RANDOMISED CONTROL TRIAL ON THE EFFECTS OF LETROZOLE AND CLOMIPHENE CITRATE FOR INDUCTION OF OVULATION IN POLYCYSTIC OVARIAN SYNDROME (PCOS).

By:

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Dissertation Submitted in Partial Fulfilment Of The Requirements for the Degree Of Master of Medicine (Obstetrics and Gynaecology)

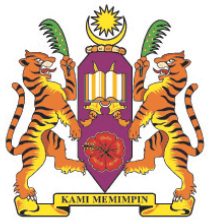

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TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AIs	Aromatase inhibitors
ART	Assisted reproductive technique
ASRM	American Society of Reproductive Medicine
BMI	Body mass index
CC	Clomiphene citrate
cm	centimeter
D	Day
D5	Day 5
D9	Day 9
DF	Dominant follicle
dL	deciliter
ET	Endometrial thickness
E	Estrogen
ER	Estrogen receptor
ESHRE	European Society of Human Reproduction an Embryology
FSH	Follicular stimulating hormone

GnRH	Gonadotrophin Releasing Hormone
hCG	Human Chorionic Gonadotrophin
HSB	Hospital Sultanah Bahiyah
HUSM	Hospital Universiti Sains Malaysia
HTAA	Hospital Tengku Ampuan Afzan
HMG	Human menopausal Gonadotrophin
i.e.	*id est*, that is
IIUM	International Islamic University Malaysia
IM	Intramuscular
IU	International Unit
IUI	Intrauterine Insemination
kg	kilogram
LOD	Laparoscopic ovarian drilling
LOS	Laparoscopic ovarian surgery
LFT	Liver function test
LH	Luteinizing Hormone
L	Letrozole

miu/ml	milli international unit/ millimiter
MPA	Medroxyprogesterone acetate
mm	millimeter
mmHg	millimeter mercury
mg	miligram
n	number
OHSS	Ovarian Hyperstimulation Syndrome
OD	Once daily
PCOS	Polycystic Ovarian Syndrome
RFT	Renal Function Test
RCOG	Royal College of Obstetricians and Gynaecologists
SD	Standard deviation
SC	Subcutaneous
SFA	Seminal fluid Analysis
SHBG	Sex steroid hormone binding globulin
SPSS	Statistics program for social sciences
T	Testosterone

TDS	Three times a day
TVS	Transvaginal ultrasound
W	Watt
WHO	World Health Organization
WC	Waist curcimference
WHR	Waist hip ratio
UK	United Kingdom
vs	Versus

ABSTRAK (VERSI BAHASA MALAYSIA)

Objektif :

Kajian ini bertujuan untuk mengkaji kesan perbandingan di antara Letrozole dan clomiphene citrate (CC) sebagai agen ovulasi di kalangan wanita yang mengalami Sindrom Ovari Polisistik atau *'Polycystic Ovarian Syndrome'* yang mengalami masalah ketidaksuburan. Kajian ini juga bertujuan untuk mengkaji keberkesanan antara dua jenis ubat seperti yang disebut diatas terhadap kadar kehamilan, ketebalan lapisan (dinding) endometrium dan bilangan jumlah folikel yang dihasilkan.

Metodologi :

Wanita yang telah dikenalpasti mengalami Sindrom ovari polisistik (mengikut Revised Rotterdam ESHRE/ASRM criteria, 2004) yang mendapatkan rawatan di klinik Hospital Sultanah Bahiyah, Alor Star, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan dan Hospital Tengku Ampuan Afzan, Kuantan, Pahang akan mengikuti kajian ini. Mereka telah dibahagikan kepada dua kumpulan secara rawak iaitu Kumpulan Letrozole (Letrozole, n=75) dan Kumpulan CC (CC, n=75). Semasa lawatan pertama, indeks jisim badan dan ukur lilit pinggang, aras hormon perangsang folikel (Follicular Stimulating Hormone), hormon peluteinan (Luteinising Hormone), hormon prolaktin, darah fungsi hati dan darah fungsi ginjal diambil. Kumpulan Letrozole telah menerima Letrozole 5.0mg sehari sekali, diambil bermula pada hari ke lima hingga hari ke sembilan kitaran haid. Sementara kumpulan clomiphene citrate mengambil tablet

clomiphene citrate. Dose clomiphene citrate yang diambil ialah 100 mg sekali sehari, juga bermula pada hari ke 5 hingga ke 9 kitaran haid. Untuk setiap kumpulan, ovulasi dipastikan dengan membuat imbasan ultrabunyi faraj (transvaginal scan) secara berkala melalui faraj (transvaginal scan) bermula pada hari ke dua hingga hari ke lima sebagai ukuran dasar (baseline). Inbasan ultrabunyi berkala akan diteruskan pada hari ke 10 sehingga hari ke 20 selepas haid untuk melihat tanda-tanda ovulasi. Pada masa yang sama ketebalan lapisan endometrium akan diukur dan bilangan folikel akan dikenal pasti.

