# Patient Criteria for Successful Induction of Ovulation by Clomiphene Citrate in Patients with Polycystic Ovary Syndrome

**Thesis**

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# Abstract

Polycystic ovary syndrome is one of the most common endocrine disorders in women of reproductive age and metabolic disorder in which patients will benefit for early recognition and treatment., The prevalence of PCOS varies between 5% and 10% of all women. Polycystic ovary syndrome is clinically characterized by chronic anovulation, menstrual irregularities, infertility and obesity in combination with some evidence of androgen excess such as hirsutism, acne and increased serum androgen concentrations **.**

The fundamental pathophysiologic defect still remains unknown. PCOS appears to be a heterogeneous disorder in which ovarian, and possibly adrenal androgen excess is present along with varying degrees of gonadotropic and metabolic abnormalities**.**Additionally insulin resistance, hyperinsulinism, type II Diabetes Mellitus, endometrial carcinoma, dyslipidemia and psychosocial dysfunction are presented as other clinical consequences associated with PCOS **.**



**Key Words :**

Polycystic ovary syndrome - Luteinizing hormone - C- reactive protein.

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**Kamel Abd El-Azeem Shaltout**

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| PCOS | Polycystic ovary syndrome. |
| CC | Clomiphene citrate. |
| NICH | National institute of child health and human development. |
| ESHRE | European society of human reproduction and embryology. |
| ASRM | American society for reproductive medicine. |
| LHTIC | Luteinizing hormone theca interstitial cell. |
| LH | Luteinizing hormone. |
| TIC | Theca interstitial cell. |
| FSH-GC | Follicular stimulating hormone granulosa cell. |
| FSH | Follicular stimulating hormone. |
| IGF | Insulin like growth factor. |
| GnRH | Gonadotropins releasing hormone. |
| SHBG | Sex hormone binding globulin. |
| OCP | Oral contraceptive pills. |
| 17-B-HSD | 17 β hydroxysteroid dehydrogenase. |
| SCC | Side chain cleavage enzyme. |
| STAR | Steroidogenic acute regulatory protein. |
| 3B-HSD | 3 β hydroxysteroid dehydrogenase. |
| HPCO | Hyperandrogenism and polycystic ovary. |
| HCA | Hyperandrogenism and chronic anovulation. |
| PCO-CA | Polycystic ovary and chronic anovulation. |
| HCA-PCO | Hyperandrogenism chronic anovulation and polycystic ovary. |
| B.M.I | Body mass index. |
| AIDS | Aquired immune deficiency syndrome. |
| F.D.A | Food and drug administration. |
| T.S.H. | Thyroid stimulating hormone. |
| O.H.S.S. | Ovarian hyperstimulation syndrome. |
| F.A.I | Free androgen index. |
| DHEAS | Dehyrdoepiandrosterone sulfate. |
| GDM | Gestational diabetes mellitus. |
| CRP | C- reactive protein. |
| HDL | High density lipoprotein. |

# Introduction

**Polycystic ovary syndrome (PCOS)** is a medical condition in which women experience irregular or absent menstrual bleeding, increased hair growth, infertility, and excessive weight gain. This syndrome was first described in 1935 by Drs. Stein and Leventhal, and for many years PCOS was known as the Stein-Leventhal Syndrome. Women wth PCO have enlarged ovaries containing multiple small cysts which have led to the descriptive term, polycystic ovaries.(Reproductive Science Center of San Francisco Bay Area).

Early administration of Clomiphen Citrat( CC ) in patients with PCOS will lead to more follicular growth and endometrial thickness, which might result in a higher pregnancy rate (PR)**.(Badawy et al.,2009).**

Treatment with CC is associated with higher rates of pregnancy if started early (days 1 to 5) in the menstrual cycle**.(Dehbashi et al.,2006).**

The extended clomiphene citrate regimen resulted in modest ovulation and pregnancy rates with no side effects. This therapy seems to offer economic, efficacy and safety advantages and it is worth undergoing before starting more expensive or sophisticated alternatives. **(Badawy et al.,2008)**

Clomiphene citrate should be the first-line treatment for ovulation induction in anovulatory patients with PCOS**.( Mohd Zain et al .,2009).**

The ovulatory rate and the pregnancy rate with the metformin-CC combination was found to be higher when compared with CC alone. Metformin increased the ovulatory rate in CC failures, also implying increased sensitivity to CC**.(Dasari et al.,2009)**

# Aim Of Work

The aim of our work is To Identify the Patient Criteria For Successful Induction of Ovulation by Clomiphene Citrate In patients suffering from polycystic ovary syndrome .

