A Comparative Study of Letrozole and Clomiphene Citrate for Induction of Ovulation with ultrasonographic assessment of ovarian volume and ovarian blood flow

A thesis submitted in the fulfillment of M.D degree in obstetrics and gynecology

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بسم الله الرحمن الرحيم

إقرأ باسم ربك الذى خلق ﴿١﴾ خلق الإنسان

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List of Abbreviation

AES	• **Androgen Excess Society**
AIs	• **Aromatase Inhibitors**
ASRM	• **American Society of Reproductive Medicine**
ATD	• **١,٤,٦-androstatrien-٣,١٧-dione**
CC	• **Clomiphene citrate**
dB	• **decibele**
DHEAS	• **Dehydroepiandrosterone sulfate**
E٢	• **Estradiol**
ER	• **Estrogen receptor**
ESHRE	• **European Society for Human Reproduction & Embryology**
FSH	• **Follicular stimulating hormone**
FDA	• **Food drug administration**
GnRH	• **Gonadotropin releasing hormone**
hCG	• **Human chorionic gonadotropin**
HMG	• **Human menopausal gonadotropin**
Hz	• **Hertz**
IGF-I	• **Insulin growth factor one**
IUGR	• **Intrauterine growth retardation**
IVF	• **In vitro fetilization**
KHz	• **Kilohertz**
LH	• **Lutenizing hormone**
MHz	• **Megahertz**
mRNA	• **Messenger ribonucleacic acid**
NIH	• **National Institutes of Health**
OHSS	• **Ovarian hyperstimulation syndrome**
PI	• **Pulsatile index**
P	• **Progestrone**
PCOS	• **Polycystic ovarian syndrome**
PIF	• **Fourier pulsatile index**
PPI	• **Peak to peak pulsatility index**
RI	• **Resistance index**
S/D	• **Systolic/diastolic ratio**
TAMV	• **Time averaged maximum velocity**
TGF-α	• **Transforming growth factor alpha**
RecFSH	• **Recombinant follicular stimulaing hormone**
IUI	• **Intrauterine insemenemation**

List of Contents

List of Tables

List of Figures

REVIEW OF LITERATURE

Introduction

It is now more than ٤٥ years since Greenblatt first reported a new, anti-estrogen, compound capable of inducing ovulation for anovulatory women **(Greenblatt et al., ١٩٦١).** Otherwise, known as clomiphene citrate (CC), this preparation became the first-line treatment for women with absent or irregular ovulation.

It is frustrating that the restoration of ovulation by CC does not produce a much higher pregnancy rate. This discrepancy between ovulation and pregnancy rates (only ٥٠٪ of those who ovulate will conceive) may be partly explained by the peripheral anti-estrogenic effects of CC at the level of the endometrium and cervical mucus or by hypersecretion of LH **(Shoham et al ., ١٩٩٠)** .

Therefore Aromatase inhibitors have been proposed as an alternative which do not have a negative effect on the endometrium or the cervical mucous. Aromatase inhibitors work by inhibiting the action of the enzyme aromatase, which converts androgens into estrogens by a process called aromatization. As breast tissue is stimulated by estrogens, decreasing their production is a way of suppressing recurrence of the breast tumor tissue. Aromatase inhibitors have been extensively studied in the management of breast cancer (hormone-receptor-positive) especially after menopause. Letrozole has shown promising results in the induction of ovulation **(Rosenfeld et al., ٢٠٠٢).**

The aim of work:

The aim of work in this study is to compare the use of letrozole versus clomiphene citrate for induction of ovulation in patients with polycystic ovarian syndrome and to compare the effect of both drugs on the number of follicles equal or greater than ١٨ cm, the endometrial thickness, the ovarian volume, the ovarian blood flow, the ovulation rate and the pregnancy rate.

Physiology of ovulation

Physiology of ovulation

The female menstrual cycle is determined by a complex interaction Of hormones. The predominant hormones involved in the menstrual cycle are gonadotropin releasing hormone (GnRH), follicle stimulating hormone (FSH), luteinizing hormone (LH), estrogen, and progesterone.

TheGnRH secreted by the hypothalamus stimulates the release of LH And FSH from the anterior pituitary, which in turn stimulate the release of estrogen and progestin at the level of the ovary.

During the menstrual cycle, the interplay between pituitary and ovarian hormones gives rise to a stereotyped pattern of hormone levels .

The graph below shows relative hormone levels in an average ٢٨-day cycle.