Keputusan

Seramai 150 orang pesakit yang telah dikenal pasti mengalami PCOS yang kesemuanya yang menjalani rawatan dianalisa. Daripada kajian ini didapati tiada perbezaan di antara kumpulan letrozole dan CC dari segi sosio-demografik, antropometrik dan tempoh infertiliti. Ini menunjukkan bahawa pembahagian pesakit adalah sekata di antara kedua-dua kumpulan kajian. Hasil kajian ini menunjukkan terdapat perbezaan antara ubat letrozole dan CC yang signifikan dari segi kadar ovulasi dimana kadar ovulasi pada pesakit-pesakit dalam kajian ini, 59 (78.7%) bagi kumpulan letrozole dan 40 (53.3%) bagi kumpulan CC dengan nilai p=0.001. Letrozole juga menunjukkan lebih banyak menghasilkan satu folikel (monofollicle) berbanding CC. Peratusan pesakit yang hamil juga adalah lebih tinggi pada kumpulan letrozole berbanding CC, bagi kumpulan letrozole 19 (32.0%) pesakit dan 12 (30.0%) bagi kumpulan CC; p=0.871 tetapi perbezaaan ini adalah tidak signifikan secara stastistik. Kajian ini juga menunjukkan perkembangan yang positif kepada kumpulan letrozole dimana jika dilihat pada ketebalan dinding endometrium letrozole meningkatkan ketebalan lapisan endometrium berbanding CC.

Maka ia dijangkakan boleh meningkatkan peluang kehamilan. Walaubagaimanapun perbezaan tersebut tidak signifikan (p=0.861). Kajian ini juga menunjukkan tiada pesakit dari mana-mana kumpulan mendapat komplikasi seperti ovari yang terlebih ransang (ovarian hyperstimulation). Legresi logistik pelbagai (MLR) 'Multiple logistic regession' menunjukkan kumpulan letrozole mengalami peningkatan ovulasi adalah sebanyak tiga kali ganda berbanding kumpulan CC setelah faktor-faktor seperti umur, tempoh perkahwinan, jenis ketidaksuburan, tahap hormon dan BMI dikawal. Hanya BMI yang penting dalam menentukan keberkesanan ovulasi, dengan mengurangkan 1 unit kg/m^2 akan meningkatkan sembilan peratus keberkesanan ovulasi.

Kesimpulan

Ubat letrozole adalah lebih efektif sebagai agen stimulasi kesuburan dari segi kadar ovulasi dan respon kepada ketebalan lapisan endometrium berbanding ubat CC.

ABSTRACT (ENGLISH VERSION)

Objectives:

To compare the effectiveness of Letrozole and Clomiphene Citrate as ovulation induction agent in Polycystic Ovarian Syndrome (PCOS) in infertility.

Methodology:

Women who was diagnosed to have Polycystic Ovarian Syndrome (according to the revised Rotterdam ESHRE/ASRM criteria, (2004) attending Infertility Clinic at Hospital Sultanah Bahiyah, Alor Star, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan and Hospital Tengku Ampuan Afzan, Kuantan, Pahang were recruited in this study. They were later randomized by using computer generated to undergo on cycle of Letrozole (n=75) or Clomiphene Citrate (n=75) induction. During initial visit, the Body Mass Index was measured and baseline investigations were taken which include Follicular Stimulating Hormone, Luteinising Hormone, Liver Function Test, Renal Function Test and serum prolactin. In Letrozole Group, Letrozole 5.0 mg daily was given from the fifth until the ninth day of menstruation. Clomiphene citrate 100 mg daily was given for those patients in CC Group from the fifth until the ninth day of menstruation as well. Serial tranvaginal scan were done at D2-D5 as a baseline then D10 of menses till to see the dominant follicles, endometrial thickness and number of follicles. Tranvaginal scan were repeated to look for evidence of ovulation. .

Result

Total of 150 subjects enrolled in this study, completed the ovulation induction cycle and included in data analysis. There were no statistical differences noted in term of sociodemographic, anthropometrics and duration of infertility in between these two study groups suggestive that the subjects were homogenously distributed. The difference between letrozole and CC in term of ovulation rate, 59 (78.7%) vs 40 (53.3%); p <0.001 which was statistically significant, and pregnancy rate, 19 (32.0%) versus 12 (30.0%); *p* 0.817 which was statistically not significant. Letrozole also produce better dominant follicle which is monofollicle compare to CC, 33 (46.5%) versus 20 (26.7%) patients respectively. Endometrial response also yielded similar result with *p* value not significant. No incidence of adverse pregnancy outcome like Ovarian Hyperstimulating Syndrome (OHSS) observing in this study. Multiple logistic regression (MLR) shows letrozole group had three times more likely having ovulation outcome compare to CC group after controlling other variables of age, duration of infertility, type of infertility, baseline hormonal profile and BMI. Only BMI made significant contribution to predict successful ovulation. If BMI of a patient reduces by 1 unit kg/m^2, there is a nine percent of chance of her to have successful ovulation.

Conclusion

Letrozole provide a more efficient stimulation to CC in term of ovulation induction and thicken the endometrial thickness even though the pregnancy rate was not significant among PCOS women undergoing ovulation induction.

CHAPTER 1: INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most common endocrinopathy among women of reproductive age group and is one of the leading causes of infertility. It affects 5-10% of women in reproductive age. It is characterized by chronic anovulation and hyperandrogenism with variable clinical manifestations that include oligomenorrhea, infertility, hirsutism, and acne. Based on the Rotterdam *American Society Reproductive Medicine / European Society Health Reproductive Embryology (ASRM/ESHRE)2004*, PCOS can be diagnosed by the presence of any two of the three criterias:

i. Oligo and / or anovulation,

ii. Clinical and / or biochemical signs of hyperandrogenism

iii. Polycystic ovaries with exclusion of congenital adrenal hyperplasia and androgen secreting tumors.

