# Studying the effect of pretreatment normalization of FSH/LH ratio on the response to induction of ovulation and pregnancy rate in Polycystic ovarian syndrome patients.

***THESIS***

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# LIST OF ABBREVIATIONS:

| | |
|---|---|
| 17β-HSD | : 17 beta-hydroxy steroid dehydrogenase. |
| AAES | : American Androgen Excess society. |
| AFC | : Antral Follicle Count. |
| ART | : Artificial reproduction technique |
| ASRM | : American Society for Reproductive Medicine. |
| BMI | : Body Mass Index. |
| CC | : Clomiphene Citrate. |
| Cm | : Centimeter. |
| COH | : Controlled Ovarian Hyper stimulation. |
| DHEAS | :Dihydroepiandrostendion. |
| DHT | :Dihydrotestosterone. |
| e.g. | : Example |
| $E_2$ | : Estradiol. |
| ER | : Estrogen receptors. |
| ESHRE | : European Society of Human Reproduction and Embryology |
| FDA | : Food and Drug Administer. |
| FSH | : Follicle Stimulating Hormone. |
| FSH -GC | : Follicle Stimulating Hormone- Granulosa Cells. |
| GnRH | : Gonadotropins Releasing Hormone. |
| GnRHa | : Gonadotropins Releasing Hormone agonist. |

HCA : Hyperandrogenism and Chronic Anovulation.

HCA-PCO : Hyperandrogenism Chronic Anovulation, polycystic ovaries.

HCG : Human Chorionic Gonadotropin.

HMG : Human Menopausal Gonadotropin.

HPCO : Hyperandrogenism and polycystic ovaries.

HPO : Hypothalamic Pituitary Ovarian Axis.

IGF : Insulin Growth Factor.

IU : International unite.

IUI : Intra Uterine Insemination.

IU/L : International unite / Liter.

IVF : In Vitro Fertilization.

$Kg/m^2$ : Kilogram /square.

LH : Luteinizing Hormone.

LHTIC : Luteinizing Hormone Theca Interstitial Cells.

LOD : Laparoscopic Ovarian Drilling

Mg : Milligram.

Mm : Millimeter.

NAC : N-acetyl cysteine.

NICHD : National Institute of Child Health and Human Development.

NIH : National Institute of Health.

OCP : Oral Contraceptive Pills.

OHSS : Ovarian Hyper Stimulation Syndrome.

PCO : Polycystic Ovary.

PCO-CA : Polycystic ovaries and chronic anovulation

PCOM : Polycystic ovarian morphology.

PCOS : Polycystic ovarian Syndrome.

PR : Pregnancy Rate.

RCT : Randomized Controlled Trial.

Ref. : Reference.

SD : Standard Deviation.

SHBG : Sex Hormone Binding Globins.

TI : Timed Intercourse.

TIC : Theca Interstitial Cells.

TVU : Trans Vaginal Ultrasound.

US : Ultrasound.

% : Percent.

< : Less.

> : More.

= : Equal.

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# دراسة تأثير تعديل نسبة هرموني المحفز للحويصلات /هرمون المدعم للجسم الأصفر قبل بدء العلاج في متلازمة تكيسات المبايض على نتائج تنشيط التبويض ومعدلات الحمل

**توطئة للحصول على درجة الماجستير في**

**التوليد وأمراض النساء**

مقدمة من


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## ABSTRACT

**OBJECTIVE:** to study the effect of normalized FSH/LH ratio in PCOS patients via the use of a short pre treatment course of OCP on the success of ovulation induction and pregnancy rate.

**SETTINGS:** Kasr Al-Aini Hospital.

**STUDY DESIGN:** Retrospective observational comparative study.

**MATERIALS AND METHODS:** This study has been conducted on 150 patients attended the infertility outpatient clinic of Obstetrics and Gynecology Department-Faculty of Medicine -Cairo University from November 2014 till June 2015.

Patients were divided into two groups; group 1 induction by CC and/ or HMG with pre treatment OCP, group 2 CC and/or HMG without OCP pretreatment .

**RESULTS**: we found

- The No. of mature follicles ( mean): in group 1 is 2.91 , while in group 2 is 1.25 .The p value < 0.001 indicate highly significant difference in the ovulation outcome .
- The pregnancy rate: pregnancy test were done in 117/150 cases Only 32 cases had positive pregnancy test and 85 had negative pregnancy test. Group 1 22 cases got pregnant ,while in group 2 only 10 cases got pregnant. The p value <0.041 indicate that there is a significant difference between the pregnancy rates in both groups
- Cancelled cycles: after the stimulation protocols 21.3% of cases were cancelled; in group 1 were 7 cases ( 9.5%) of patients, and group 2 were 25 (32.9%) , more cancelled cycles in group 2 than group 1.

