doses ranging from 25 to 100 mg twice a day due to its safety, availability, and affordability. Contraception is advised for PCOS patients utilizing antiandrogens due to the elevated risk of teratogenicity (opposing genital development) to male fetuses. (19).

#### **Oral contraceptives**

If a woman has PCOS but doesn't want to become pregnant, she may want to think about oral contraception (OCs). OCs mainly control menstrual cycles as its mode of action in the therapy of PCOS. Acne, androgen, and hirsutism are also decreased by these medications. The main OCs used to treat PCOS-related hirsutism and acne are estrogen and progestin combos. (20).

#### **Other Therapies**

##### **Medroxyprogesterone acetate**

Medroxyprogesterone acetate (MPA) may be utilized to medicate amenorrhea or malfunctioning uterine hemorrhage in PCOS patients who do not want to become pregnant and are not at risk for conception. The recommended dose range for MPA is five to ten mg/day for ten to fourteen days per month. Although ovarian androgen production is not suppressed by monthly progestin medication, it prevents aberrant endometrial growth. (21). In PCOS individuals, MPA may potentially enhance lipid profiles and insulin sensitivity. (22).

## Statins

Due to their capacity to lower testosterone concentrations as well as total cholesterol, triglycerides, and low-density lipoprotein-cholesterol (LDL-C), statins are assumed to have a position in the management of PCOS. (23). Simvastatin (Zocor, Merck) and metformin both decreased total testosterone values in women with PCOS, with reductions of 17.1% and 13.6%, respectively. (24).

## Induction of Ovulation in PCO

Up to 25 percent of all instances of infertility are due to anovulatory failure. The most typical kind of anovulatory infertility is normogonadotropic anovulation, which is categorized as World Health Organization (WHO) group II. The most prevalent condition in this category, as well as the most prevalent endocrine problem and anovulation-causing factor, is PCOS. (25).

Women with PCOS often exhibit chronic oligo/anovulation and hyperandrogenism, both of which have an adverse impact on fertility. In many groups where reproduction is highly valued as a form of survival, the drive to reproduce is quite strong. (26).

The inducement of ovulation is essential to the treatment of women with PCOS-related infertility. CC, LOD, gonadotropins, and assisted reproduction technology are available treatments for PCOS-related infertility in females. (25).

## Weight loss and ovulation stimulation

The investigations did find increased total testosterone, fasting insulin, androgen index, fasting blood glucose, hirsute, and worsened lipid profiles in the obese women, despite systematic reviews not finding research showing that ovulation and other diagnostic reproductive findings improved with weight loss in women with PCOS. Because of this, research has not shown that women may resume spontaneous ovulation with diet, exercise, or other lifestyle modifications. (27).

According to American organizations researching PCOS, losing weight is the main treatment for the condition. that a 5- to 10-percent drop in body weight might normalize menstruation and enhance a patient's responsiveness to ovulation induction and fertility drugs (26).

Since lifestyle changes have increased the rates of spontaneous ovulation and natural conception, they are advised in many nations. (28).

The disadvantages of this course of treatment include the fact that these women lack the drive to stick with their diet and exercise regimens, may not be capable of losing enough pounds to trigger natural ovulation, and frequently require the addition of pharmacological agents to facilitate ovulation. (28).

In a USA research, women with PCOS who combined lifestyle changes with weight reduction before pharmacologic ovulation inducing medications saw better ovulation and live birth rates and needed lower dosages of the drugs to induce ovulation. (29).

## Medical Methods to Induce Ovulation

### Clomiphene Citrate (Clomid, Serophene)

Selected estrogen receptor modulator (SERM) clomiphene citrate (CC) is still the go-to medication for anovulatory PCOS women who want to induce ovulation. (30).

En- and zu-clomiphene stereoisomers make up the racemic combination known as CC, both of which are considered to be involved in the antagonistic effects on the estrogen receptor. (31). The more powerful isomer of clomiphene, called en-clomiphene, is what causes ovulation. En-clomiphene has a short half-life, therefore after therapy, blood concentrations increase and decrease rapidly. (31).

After a single 50 mg dosage of CC, zu-clomiphene exhibits prolonged plasma and tissue retention with quantifiable plasma levels for minimum a month. (31).

With each treatment start strategy, ovulation, conception levels, and birth outcomes are comparable. The suggested maximum dosage for CC by the ACOG and ESHRE/ASRM Committee is 150 mg/day, which may be gradually raised up to 50 mg/day until ovulation has place. The US FDA advises against taking more over 100 mg/day of CC. (32).