Syndromes with similar presenting features, e.g. congenital adrenal hyperplasia, androgen-secreting tumours or Cushing's disease, should be excluded.

Oligomenorrhea or anovulation: Ovulation occurs less than once every 35 days.

Hyperandrogenism: Clinical signs include hirsutism, acne, alopecia (male-pattern balding) and frank virilization. Biochemical indicators include raised concentrations of total testosterone and androstenedione, and an elevated free androgen index that entails the

measurement of total testosterone and sex hormone binding globulin (SHBG). However, the measurement of these biochemical markers for hyperandrogenism has proved markedly inconsistent due to problems with various assays.

Polycystic ovaries: The presence of 12 or more follicles in either ovary measuring 2–9 mm in diameter and/or increased ovarian volume (>10 mL).

Clearly, according to the Rotterdam diagnostic criteria, the majority of women with PCOS can be diagnosed without the need for laboratory examinations (Broekmans *et al.*, 2006).

The most common features of PCOS are chronic anovulation and infertility in addition to the hyperandronenism. Up to 70% of PCOS associated with infertility.

Several methods have been described to induce ovulation in PCOS patients such as weight reduction, laparoscopic ovarian drilling and the use of various induction ovulation agents like clomiphene citrate (CC), aromatase inhibitors (AIs) and gonadotrophins.

CC is the first line of drug treatment and has been most widely used and standard drug for treatment for PCOS. It has been used for women with PCOS for the last 40 years. Clomiphene citrate is a non-steroidal selective estrogen receptor modulator, which acts primarily by binding with estrogen receptors at the hypothalamus. The use of CC was

appropriate because it is the easiest method and least complicated. Early studies had proved that up to 80% of the patients with anovulation responded well (by achieving ovulation) with CC and about half of those who ovulated achieved pregnancy. However, about 20% of them required a high dose of CC (200mg daily taken for 5 days early in the cycle). Discrepancy between ovulation and pregnancy rate is related to anti-estrogenic activity on endometrium and cervical mucus is due to CC has a long half life of 5 to 7 days.

The main option to CC usually involved parenteral gonadotropin preparation that were significantly more complicated and uncomfortable to administer, very expensive and were associated with more frequent and more complications.

In view of disappointing result of CC treatment with many adverse effect and cost and possible complication of gonadotropin, the concept of aromatase inhibition was proposed as a new method of ovulation that are easy to use, less expensive and more effective drugs. Letrozole is an oral, potent, reversible, and highly selective aromatase inhibitor that prevents androgen-to-estrogen (E) conversion. These aromatase inhibitors have a short half life (45 hours), hence is rapidly eliminated from the body. No adverse effect on E target tissues is seen with letrozole due to this short half life; furthermore, it does not down regulate the ER compare to CC (Badawy *et al.*, 2009).

The main impetus for the development of aromatase inhibitor as ovulation induction agents was to avoid the peripheral antiestrogenic effects of CC, especially the frequent occurrence of a thin endometrial lining (Sohrabvand *et al.*, 2006).

The aim of this study is to compare the effectiveness of letrozole compare to clomid as ovulation induction to PCOS patient. It also to evaluate the pregnancy rate and to determine the endometrial thickness between letrozole and CC.

1.1 Rationale of performing the study

As both medications i.e. CC and letrozole have been shown to be effective in inducing ovulation in PCOS patients, this study was performed in order to evaluate which regime (whether CC or letrozole) is the best to be used as the first line treatment for PCOS patients with infertility for local population. The best regime will therefore could be included in the protocol of management of infertility patients with PCOS so that the quality of patients' care could be improved.

CHAPTER 2: LITERATURE REVIEW

Polycystic ovarian syndrome (PCOS) is one of the most common hormonal disorders affecting women, although the true incidence and pathophysiology have yet to be determined (Hart *et al.*, 2004). The heterogenecity of both the ovarian morphology and clinical findings in women with polycystic ovaries has been well recognized since Stein & Leventhal's in 1935 first reported and gradually led to the establishment of the term polycystic ovarian syndrome.

Clinically, PCOS is associated with short and long-term consequences. The short term consequences include three groups of disorder: hyperandrogenic, reproductive and metabolic. These manifestations co-exist in variable combinations in different women with PCOS. The long-term sequelae include diabetes mellitus, dyslipidaemia, hypertension, cardiovascular disease and endometrial carcinoma. The reproductive problems associated with PCOS relate to anovulatory subfertility and early pregnancy loss (Amer *et al.*, 2009).

Chronic anovulation is very common in women with PCOS, affecting more than 80% of them, and is often associated with menstrual irregularities, mainly oligomenorrhoea or amenorrhoea (about 66%), which characteristically date from the time of the menarche. Polymenorrhoea, menorrhagia and dysfunctional uterine bleeding are relatively less common, affecting 4–14% of these women.

2.1 Aetiology

The aetiology of polycystic ovarian syndrome is uncertain. PCOS appears to cluster in families and it has been suggested that it is inherited in an autosomal-dominant pattern. A family history is usually present for hirsutism, menstrual dysfunction and PCO. More recently, this list has been extended to include breast cancer, heart disease and premature male pattern baldness. Although several loci have been proposed as PCOS genes including CYP11A, the insulin gene and a region near the insulin receptor gene, the evidence supporting linkage is not overwhelming (Amer *et al.*, 2009).