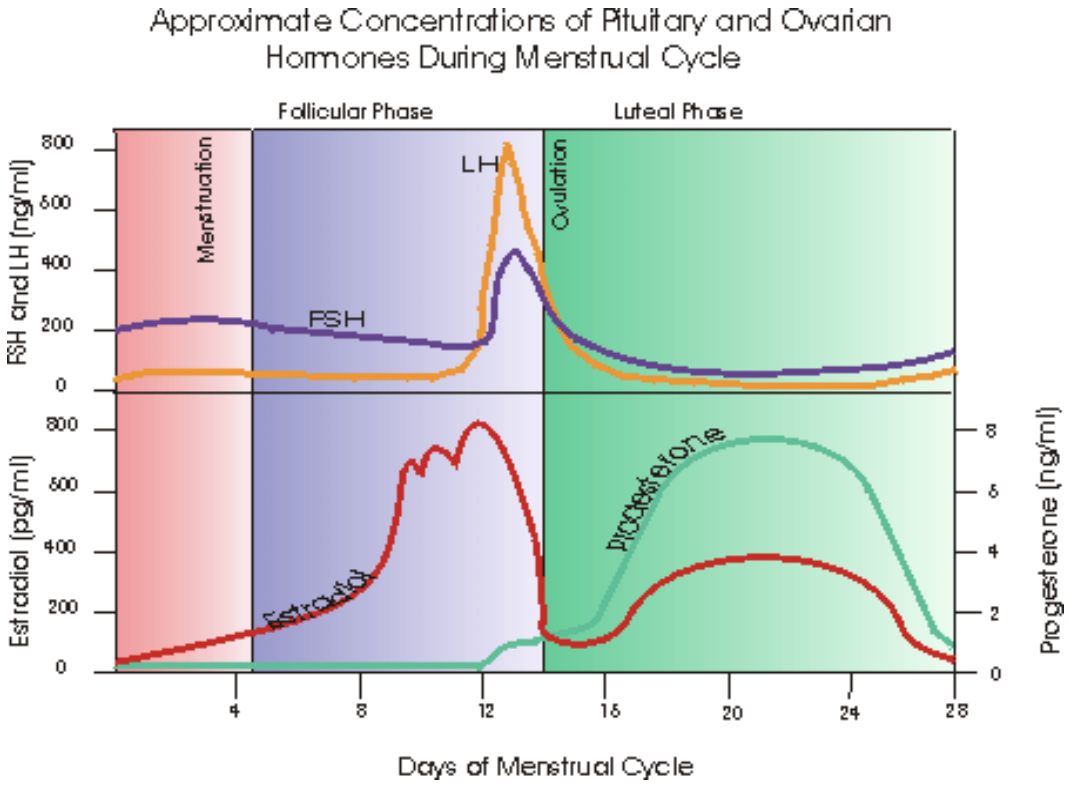

Figure ١: The sequence of events in the menstrual cycle is determined by the relative hormone levels at each stage(Filicori et al ., ١٩٨٦)

Initiation of growth of primordial follicles, referred to as "primary recruitment", occurs continuously and in a random fashion. Follicle development from the primordial to the preovulatory stage usually takes several months**(McGee etal.,٢٠٠٠)**.

The great majority of primordial follicles that enter this development phase undergo atresia before reaching the antral follicle stage through a process of apoptosis. The degree to which early stages of follicle development are influenced by FSH remains unclear. But in human FSH receptor mRNA is only expressed from the primary follicle onward. Studies in women with a mutated FSH β-subunit have shown follicular growth to occur up to the stage of secondary recruitment **(Barnes et al.,٢٠٠٢)**.

In addition, exogenous FSH can stimulate follicle growth up to the preovulatory stage in hypophysectomized women**(Schoot et al.,١٩٩٢).**

Factors such as TGF-α from theca cells, growth differentiation factor ٩, and bone morphogenetic protein ١٥ produced by the oocyte may limit the effects of FSH on granulosa cell differentiation and follicle development at this early stage**(Quet al .,٢٠٠٠).**

Only at more advanced stages of development the follicles become responsive to FSH and obtain the capacity to convert the theca-cell derived androstenedione to estradiol ($E^{٢}$) by the induction of the aromatase enzyme activity**(Gougeon et al.,٢٠٠٤).**

Due to the demise of the corpus luteum during the late luteal phase of the menstrual cycle, $E^{٢}$, inhibin A, and progesterone (P) levels fall. This results in an increased frequency of pulsatile GnRH secretion, inducing rising FSH levels at the end of the luteal phase **(Hall et al ., ١٩٩٢,LeNestour et al., ١٩٩٣).**

Although each growing follicle may initially have an equal potential to reach full maturation, only those antral follicles that happen to be at a more advanced stage of maturation during this intercycle rise in FSH (levels surpassing the so-called threshold for ovarian stimulation) gain gonadotropin dependence and continue to grow**(McGee et al.,٢٠٠٠).**

This process is referred to as cyclic, gonadotropin-dependent or "secondary" recruitment, as opposed to the initial gonadotropin-independent "primary" recruitment of primordial follicles

In the subsequent follicular phase, FSH levels reach a plateau during the initial days**(Schipper et al.,١٩٩٨),(Groome et al.,١٩٩٦).**
and are gradually suppressed thereafter by ovarian inhibin B (**Baird et al.,١٩٨٧)** and E٢negative feedback**(Welt et al.,١٩٩٧).**

Gonadotropin withdrawal studies have demonstrated the association between FSH and inhibin production**(Welt et al.,١٩٩٩),(Stouffer et al .,١٩٩٣).**

There is a direct endocrine role for inhibin A in the negative feedback on pituitary FSH production, whereas inhibin B does not contribute to the dynamic changes within a menstrual cycle**(Molsknesset al .,١٩٩٦) (vansantbrink et al .,١٩٩٥).**

Decremental follicular phase FSH levels appear to be crucial for selection of a single dominant follicle from the recruited cohort **(Zeleznik et al .,١٩٨٦).**

As FSH levels fall, all but the dominant follicle (with its increased sensitivity to FSH) lose the stimulus to further development and become atretic**(Fluker et al .,١٩٩١)**

The important concept of increased sensitivity of the dominant follicle for FSH has been confirmed by human studies showing