An additional method of treatment is necessary for the 20 to 25% of women who are CC resistant (remain anovulatory while taking the highest recommended doses of CC). (33). Some suggest utilizing a step-up strategy, which involves administering CC at a larger dosage a second time without breaking the stimulation schedule, in cases when patients are resistant to the drug. (28).

Even though up to 85percent of females ovulate while using CC, only 30 to 40% of females who use CC for six cycles will get pregnant. The chance of therapeutic success has been correlated with the level of obesity, the severity of hyperandrogenemia, the presence of hirsutism, and the age of patients. (33).

The strictness of cycle monitoring or the ovulatory stimulation have not been found to have an effect on the success of CC cycles (Administration of exogenous hCG vs an increase in endogenous LH). While endometrial thickness information and indications of a mono follicular response from ultrasound monitoring of ovarian responses are not

essential to forecast the cycle's success, they may be especially important for certain individuals. (34). Human chorionic gonadotropin (hCG) ovulatory trigger dosage augmentation has not been demonstrated to increase pregnancy, miscarriage, or ovulation rates associated with CC. However, an ovulatory trigger for a specific patient enables prompt scheduling of adjunct treatments like intrauterine fertilization, and the predictability and timeliness of following occurrences may lessen stress therapies for others. (34).

### **Aromatase Inhibitors**

In place of CC treatment, aromatase inhibitors (AI) have been suggested as an alternate method of ovulation induction. The highest concentrations of aromatase, a part of the cytochrome P450 enzyme group, are found in the ovary's granulosa cells of premenopausal women, as well as other places such as adipose tissue, the brain, and skin fibroblasts. (35).

An abstract given in 2005 indicated a rise in fetus cardiac and bone anomalies with letrozole treatment in premenopausal women; an early study had raised concerns about AI related teratogenicity. (36). But later, bigger studies failed to find a connect between exposure to AI and the likelihood of congenital malformations. (36).

### **Gonadotropin Therapy**

When CC fails to produce a pregnancy (A daily dose of 150 mg of CC or 4-6 ovulation cycles without a pregnancy had not been associated with any sensitivity), gonadotropin therapy is frequently utilized as the second line strategy of ovulation initiation in anovulatory women with PCOS. Small antral follicles in polycystic ovaries are twice as many or even more than in a normal ovary, and they are all responsive to FSH stimulation. (37).

### **GnRH Agonists**

GnRH agonists have an unquestioned role in IVF therapeutic regimens due to their capacity to reduce LH levels both before and during ovarian stimulation. They have the benefit of almost eliminating the bothersome incidence of early luteinization. (38).

Medication with GnRH agonist seemed to boost the PCO follicles' sensitivity to gonadotrophin stimulating after the threshold FSH dosage had been achieved, but it did not completely eradicate the inter- or intraindividual variation of the FSH dosage necessary to promote continued follicular growth. (39).

### **Gonadotrophin-Releasing Hormone Antagonists**

Because gonadotrophin release hormone antagonists work via a mode of competitive binding, which enables dosage modification to control the degree of hormonal suppression, they have a number of potential benefits over those hormones. Additionally, antagonists stop gonadotrophin secretion within a few hours, do not cause a flare-up, and gonadal functions returns without a lag when they are stopped.

One experiment using FSH recombinant and a GnRH inhibitor, exclusively for PCOS-affected women, has been reported to far. On the 2<sup>nd</sup> day of the cycle, a GnRH antagonist was begun in 20 individuals after pretreatment with OCs. (40).

### **Metformin**

The US FDA has authorized the biguanide metformin for usage as an oral antihyperglycemic medication to treat T2DM. (41).

Additionally, it prevents ovarian gluconeogenesis, perhaps by a direct impact, which lowers the generation of ovarian androgen. (41).

Metformin dramatically enhanced ovulation and pregnancy rates with CC medication in a randomized, controlled study on clomiphene resistant, infertile individuals with PCOS who were treated with metformin instead of a placebo. (38).

### **Tamoxifen**

Recently, the fertility aid tamoxifen (Tx), an antiestrogenic chemical with structural similarities to CC, has been studied. Ovulation rates were observed as 50–90% and gestation as 30–50% in the little literature on the usage of Tx for ovulation induction. (42).

A meta-analysis found that CC and Tx both work well for ovulation induction. (43).

Tx was quite successful in anovulatory women who were unable to ovulate or get pregnant with CC. In instances of clomiphene failure, the rates of ovulation and gestation were 61.8% and 28.5%, respectively. There were only single pregnancies, and none of them resulted in hyperstimulation or any other negative effects. (29).

Since its debut in 1956, CC has been the standard procedure for ovulation stimulation in couples with anovulatory infertility. When taking CC, around 80% of women ovulate; however, only 40% of women will get pregnant. The antiestrogenic impacts of CC on the uterus, cervix, and vagina have been theorized to be the cause of this discrepancy's thin endometrial lining and poor cervical mucus. (44).