2.2 Pathogenesis

The pathophysiology of PCOS appears to be multifactorial and polygenic. The definition of the syndrome has been much debated. There are many extra-ovarian aspects to the pathophysiology of PCOS yet ovarian dysfunction is central. Chronic anovulation in PCOS seems to be the result of two main underlying ovarian disorders: abnormal folliculogenesis and steroidogenesis. Although these two disorders are interlinked, it is difficult to determine the initiating disorder.

2.21 Abnormal folliculogenesis

Follicular development normally starts before birth with the daily recruitment of a cohort of primordial follicles. Under an unknown stimulus, these follicles are transformed

into primary, secondary and then small antral follicles of 2–5mm diameter. This initial development requires low levels of follicle-stimulating hormone (FSH) and takes about 70–80 days. Once the follicles reach that stage, they become FSH-dependent. In the absence of an adequate FSH stimulus, these follicles will undergo atresia by default. At puberty and with the maturation of the hypothalamo-pituitary system, FSH rises to the levels which initiate ovulatory cycles. In the late luteal phase of normally cycling women and with the intercyclical elevation of FSH above a certain threshold, several of these small antral follicles are recruited (i.e., rescued from atresia) and undergo further growth. Once a leading follicle reaches a diameter of 9–10 mm, the granulosa cells acquire luteinising hormone (LH) receptors, and further follicular development becomes LH-dependent. The rising oestrogen secretion by the leading follicle will result in a negative-feedback decline of FSH and a positive-feedback increase in LH. As a result, the dominant follicle continues to mature owing to the rising level of LH, while all the other follicles undergo atresia owing to the fall in FSH (Amer *et al.*, 2009).

In PCOS, despite a normal stock number of primordial follicles and a normal early FSH-independent follicular development, follicular growth becomes arrested at the small antral phase, with failure of dominance and escape from the natural process of atresia. This results in an increased number of primary, secondary and small antral follicles (2–8mm in diameter). The mechanism of this disturbed folliculogenesis in PCOS remains largely unknown. Several theories have been postulated to explain the maturation arrest and the escape from atresia of the antral follicles in PCOS. Theories explaining follicular arrest

include relative FSH deficiency, abnormal LH stimulus, a deficiency of certain local growth factors and abnormal ovarian steroidogenesis (Amer *et al.*, 2009).

The hypothesised relative FSH deficiency may be due to an abnormally increased inhibin B secretion by the increased number of small antral follicles and/or increased ovarian and/or peripheral oestrogen production as a result of hyperandrogenaemia. An abnormal LH stimulus has also been postulated to explain the premature follicular arrest in PCOS. There is evidence that the granulosa cells of small antral follicles in anovulatory women with PCOS acquire LH receptors prematurely (at follicular diameter of 4 mm), possibly due to hyperinsulinaemia. LH receptor acquisition of the granulosa cells seems to switch the follicle from proliferation to differentiation, resulting in a suppression of granulosa cell growth and ultimately inducing an arrest of follicular development and a failure of dominance.

2.22 Abnormal steroidogenesis

Normally, the secondary follicle acquires a theca layer characterised by LH receptors and steroidogenic capacity, whereas the granulosa cells contain receptors for FSH. According to the two-cell, two-gonadotrophin model, LH stimulates the theca cells to produce androgens, which are the precursors for oestrogen synthesis. The androgens then diffuse to the granulosa cells, where FSH stimulates the expression of cytochrome P450 aromatase, which converts the androgens to oestrogens. The rising intraovarian oestrogen and inhibin B concentrations result in a negative feedback on FSH secretion and a positive feedback on

LH secretion. The resulting increase in LH, together with the rising inhibin B level, leads to an increase in thecal androgen production.

The granulosa cells of the dominant follicle gradually acquire LH receptors, and most of the physiological actions of FSH on granulosa cells can be exerted by LH. In the presence of increasing levels of androgen precursors, the granulosa cells of the dominant follicle, stimulated by the rising LH, continue to produce increasing levels of oestrogens despite decreasing FSH levels. LH results in an increase in steroidogenesis, early progesterone production and luteinisation. Through a positive-feedback mechanism, progesterone, together with the high oestrogen levels, induces the mid-cycle LH surge, which results in ovulation.

In PCOS, excess ovarian androgen production appears to be central in the pathogenesis of PCOS. Whether hyperandrogenaemia is the cause or the result of disordered folliculogenesis remains to be elucidated. Although it is possible that the increased number of small antral follicles produces excess androgens, it is also possible that a genetically determined hypersecretion of androgens is responsible for the disordered folliculogenesis. The excess androgen secretion by the theca cells results in an increased availability of precursors for oestrogen production in the granulosa cells. The granulosa cells in anovulatory women with PCOS show LH-induced aromatase activity in the small antral follicles (secondary to hyperinsulinaemia), resulting in enhanced oestrogen production. The increased levels of circulating oestrogens result in an increased positive feedback on LH and

a negative feedback on FSH secretion, thus causing disordered folliculogenesis, abnormal steroidogenesis and abnormal gonadotrophin secretion.

