PROSPECTIVE RANDOMIZED CONTROL TRIAL COMPARING METFORMIN AND CLOMIPHINE CITRATE AS OVULATION INDUCTION AGENT IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME AT ALOR STAR HOSPITAL, MALAYSIA.

BY

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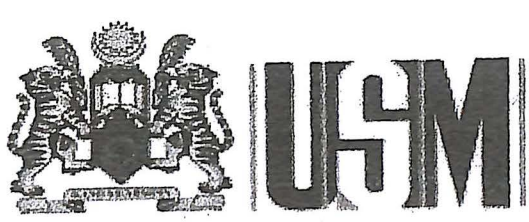

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ABBREVIATIONS

ASRM	American Society of Reproductive Medicine
BMI	Body mass index
CC	Clomiphene citrate
CI	Confidence interval
cm	Centimeter
D2	Day 2
D9	Day 9
D12	Day 12
D16	Day 16
DF	Dominant follicle
dL	Deciliter
ESHRE	European Society of Human Reproduction an Embryology
FSH	Follicular stimulating hormone
GDM	Gestational Diabetes Mellitus
HMG	Human Menopausal Gonadotrophin
kg	Kilogram
LOD	Laparoscopic ovarian drilling
LFT	Liver function test
M	Metformin
LH	Luteinising hormone
mg	Milligram
M + CC	Combination of Metformin and Clomiphene Citrate
NICE	National Institute for Clinical Excellence
N	Number
OHSS	Ovarian Hyperstimulation Syndrome
OD	Once daily
OR	Odd Ratio
PCOS	Polycystic Ovarian Syndrome
PCO	Polycystic Ovary
RFT	Renal Function Test
SD	Standard deviation
T	Testosterone
TVS	Transvaginal ultrasound
UK	United Kingdom
W	Watt
WHR	Waist hip ratio
	World Health Organization
1/52	One week
1/7	One day
>	More than

ABSTRAK (VERSI BAHASA MALAYSIA)

Objektif :

Kajian ini bertujuan untuk mengkaji kesan metfromin terhadap penurunan berat badan, nisbah kadar ukur lilit pinggang dan pinggul dan kitaran haid wanita tersebut. Selain daripada itu, ia juga bertujuan untuk mengkaji keberkesanan metformin, clomiphene citrate serta kombinasi metformin dan clomiphene citrate terhadap ovulasi.

Metodologi :

Seramai 115 orang wanita yang mengalami sindrom polycystic ovari terlibat di dalam kajian ini. Mereka telah dibahagikan kepada 3 kumpulan secara rawak iaitu A , B dan C. Semasa lawatan pertama, ukur lilit pinggang dan pinggul diukur. Paras hormon 'follicular stimulating hormone', 'luteinising hormone', testosterone, prolactin, darah fungsi hati dan darah fungsi ginjal diambil. Kumpulan A (n = 38) telah menerima metformin 500 mg tds sementara kumpulan B (n = 39) mengambil clomiphene citrate. Dos clomiphene citrate yang diambil ialah 100 mg sekali sehari bermula pada hari ke 2 hingga ke 6 kitaran haid dan dos akan dinaikkan sebanyak 50mg setiap kitaran sehingga dos maksima 200 mg sekiranya tiada ovulasi berlaku. Untuk kumpulan C (n=38) , kombinasi metformin dan clomiphene citrate diberikan sama seperti kumpulan A dan B. Untuk setiap kumpulan, ovulasi dipastikan dengan membuat pemeriksaan ultrabunyi melalui faraj ('transvaginal scan'). Paras hormon 'follicular stimulating hormone', 'luteinising hormone', testosteron dan ukur lilit pinggang dan pinggul diukur semula setiap tiga bulan.

Keputusan :

Metformin tidak menunjukkan sebarang perubahan pada berat badan dan ukur lilit pinggang dan pinggul. Sebanyak 36.8% (14 daripada 38 pesakit) daripada kumpulan A mengalami haid secara spontan setelah 5 bulan pengambilan metformin, manakala 57.9% (22 daripada 38 pesakit) daripada kumpulan yang sama mengalami haid yang spontan setelah 6 bulan mengambil metformin. Walau bagaimanpun, kedatangan haid yang spontan mungkin bukan disebabkan oleh metformin. Sejumlah 9 daripada 38 (23.7%) pesakit yang mengambil metformin telah mengalami ovulasi. Walau bagaimanapun, didapati seramai 28 daripada 39 pesakit (71.8%) yang mengambil clomiphene citrate sahaja telah mengalami ovulasi di dalam tempoh 6 bulan pengambilan ubat. Perbezaan tersebut didapati sangat signifikan (p= 0.000). Tiada terdapat perbezaan nyata di dalam penghasilan ovulasi di antara pesakit- pesakit yang mengambil clomiphene citrate sahaja (28 daripada 39 pesakit, 71.8%) berbanding pesakit- pesakit yang mengambil kombinasi metformin dan clomiphene citrate (26 daripada 38 pesakit, 68.4%; p = 0.470).