## **References**

1. Umland EM, Weinstein, LC, Buchanan EM. Pharmacotherapy: A Pathophysiologic Approach, 2011.

2. **Lin, L. H., Baracat, M. C., Maciel, G. A., Soares, J. M., Jr, Baracat, E. C.** Androgen receptor gene polymorphism and polycystic ovary syndrome. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*, **2013**; 120(2), 115–118.
3. **McFarland C.** Treating polycystic ovary syndrome and infertility. *MCN. The American journal of maternal child nursing*, **2012**; 37(2), 116–121.
4. **Bani Mohammad, M., Majdi Seghinsara, A.** Polycystic Ovary Syndrome (PCOS), Diagnostic Criteria, and AMH. *Asian Pacific journal of cancer prevention: APJCP*, **2017**; 18(1), 17–21.
5. **Rosenfield, R. L., & Ehrmann, D. A.** The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. *Endocrine reviews*, **2016**; 37(5), 467-520.
6. **Escobar-Morreale, H. F.** Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. *Nature Reviews Endocrinology*, **2018**; 14(5), 270.
7. **Liu, J., Wu, Q., Hao, Y., Jiao, M., Wang, X., Jiang, S., et al.** measuring the global disease burden of polycystic ovary syndrome in 194 countries: Global Burden of Disease Study 2017. *Human Reproduction*, **2021**; 36(4), 1108-1119.
8. **Rasquin Leon LL, Mayrin JV.** Polycystic Ovarian Disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, **2021**; - . Available from: <https://www.ncbi.nlm.nih.gov/books/NBK459251/>
9. **Genazzani, A.** Expert's opinion: Integrative treatment with inositols and lipoic acid for insulin resistance of PCOS. *Gynecol. Reprod. Endocrinol. Metab*, **2020**; 1: 146-157.
10. **Galhardo, M. S.** Integrated analysis of transcript-level regulation of human adipogenesis and cell type-selective disease association of high regulatory load genes (Doctoral dissertation, University of Luxembourg, Luxembourg, Luxembourg), **2015**.
11. **Chang, R. J., & Dumesic, D. A. (2019).** Polycystic ovary syndrome and hyperandrogenic states. In Yen and Jaffe's reproductive endocrinology (pp. 520-555).
12. **H Ortega, H., U Díaz, P., R Salvetti, N., J Hein, G., E Marelli, B., M Rodríguez, F., et al.** Follicular cysts: A single sign and different diseases. A view from comparative medicine. *Current pharmaceutical design*, **2016**; 22(36), 5634-5645.
13. **Ndefo, U. A., Eaton A., Green, M. R.** Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. *P & T : a peer-reviewed journal for formulary management*, **2013**; 38(6), 336-355.
14. **Papadakis, G. E., Xu, C., Pitteloud, N.** Hypothalamic Disorders during Ovulation, Pregnancy, and Lactation. In *Maternal-Fetal and Neonatal Endocrinology*, **2020**; 217-240.
15. **Lee TT, Rausch ME.** Polycystic ovarian syndrome: Role of imaging in diagnosis. *Radiographics*. 2012; 32(6):1643–1657.
16. **Terry NL, Ryan ME.** Polycystic Ovary Syndrome (PCOS) 2012. Bethesda, Md: National Institutes of Health Library; 2012. Accessed March 27, 2013.
17. **Farquhar C, Brown J, Marjoribanks J.** Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2012 Jun; (online)
18. **Studen KB, Sebestjen M, Pfeifer M.** Influence of spironolactone treatment on endothelial function in non-obese women with polycystic ovary syndrome. *Eur J Endocrinol*. 2011; 164(3):389–395.
19. **Nair S.** Hirsutism and acne in polycystic ovary syndrome. In: Merchant R, Allahbadia GN, Agrawal R, editors. *Polycystic Ovary Syndrome*. Kent, U.K.: Anshan Ltd.; 2009. pp. 183–184.
20. **Tredway D, Schertz JC, Bock D.** Anastrozole vs. clomiphene citrate in infertile women with ovulatory dysfunction: A phase II, randomized, dose-finding study. *Fertil Steril*. 2011;95(5):1720–1724.
21. **Haydardedeoglu B, Simsek E, Kilicdag EB.** Metabolic and endocrine effects of metformin and metformin plus cyclic medroxyprogesterone acetate in women with polycystic ovary syndrome. *Int J Gynaecol Obstet*. 2009;105(1):32–35.
22. **Ozdemir S, Gorkemli H, Gezginc K.** Clinical and metabolic effects of medroxyprogesterone acetate and ethinyl estradiol plus drospirenone in women with polycystic ovary syndrome. *Int J Gynaecol Obstet*. 2008;103(1):44–49.