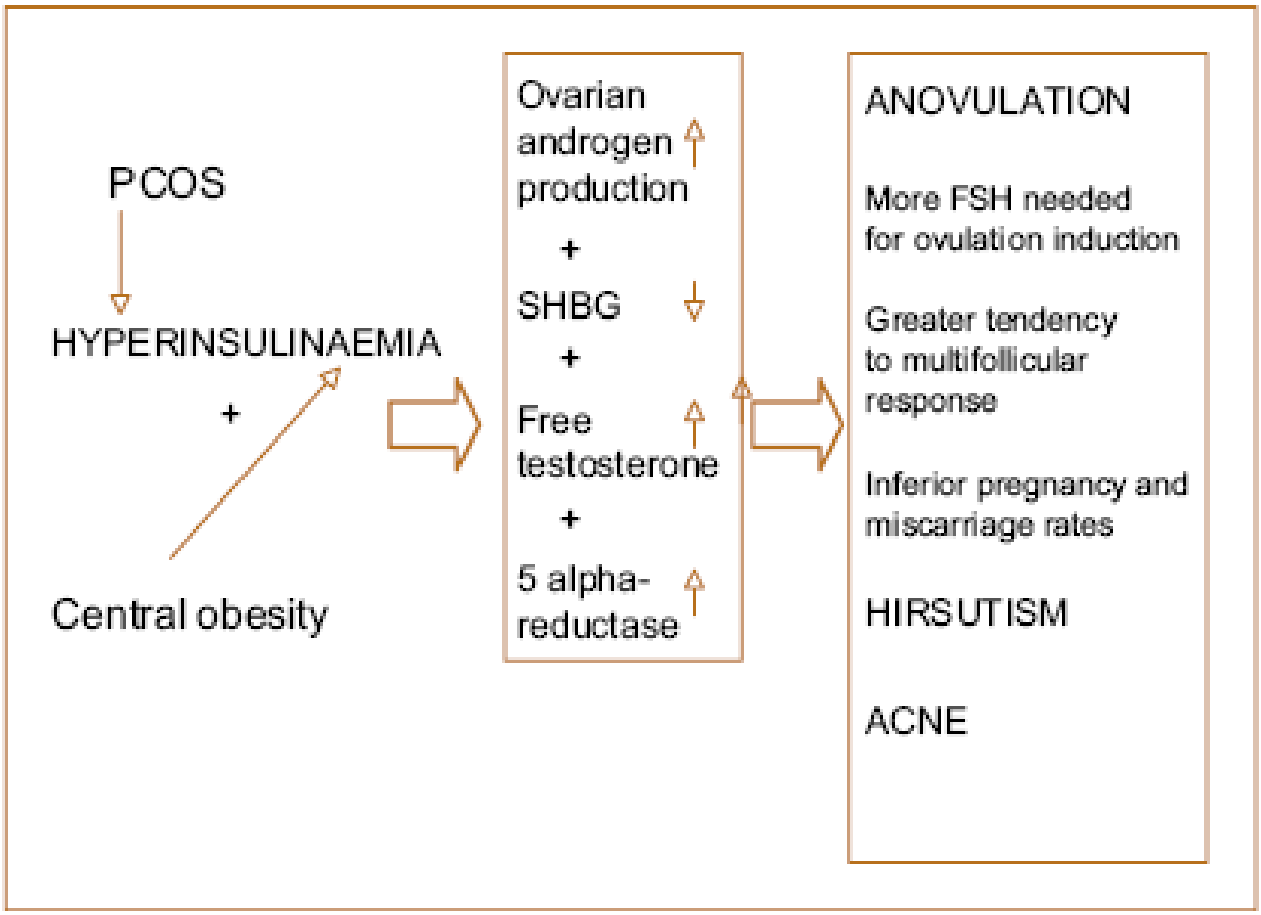

Figure 1: Pathophysiology of PCOS

2.3 Clinical features

Anovulatory symptoms Chronic anovulation is very common in women with PCOS and is often associated with menstrual irregularities, which characteristically date from the time of the menarche. The majority of PCOS women present with oligo- or amenorrhoea, although other menstrual disorders such as polymenorrhoea and irregular bleeding can be seen in ~10% of women with PCOS. About 15-20% of women with PCOS have regular menstrual cycles and some women with menstrual abnormalities may resume regular ovulatory cycles for prolonged periods of time.

Hyperandrogenic symptoms Hyperandrogenic symptoms are common in women with PCOS and are typically mild to moderate. These include hirsutism, acne and alopecia, which have been described in ~70%, 30% and 8% of women with PCOS, respectively. Hirsutism typically starts in the decade between 15 and 25 years and progresses slowly to become noticeable after 1 year from its onset. Virilisation (e.g. clitoromegaly, temporal baldness, deepening of voice or increase in muscle mass) is very rare in PCOS and should be investigated to exclude other causes.

Metabolic symptoms Overweight/obesity (body mass index (BMI) > 25 kg/m2) affects ~ 50% of women with PCOS and is typically characterized by an upper-body obesity, which is defined as a ratio of waist to hip circumference exceeding 0.85. This type of distribution, which is associated with increased insulin-resistance, is found even in lean women with PCOS. Acanthosis nigricans is a non-specific cutaneous marker of moderate to severe

insulin-resistance, which is found in some cases of PCOS and is more common among obese patients. It is characterized by patchy, velvety, hyperpigmented skin changes affecting the neck, axillae, underneath the breasts, body folds, extensor surfaces of the joints and vulva.

2.4 Diagnosis of PCOS

Until recently, the diagnostic criteria of PCOS have been the subject of much debate with no universally agreed definition of this common syndrome. There have been two main schools for the diagnosis of PCOS**.** The European school held that PCOS encompassed the presence of polycystic ovaries on ultrasound and one or more of the signs and symptoms of raised concentrations of serum androgen and chronic anovulation in the absence of pituitary and adrenal disease.