# Polycystic ovarian syndrome (PCOS)

Polycystic ovary syndrome is a clinical diagnosis characterized by the presence of two or more of the following features: chronic oligo-ovulation or anovulation, androgen excess and polycystic ovaries. It affects 5 to 10% of women of childbearing age and is the most common cause of anovulatory infertility in developed countries. Common clinical manifestations include menstrual irregularities and signs of androgen excess such as hirsutism, acne, and alopecia ***(Nestler, 2008).***

Polycystic ovary syndrome is a heterogeneous clinical syndrome, which has been defined as the association of hyperandrogenism with chronic anovulation in women without specific adrenal and pituitary gland disease. A family history of polycystic ovary syndrome may be present in a subset of patients; however, the genetic basis of the syndrome remains unclear. Most often, the age of onset is perimenarchal and it is characterized by the appearance of menstrual disturbances, hirsutism, acne, and more rarely, a male pattern of alopecia. Polycystic ovary syndrome is also associated with metabolic disturbances, such as obesity and insulin resistance with hyperinsulinemia ***(Pelusi and Pasquali, 2003).***

**Definition:**

PCOS is one of the most common endocrine disorders in women of reproductive age and it is the most common cause of androgen excess in women and girls. Difficulties in the diagnosis of PCOS and controversies in definition arise from the heterogeneous nature of the disorder. Even in the classic 1935 report by Stein and Leventhal describing PCOS in adult women as a syndrome consisting of amenorrhea, hirsutism, and polycystic ovaries **(Brien et al., 2008).**

There is no consensus on the diagnostic criteria and definitions of PCOS. Until recently, two definitions were followed: one is the National

Institute of Child Health and Human Development (NICHD) conference Human Reproduction and Embryology (ESHRE) /American Society for Reproductive Medicine (ASRM). The third definition has been proposed recently by the Androgen Excess Society, which takes into account both the criteria existent till date. The three definitions are summarized in table (1) ***(Dasgupta and Reddy, 2008).***

Difficulties in the diagnosis of PCOS and controversies in definition arise from the heterogenous nature of the disorder ***(Franks, 2006).*** Even in the classic 1935 report by Stein and Leventhal describing their case series of seven women with amenorrhea associated with bilateral polycystic ovaries treated with wedge resection of the ovaries, only three of these women were obese, only four were hirsute (one obese), and one had acne ***(O'Brien and Emans, 2008).***

**Table (1):** Diagnostic criteria for PCOS according to different published definitions

| Definition/year (Ref.) | Diagnostic criteria | Possible phenotypes | Exclusion criteria | Clinical hyperandrogenism | Biochemical hyperandrogenism | PCOM (PCOS) |
|---|---|---|---|---|---|---|
| NICHD/1990 (1 ) | Requires the simultaneous presence of<br>1) clinical and/or biochemical hyperandrogenism and<br>2) menstrual dysfunction | Clinical and/or biochemical hyperandrogenism plus menstrual dysfunction | Congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, and hyperprolactinemia | Hirsutism, alopecia, and acne | 1) Total testosterone, 2) free testosterone, 3) androstenedione, and 4) DHEAS | Not included |
| Rotterdam/2003 (2) | Requires the presence of at least two criteria:<br>1) clinical and/or biochemical hyper-androgenism,<br>2) ovulatory dysfunction, and<br>3) PCOM | 1) Clinical and/or biochemical hyperandrogenism plus ovulatory dysfunction;<br>2) clinical and/or biochemical hyperandrogenism plus ovulatory dysfunction plus PCOM;<br>3) clinical and/or biochemical hyperandrogenism plus PCOM;<br>4) PCOM plus ovulatory dysfunction | Congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing's syndrome | Hirsutism, acne, and androgenic alopecia? | 1) Free androgen index or free testosterone,<br>2) total testosterone, and<br>3) DHEAS | At least one ovary showing either:<br>1) 12 or more follicles (2–9 mm in diameter) or<br>2) ovarian volume > 10 ml |
| AAES/2006 (3) | Requires the presence of hyperandrogenism, clinical or biochemical, and either<br>1) oligo-anovulation or<br>2) PCOM | 1) Clinical and/or biochemical hyperandrogenism plus oligo-anovulation;<br>2) clinical and/or biochemical hyperandrogenism plus oligo-anovulation plus PCOM;<br>3) clinical and/or biochemical hyperandrogenism plus PCOM | Congenital adrenal hyperplasia, androgen-secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing's syndrome, syndromes of severe insulin resistance, thyroid dysfunction, and hyperprolactinemia | Hirsutism | 1) Free androgen index or free testosterone,<br>2) total testosterone,<br>3) DHEAS, and<br>4) androstenesdione | At least one ovary showing either<br>1) 12 or more follicles (2–9 mm in diameter) or<br>2) ovarian volume > 10 ml |

**PCOM:** Polycystic ovarian morphology

***(Ethelcodner and Hector, 2007)***

**Prevalence**:

The prevalence of PCOS cannot be determined with precision because it depends on the definition: A strict research-based definition that relies on endocrine characteristics is associated with a 3% prevalence of PCOS ***(Guzick, 1998)*** and for the clinical definition using chronic anovulation plus androgen excess, the prevalence of PCOS is 5-10% of premenopausal females ***(Slowey, 2001).***