23. **Gao L, Zhao FL, Li SC.** Statin is a reasonable treatment option for patients with polycystic ovary syndrome: A meta-analysis of randomized controlled trials. *Exp Clin Endocrinol Diabetes*. 2012; 120(6):357–375.
24. **Banaszewska B, Pawelczyk L, Spaczynski RZ.** Comparison of simvastatin and metformin in treatment of polycystic ovary syndrome: Prospective randomized trial. *J Clin Endocrinol Metab*. 2009; 94:4938–4945.
25. **Sirmans SM, Pate KA.** Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clinical Epidemiology*. 2014;6:1-13. DOI: 10.2147/CLEP.S37559
26. **Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, Carmine E, et al.** American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society Disease State clinical review: Guide to the best practices in the evaluation and treatment of polycystic ovary syndrome – Part 1. *Endocrine Practice*. 2015;21(11):1291-1300.
27. **Moran LJ, Hutchison SK, Norman RJ, Teede HJ.** Lifestyle changes in women polycystic ovarian syndrome. *Cochrane Database of Systematic Reviews*. 2011 Feb 16;(2):CD007506. DOI: 10.1002/14651858
28. **Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al.** Clomiphene, metformin, or both for infertility in polycystic ovary syndrome. *N Engl J Med*. 2015; 356: 551–66.
29. **Legro RS, Dodson WC, Kunselman AR.** Benefit of delayed fertility therapy with preconception weight loss over immediate therapy in obese women with PCOS. *The Journal of Clinical Endocrinology and Metabolism*. 2016;101:2658-2666. DOI: 10.1210/jc.2016-1659
30. **Speroff L, Fritz MA.** Induction of Ovulation. In: Speroff L, Fritz MA, editors. *Clinical gynecologic endocrinology and infertility*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011. p. 145–85.
31. **Casper RF, Mitwally MFM.** A historical perspective of aromatase inhibitors for ovulation induction. *Fertil Steril*. 2012; 98(6):1352–5.
32. **Torrealday S, Pasquale P.** "Managing PCOS-related infertility: ovulation induction, in vitro fertilization, and in vitro maturation." *Polycystic Ovary Syndrome*. Springer, New York, NY, 2014. 205-221.
33. **Costello MF, Misso ML, Wong J, Hart R, Rombauts L, Melder A, et al.** The treatment of infertility in polycystic ovary syndrome: a brief update. *Aust N Z J Obstet Gynaecol*. 2012; 52:400–3.
34. **Emperaire, Jean-Claude.** "Ovulation Stimulation with Gonadotropins, 2015."
35. **Pavone ME, Bulun SE.** The use of Aromatase Inhibitors for ovulation induction and superovulation. *J Clin Endocrinol Metab*. 2013;98(5):1838–44.
36. **He D, Jiang F.** Meta-analysis of letrozole versus clomiphene citrate in polycystic ovary syndrome. *Reprod Biomed Online*. 2011; 23:91–6.
37. **Badawy A, Elnashar A.** Treatment options for polycystic ovary syndrome. *International Journal of Women's Health*. 2011; 3:25.
38. **Qiao, Jie, Yan Yang, and Rong Li.** "Polycystic ovary syndrome: Fertility management." *Current Obstetrics and Gynecology Reports* 1.4 (2012): 159-165.
39. **Raju, G, Achyuta R.** "Luteinizing hormone and follicle stimulating hormone synergy: A review of role in controlled ovarian hyperstimulation." *Journal of human reproductive sciences* 6.4 (2013): 227.

40. **Homburg R.** "Ovulation induction for women with polycystic ovary syndrome." U: Polycystic Ovary Syndrome. Kovacs G, Norman R, urednici, Cambridge (2010): 140-158.
41. **Torres W.** "Anti-Aging Effect of Metformin: A Molecular and Therapeutical Perspective." *Current Pharmaceutical Design* 26.35 (2020): 4496-4508.
42. **Dhaliwal LK, Suri V, Gupta KR, Sahdev S.** Tamoxifen: An alternative to clomiphene in women with polycystic ovary syndrome. *Journal of human reproductive sciences*, **2011**;4(2):76
43. **Kahyaolu S, Bülent Y, Ahmet Z.** "Pharmacokinetic, pharmacodynamic, and clinical aspects of ovulation induction agents: A review of the literature." *Journal of the Turkish German Gynecological Association* 18.1 (2017): 48.
44. **Steiner A. Z., Terplan, M., Paulson, R. J.** Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis. *Human reproduction*, **2005**; 20(6), 1511-1515.