The North American School diagnosed PCOS as a condition where there is a combination of hyperandrogenism and menstrual/ ovulatory dysfunction, in the absence of non-classic adrenal hyperplasia. There was no need to identify the presence of polycystic ovaries by ultrasound. This difference resulted in challenges in research and clinical management, as the findings of clinical research studies carried out in either Europe or America were not necessarily applicable to a local population due to different diagnostic criteria for PCOS.

Therefore, in an attempt to resolve this conflict, a joint consensus meeting of the American Society for Reproductive Medicine and the European Society of Human Reproduction an

Embryology (ASRM/ESHRE) refined the definition of PCOS. It was agreed that PCOS was primarily a condition of ovarian dysfunction and in the absence of other aetiologies (such as prolactinoma, congenital adrenal hyperplasia or an androgen-secreting tumour) (Geisthovel, 2003).

The Rotterdam ASRM/ESHRE – sponsored PCOS consensus workshop (2004) also agreed that two of the following three criteria's are required in order to diagnose the condition after exclusion of other causes of androgen excess. The criteria are:

a) oligo – and / or anovulation
b) clinical and / or biochemical signs of hyperandrogenism
c) polycystic ovary morphology on ultrasound scan, defined as the presence of 12 or more follicles in each ovary (with one being sufficient for diagnosis) measuring 2 to 9 mm in diameter and or increased ovarian volume more than 10 ml.

Currently, ASRM/ESHRE (2004) consensus definition is accepted as the ideal definition of PCOS. The key advantages are its ability to standardize definition used in research studies of the epidemiology, pathophysiology and treatment of PCOS.

2.5 PCOS and infertility

It has been well accepted that the infertility in PCOS patients is caused by anovulation. It is one of the end products of hyperandrogenism and hyperinsulinaemia which suppresses the follicular stimulating hormone (FSH) secretion, thus inhibiting the intraovarian conversion of androgens to oestrogens, keeping the ovaries in hyperandrogenic state with arrest of follicular maturation. Anovulation caused by PCOS contributes about 75% of anovulatory cycles. Restoring ovulation is therefore the mainstay aim of treating infertility among PCOS patients.

2.6 Management of anovulatory infertility

Management of PCOS includes a symptom-orientated approach to the presenting problem and a preventive strategy for the associated long-term morbidity. A general approach to tackle both the short-and long-term consequences of PCOS is to encourage weight loss in all overweight/obese patients. It is well established that weight reduction improves all PCOS symptoms and corrects the endocrine profile.

For anovulatory infertility in women with PCOS, several methods have been widely used to restore ovulation and thereby fertility, including: weight reduction, CC, metformin, letrozole, gonadotropin therapy and laparoscopic ovarian drilling (LOD).

However, the choice of first and second lines of treatment has been the subject of debate. In 2007, ESHRE and ASRM have jointly held a workshop involving international experts to establish a consensus on a management strategy for women with infertility and PCOS.

2.61 Weight control

Infertility in PCOS is more commonly seen in women who are obese or overweight; more than 30-50% of PCOS patients are obese. Obesity not only exaggerates the disordered ovarian function but also increases ovarian resistance to various methods of ovulation induction in women with PCOS. In addition, obesity is associated with early pregnancy loss and late pregnancy complications (e.g.preeclampsia, gestational diabetes and macrocosmia). Weight loss of just 5-10% has been shown to reverse the deleterious effects of obesity on ovarian function and can restore reproductive function in a majority of patients within 6 months of weight reduction. However, although effective, cheap and safe, weight loss presents a major challenge to clinicians as only a small proportion of obese women manage to achieve a significant weight reduction. Several approaches are available for weight reduction including behavioural counseling, lifestyle measures (diet and exercise), pharmacological agents and bariatric surgery.

2.62 Drug therapy

a. Clomiphene citrate

Clomiphene citrate (CC) has been most widely used and standard drug for the treatment of PCOS with infertility. It is the easiest way, low cost, carrying the least complications to the patients and relatively safe. CC was introduced into clinical medicine for the treatment of anovulation in the 1960's. Its introduction represented a major breakthrough in the medical management for ovulation induction.

Clomiphene citrate (CC) is a non-steroidal selective estrogen receptor modulator, which acts primarily by binding with estrogen receptors at the hypothalamus (Kurl and Morris, 1978). This competitive inhibition results in a perceived drop of circulating estrogen to the hypothalamus, eventually leading to increased gonadotrophin secretion and subsequent induction of ovulation. Augmenting endogenous FSH with CC treatment is associated with a risk of ovarian hyperstimulation syndrome and multiple gestations. Although CC results in ovulation in most patients, the pregnancy rates are disappointing. This has been attributed to its peripheral anti-estrogenic effects, mainly on the quality or quantity of cervical mucus, and endometrial growth and maturation that could prevent pregnancy in the face of successfully induced ovulation. Long-lasting estrogen receptor depletion has been involved in the anti-estrogenic mechanism of action of CC. It also appears that CC accumulates in the body because of its long half-life.

It is known that clomiphene citrate results in an ovulation rate of 60-85%, but a conception rate of only around 20%. About 20-25% of women are resistant to CC and do not ovulate. Discrepancy between ovulation and pregnancy rate is related to anti-estrogenic activity on endometrium and cervical mucus is due to CC has a long half life of 5 to 7 days.