Kesimpulan :

Penggunaan metformin tidak mempengaruhi penurunan berat badan dan nisbah ukur lilit pinggang dan pinggul pesakit- pesakit sindrom polycystic ovari. Ia tidak sepatutnya digunakan untuk membuat kitaran haid teratur pesakit – pesakit sindrom polycystic ovari. Walau bagaimanapun, ia tidak berkesan untuk menghasilkan ovulasi berbanding dengan clomiphene citrate serta penggunaannya sebagai tambahan kepada clomiphene citrate tidak memberi sebarang kebaikan. Oleh itu, perawatan sindrom polycystic ovari yang mempunyai masalah ketidaksuburan seharusnya dilakukan sebagaimana protokol standard yang sedia ada.

ABSTRACT (ENGLISH VERSION)

Objectives:

To evaluate the effects of metformin on weight reduction , waist hip ratio , menstrual cycle and ovulation rates among women with polycystic ovarian syndrome with infertility taking metformin alone , clomiphene citrate alone and combination of metformin and clomiphene citrate.

Methodology:

115 patients diagnosed to have polycystic ovarian syndrome (according to the revised Rotterdam ESHRE/ASRM criteria, 2003) attending Infertility Clinic of Alor Star were recruited into the study and later randomized into three group i.e. Group A (metformin alone, n=38), Group B (CC alone, n=39) and Group C (combination of metformin and CC, n=38). During initial visit, the WHR were measured. Baseline investigations were taken which include follicular stimulating hormone, luteinising hormone, testosterone, liver function test, renal function test and serum prolactin. In Group A, metfromin 500mg tds were given up to 6 months. Clomiphene citrate 100mg daily was given from the second until the sixth day of menstruation for those patients in Group B. The dosage was increased by 50mg for each cycle should anovulation was noted, to a maximum of 200mg. In Group C, a combination of metformin and clomiphene citrate were given and the dosage were similar to Group A and B. For all three groups, ovulation was confirmed by performing transvaginal scan. The WHR , serum follicular stimulating hormone , luteinising hormone and testosterone was repeated every three months.

Results:

Metformin has no effects on weight reduction or waist hip ratio. 36.8% (14 out of 38 patients) and 57.9% (22 out of 38 patients) had spontaneous resumption of metformin , which might not due to the sole effect of metformin. Only 9 out of 38 patients (23.7%) taking metformin alone had ovulation compared to 28 out of 39 patients (71.8%) who take clomiphene citrate. This difference was significant statistically (p= 0.000). There was no difference in the number of patients having ovulation between those taking clomiphene citrate alone and combination of clomiphene citrate and metformin (28 out of 39 patients, 71.8% and 26 out of 38 patients, 68.4% respectively ; p= 0.470).

Conclusion:

Metformin has no effect on weight and waist hip ratio reduction. It should not be used to regulate menstrual cycle in PCOS patients. Its usage was no superior than the traditionally used clomphene citrate to bring ovulation among patients of polycystic ovarian syndrome with fertility problem. No additional advantage could be gained if it is combined with clomiphene citrate. Therefore, the current protocol to induce ovulation among polycystic ovarian syndrome with infertility patients with clomiphene citrate alone as the first line drug should remain.

CHAPTER 1 :

INTRODUCTION

CHAPTER 1: INTRODUCTION

Ever since Stein and Leventhal (Stein IL and Leventhal ML, 1935) reported on seven women with polycystic ovaries and amenorrhoea in 1935, continued research has led to a better understanding of the pathophysiology of the syndrome with promising therapeutic options. In addition to the endocrine abnormalities leading to menstrual disorders, hyperandrogenism and anovulatory infertility, many women with polycystic ovarian syndrome (PCOS) demonstrate metabolic aberrations, most importantly the association of insulin resistance, which later may lead to far long term health hazards to these women, like glucose intolerance and type II diabetes, increased risk factors for coronary heart disease, adverse lipid profile, hypertension, hyperinsulinaemia and obesity.

Since anovulatory cycles are the cause of infertility in PCOS, the goal in managing these patients is induction of ovulation. Several methods have been described to induce ovulation in PCOS patients- weight reduction, laparoscopic ovarian drilling and the use of various induction ovulation agents like clomiphene citrate (CC) and gonadotrophins. The association of the syndrome with insulin resistance makes metformin as one of the options to induce ovulation.