PCOS represents most oligoamenorrheic women (90%), most hirsute women (80%), and nearly one third of amenorrheic women ***(Stankiewicz and Norman, 2006).***

The prevalence of PCOS is increased significantly with the irregularity of the menstrual cycle pattern, finding PCOS in 9% of the women with regular menstrual cycles, 28% of the women with irregular menstrual cycles, and' 45% of oligoamenorrheic women ***(Van Hoff et al, 2000).***

PCOS is substantially more common in obese than in normal weight women. In a series of 113 premenopausal women referred for overweight or obesity, 28.3% were diagnosed as PCOS ***(Alvarez et al., 2006).***

**Etiology:**

Theories behind etiology of PCOS The main theories that have been proposed in previous studies regarding etiology of PCOS:

1. The luteinizing hormone-theca interstitial cell (LHTIC) theory suggests that the pathophysiologic mechanisms leading to abnormally elevated levels of LH underlie the phenomenon of PCOS. The theory suggests that high levels of circulating LH cause an increase in the growth of TIC in developing follicles, which leads to androgen overproduction and follicular atresia ***(Dasgupta and Reddy, 2008)***.

2. The follicle stimulating hormone-granulosa cell (FSH-GC) theory suggests that the reduced FSH leads to subnormal induction of cytochrome P450 aromatase in the granulosa cells, leading to elevated androgen levels. This may be due to insufficient bioactive FSH in the follicular microenvironment to induce P450 aromatase gene expression, dysfunctional FSH receptor signal transduction mechanism, or the presence of inhibitors (such as epidermal growth factor and insulin-like growth factor (IGF)-binding protein 3, that prevent the normal expression of P450 aromatase activity ***(Dasgupta and Reddy, 2008)***.

3. The third theory relates to the growth factor- autocrine-paracrine system. In PCOS, there is evidence of an altered IGF/insulin system, and these act as mediators of biologic responses of follicular hormones ***(Dasgupta et al., 2008).***

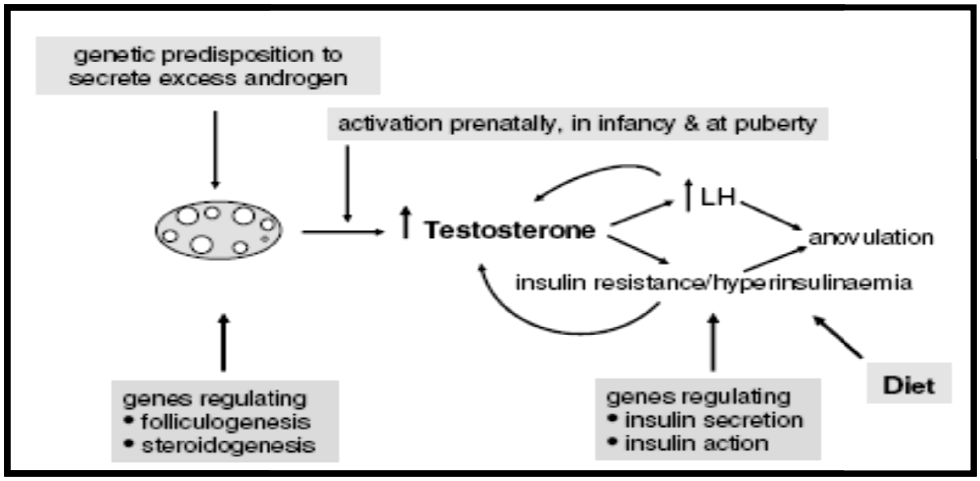


**Figure (1):** Proposed developmental aetiology of polycystic ovary syndrome (PCOS)**.** We suggest that the ovary is genetically predisposed to hypersecrete androgens, perhaps as early as intrauterine life but certainly during the activation of the hypothalamic–pituitary–ovarian axis that occurs transiently in infancy and in a sustained manner at puberty. Higher than normal circulating levels of testosterone 'programme' the hypothalamic– pituitary unit to produce high tonic levels of luteinizing hormone (LH) and also amplify the physiological insulin resistance of puberty. Higher than normal concentrations of LH and insulin further enhance ovarian androgen production and may contribute to the mechanism of anovulation ***(McCarthy et al., 2006)***.

## Pathophysiology:

The etiology of PCOS remains controversial and many factors play a role in development and disease progression ***(Witchel, 2006).*** Data are accumulating that PCOS is a complex trait with contributions from both heritable and environmental factors ***(Rosenfield, 2007).*** Multiple studies have documented a familial incidence reflecting a genetic predisposition, but the exact role of genes in the pathogenesis has not been elucidated In addition, many patients with PCOS have a family history of type 2 diabetes ***(Goodarz and Azziz, 2006).***