Drawbacks of CC treatment is associated with a miscarriage rate of up to 40%; increased risk of multiple pregnancies and a small risk of ovarian hyperstimulation syndrome (OHSS). A possible increase in the risk of ovarian cancer has been suggested if more than 12 cycles are used. In addition, there are common but less serious side effects such as hot flushes, headaches and nausea.

Traditionally the main option to CC usually involved parenteral gonadotropin preparation that were significantly more complicated and uncomfortable to administer, very expensive and were associated with more frequent and more serious complications, e.g ovarian hyperstimulation and multiple pregnancy.

In view of disappointing result of CC treatment with many adverse effect and cost and possible complication of gonadotropin, the concept of aromatase inhibition was proposed as a new method of ovulation that are easy to use, less expensive and more effective drugs.

b. Letrozole

Letrozole is a third-generation selective aromatase inhibitor that blocks the rate-limiting step in the production of estrogen from androstenedione and testosterone substrates. Letrozole is approved in Canada for use in the treatment of postmenopausal women with breast cancer. Letrozole has no significant active metabolites. It is completely absorbed after oral administration and has a mean terminal half-life of approximately 45 hours (range 30–60 hours). It is cleared from the systemic circulation mainly by the liver (Forman *et al.*, 2007). In the late 1990s, aromatase inhibitors, including letrozole, began to be used to induce ovulation by being administered in the early part of the menstrual cycle (Bayar *et al.*, 2006, Badawy *et al.*, 2008).

Estrogen production from all sources is blocked by inhibiting aromatization, releasing the hypothalamic-pituitary axis from estrogenic negative feedback and resulting in increased gonadotropin secretion and ovarian follicular stimulation.

In the ovary, aromatase inhibitors increase follicular sensitivity to FSH, as there is an accumulation of intraovarian androgens.

At the level of the endometrium, estrogen receptors may be upregulated, resulting in rapid endometrial growth once estrogen secretion is restored (after clearance of letrozole) (Casper and Mitwally, 2006, Mitwally and Casper, 2006). Aromatase inhibitors also do not antagonized estrogen receptors in the brain and therefore, feedback central mechanism

remain intact. The initiation of follicle growth accompanied by increasing concentrations of estrogens result in normal negative loop that limit FSH response and atresia of small follicles generally leading to mono-ovulatory cycle (Casper and Mitwally, 2006). Side effects from letrozole are uncommon and related to suppression of the production of estrogens as a result of aromatase inhibition induced by the drug. Side effects include hot flashes (11%), nausea (7%), fatigue (5%), alopecia and vaginal bleeding, which occur more frequently in breast cancer patients than in women treated for ovulation induction due to differences in the duration of treatment.

As the dominant follicle grows and estrogen levels rise, normal negative feedback occurs centrally, resulting in suppression of FSH and atresia of the smaller growing follicles. A single dominant follicle, and mono-ovulation, should occur in most cases (Casper and Mitwally, 2006).

As a result of the mechanisms of action described above, AIs appear as new drugs to induce ovulation in women with normal or increased levels of endogenous estrogens, such as those with PCOS which constitute the largest group of anovulatory patients. The lack of antiestrogenic effect is another interesting characteristic of the mechanism of action of AIs, thus avoiding cervical mucus and endometrial morphology interaction (Balen and Rajkowha, 2003).

Side effects from letrozole are uncommon and related to suppression of the production of estrogens as a result of aromatase inhibition induced by the drug.

Cohort studies do not show an increase of congenital malformations among offspring of mothers who conceived with letrozole treatment for infertility. Because of the short half-life of AIs, the biological plausibility of the teratogenic effects when these drugs are used in the early follicular phase can be discarded.

From the retrospective Canadian study there are no published reports of congenital anomalies in human offspring delivered after the use of letrozole.