- ❖ Hormonal profile: LH mean decreased after using the OCP from 10.539 to 5.363. As well the FSH/LH ratio mean increased after OCP from 0.533 to 1.067 which towards normalized ratio.

**CONCLUSION:** the down regulation by using the oral contraceptive pills 3 months before the induction of ovulation in PCOs patients, has a beneficial effect on improving the ovulation rate and pregnancy rate .

**KEY WORDS:**

OCP: oral contraceptive pills, PCOs: polycystic ovaries syndrome.

# Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age , it affects 5 to 10% of women of childbearing age and is the most common cause of anovulatory infertility and 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).**

It is a clinical diagnosis characterized by the presence of two or more of the following features:

chronic oligo-ovulation or an ovulation, androgen excess and polycystic ovaries in the ultrasound ***(Nestler, 2008).***

Infertility is the presenting complaint in 40% of women with PCOS and it is due to anovulation and sub fertility could be due to the presence of high LH and androgen levels. ***(Abdulmalik et al.,2005).***

LH pulse amplitude and frequency were increased in PCOS cases These elevated serum LH level has been thought to play a key role in ovulatory dysfunction in PCOS **(*Taylor et al.,1997*).**

It was suggested that high LH level in the follicular phase of the menstrual cycle caused a premature resumption of meiosis with the consequent release of a "premature oocyte". However, it would appear that several factors interact to form part of the vicious cycle of abnormal steriodogenesis, folliculogenesis, abnormal oocyte maturation, decrease endometrial receptivity and early pregnancy loss ***(Abdulmalik et al.,2005).***

The recommended first line treatment for ovulation induction remains the anti-estrogen clomiphene citrate (CC), which is reported to be highly effective with a cumulative singleton live-birth rate of 72% ***(Badway, et al., 2011).*** CC resistance more

common in PCO perhaps due to LH hyper secretion. Which may adversely affect the outcome of treatment by increasing the abortion rate & OHSS.*(***Homburg et al., 1988;).**

In an effort to optimize pregnancy outcome in this difficult group of PCO women. A newly developed stimulation protocol which is both **simple** and **inexpensive** while achieving rapid and effective down-regulation. This protocol employs pretreatment with oral contraceptive pills (OCP) prior to the induction protocol combined with relatively lower gonadotrophin dosages.

Administration of oral contraceptives (suppression of the hypothalamic-pituitary-ovarian axis) for 3 months prior to beginning a cycle of clomiphene may improve ovulation and pregnancy rates in clomiphene resistant patient, perhaps by: improving a preexisting hyperandrogenic state, reduce serum LH, estradiol and androgenic level. The progestin component suppresses LH resulting in diminished ovarian androgen production.

Finally, these hormonal changes especially the reduced androgen level, could act improving the ovarian microenvironment and the response to clomiphene in the poor responders.***(Brown J,Farquhar C, Beck J,et al ,2009)(Branigan EF, Estes MA,2003)***

# Aim of work

The aim of this work was to study the effect of using short course of pre induction OCP to correct FSH/LH imbalance in PCO patients on follicular activity and ovulation rate.

# Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders. PCOS is a complexheterogeneous disorder of uncertain etiology***(Fauser et al., 2011).*** PCOS is associated with 75% of all anovulatory disorders causing infertility, with 90% of women with oligomenorrhea, more than 90% with hirsutism and more than 80% with persistent acne ***(Homburg, 2008)***.

## *Definition:*

Difficulties in definition of PCOS 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).**PCOS is most commonly defined by Rotterdam criteria (2003), which requires at least two of three features for diagnosis**.** The Rotterdamthree features:

1. Oligo ovulation or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries by US (presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume >10 $cm^3$; calculated using the formula 0.5 x length x width x thickness). The transvaginal approach should be used.

## *Prevalence:*

Although polycystic ovaries can be found in approximately 20% of the female population. ***(Homburg, 2008).***

## *Etiology and pathogenesis of PCOS:*

PCOS has been studied intensely, although the exact etiology is still unknown***(Homburg, 2008).***

Theories behind etiology of PCOS The main theories that havebeenproposed 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 (theca interstitial cells) 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-likegrowth factor (IGF)-binding protein 3 that prevent the normal expression of P450aromatase activity. ***(Dasgupta and Reddy, 2008)***.

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