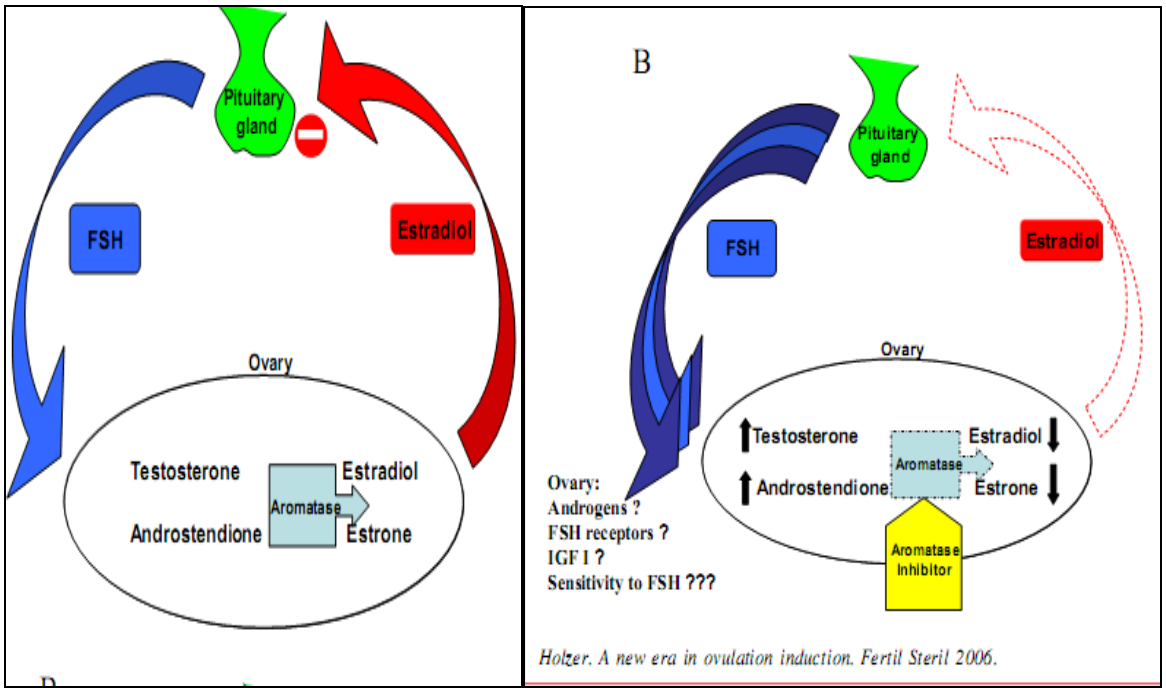

Figure 2: Mode of action of letrozole

c. Metformin

The link between insulin resistance and PCOS led many authors to consider insulin-sensitising agents for the management of this syndrome. These agents, which have been used for many years in type 2 diabetes, have recently been increasingly used worldwide in women with PCOS. The most commonly used agent is metformin, which is the only currently available biguanide drug. Despite its therapeutic benefits in PCOS, the mechanism of action of metformin in women with this syndrome remains uncertain. It improves insulin sensitivity by increasing peripheral glucose uptake in response to insulin at post receptor level. This in turn results in correction of the associated hyperinsulinaemia, which is responsible for the hypersecretion of ovarian androgens. In theory, the resulting decrease in androgen production improves the intraovarian micro environment, which leads to

normalisation of ovarian follicular development. Metformin does not cause hyperinsulinaemia and is therefore not associated with hypoglycaemia. Hypoglycaemia could, however, occur when caloric intake is deficient or when strenuous exercise is not compensated by caloric supplementation. The exact role of metformin in PCOS has still to be established. The most common indication for metformin in PCOS is to induce ovulation in women seeking fertility treatment. Most gynaecologists reserve metformin use for women with PCOS who are resistant to clomiphene citrate, although an increasing number of reproductive medicine specialists use it as a first-line treatment for ovulation induction in overweight/obese women with PCOS. If ovulation is not achieved after 3 months of metformin therapy, clomiphene citrate could be added. The exact success rate of metformin in infertile women with PCOS is still uncertain. Recent study done by Aboubakr Mohamed Elnashar Benha University Hospital, Benha, Egypt (2010), metformin as compared to placebo has been shown to improve ovulation rates, but metformin did not exert significant advantage over CC with respect to cumulative ovulation, pregnancy or live-birth rates. The combined approach of metformin plus CC is not better than CC or metformin monotherapy.

In CC-resistant patients, metformin has no benefit over placebo in ovulation, pregnancy, and live-birth rates as a single agent, but the combination of metformin and CC significantly improved ovulation and pregnancy rates when compared with CC alone. However, combined therapy did not improve the odds of live birth. Metformin pretreatment improves the efficacy of CC in PCOS patients with CC resistance.

d. Gonadotrophins

In many centres, gonadotrophin therapy is the preferred second-line treatment for induction of ovulation after CC failure in anovulatory women with PCOS. Theoretically, the preferred gonadotrophin preparation for induction of ovulation in women with PCOS is one that does not contain LH, in view of the high levels of endogenous LH in these women. However, human menopausal gonadotrophin (HMG) and pure FSH preparations have both been successfully used for ovulation induction in women with PCOS (Adams *et al.*, 1985).

Ovulation induction with gonadotrophins such as FSH has proved successful for at least three decades. FSH can be employed in patients with resistant CC. However, gonadotrophins are associated with multiple pregnancy and OHSS. Therefore, follicular development should be closely monitored with ultrasound to minimise these risks. Successful treatment with gonadotrophins has been shown in PCOS women with obesity.

2.6.2 Surgery

i. Wedge resection of the ovary

Wedge resection of the ovaries was initially described by Stein and Leventhal in 1935 when they found that ovarian biopsy, taken to make the diagnosis of PCOS led to subsequent ovulation. The rationale was to ‘normalise’ ovarian size and hence the endocrinopathy by removing 50 to 75 % of each ovary. A large review of 187 reports summarized data on 1079 ovarian wedge resections with an overall rate of ovulation of 80% and pregnancy rate of

63% (range 13 – 89 %). Wedge resection went out of favour in the 1970's with the introduction of successful medical treatment with CC and because of the realization that significant post – operative adhesion formation occurred and the initial favorable reports of pregnancy rates were not sustained.

ii. Laparoscopy and ovarian drilling (LOD)

Laparoscopic ovarian surgery (LOS) has replaced ovarian wedge resection as the surgical treatment for CC resistance in women with PCOS. It is free from the risks of multiple pregnancy and OHSS and does not require intensive ultrasound monitoring. Furthermore, ovarian diathermy appears to be as effective as routine gonadotrophin therapy in the treatment of CC– insensitive PCOS (Farquhar *et al.*, 2001).

Ovarian drilling has been used in recent years with apparently good results; a recent systemic review comparing drilling with CC and gonadotrophins proved equivalence in the studies examined.

The difficulty when deciding how to perform LOD does not know the 'dose response' for a particular patient. It has been shown that LOD using 40Watt for four seconds in four places on one ovary can lead to bilateral ovarian activity and ovulation. The ovulation rate was 50% and conception rate 40%.