Among the stated drugs and methods mentioned, CC is the easiest and least complicated method used. 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).

Traditionally, the next step to induce ovulation for those who fails to ovulate with CC has been the use of injectable gonadotrophins, for which 90% of the anovulated women who did not response to CC achieved ovulations. However, the exorbitant cost of this medication in addition to the risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy with the daily injection may be inconvenient for these women.

Metformin has been used as oral hypoglycaemic agent to control diabetes. Its action by improving the peripheral insulin sensitivity may facilitate ovulation in some women with PCOS. About 75% of those who were CC resistant were observed to ovulate with metformin.

The approach of managing infertile patients with PCOS should be geared towards providing a progressively more aggressive treatment strategies until ovulation is established and pregnancy can be achieved. However, one must be seriously consider the safety of each treatment strategy during the choice of treatment.

This study was conducted to evaluate the effectiveness of metformin (whether by giving it alone or in combination with CC) to induce ovulation in PCOS patients at Alor Star Hospital. Should it proofs that metformin gives additional benefit, it should be considered as part of the treatment for PCOS with infertility before embarking for a more expensive with higher side effects drugs like gonadotrophins.

CHAPTER 2 :

LITERATURE REVIEW

CHAPTER 2: LITERATURE REVIEW

PCOS is a common endocrine disorder, which affects 3 to 5% of women in their reproductive age (Knochenhour et al, 1998, Asuncion et al, 2000). It is a heterogeneous disorder of uncertain aetiology. The heterogenecity of both the ovarian morphology and clinical findings in women with polycystic ovaries has been well recognised since Stein and Leventhal's (1935) first reported and gradually led to the establishment of the term polycystic ovarian syndrome. The many features of this syndrome can be broadly divided into three categories: clinical, endocrine and metabolic.

The most common features of PCOS are chronic anovulation and infertility in addition to the hyperandrogenism. The clinical manifestation of chronic anovulation includes irregular menstrual cycles, oligo or amenorrhea interspersed with heavy vaginal bleeding. The menstrual dysfunction usually presents from menarche. In the absence of ovulation, the usual premenstrual molimina does not occur. In addition, because there is unopposed estrogen stimulation of the endometrium, endometrial hyperplasia and in some instances, adenocarcinoma may develop.

Other clinical manifestations of PCOS are brought about by the hyperinsulinaemic state as well as hyperandrogenic state of the patients.

2.1 Aetiology of PCOS

The aetiology of polycystic ovarian syndrome is uncertain. There is some evidence of autosomal transmission related to strong familial clustering. Potentially, a gene or series of genes renders the ovaries susceptible to insulin stimulation of androgen secretion while blocking follicular maturation (Nestler JE and Jakubowicz DJ, 1997). This genetic predisposition may be expressed as premature balding in men (Carey LH et al, 1993).

The onset may occur in late childhood since many of the metabolic and endocrine features of the disorder mimic puberty (Nobels F and Dewailley, 1992). Insulin resistance increases dramatically at the onset of puberty and then declines in early adulthood. Associated with this are increases in the pulse amplitude of luteinising hormone (LH), increasing androgen concentrations, and irregular menses. Multiple, small ovarian cysts are seen on ultrasound examination and are a common and normal feature of puberty. It is therefore possible that women genetically predisposed to PCOS fail to resume normal insulin sensitivity and continue to express metabolic and endocrine features usually confined to puberty.

2.2 Pathophysiology of PCOS

Good evidence supports the hypothesis that decreased peripheral insulin sensitivity and consequent hyperinsulinaemia are pivotal in the pathogenesis of PCOS (Dunaif A, 1997). Peripheral insulin resistance is most evident in overweight patients: obesity and polycystic ovarian syndrome each seem to have a separate and synergistic relation with insulin resistance (Dunaif A, 1997). The exact mechanism(s) for insulin resistance is uncertain, but a post-receptor defect in adipose tissue has been identified (Dunaif A, 1997). Despite insulin resistance in adipose and skeletal muscle, the ovary remains

relatively sensitive to insulin, and both insulin and insulin-like growth factor 1 have stimulatory effects on thecal androgen production (Bergh C, 1993). In fact, some lean women with polycystic ovarian syndrome, who may not have insulin resistance and therefore hyperinsulinaemia, may show enhanced ovarian sensitivity to insulin. Figure 2.1 shows how the relative excess of insulin or enhanced ovarian sensitivity to insulin, in combination with an elevated LH concentration, brings about thecal hyperplasia, increased androgen secretion, arrest of follicular development, and therefore anovulation along with menstrual disturbance.

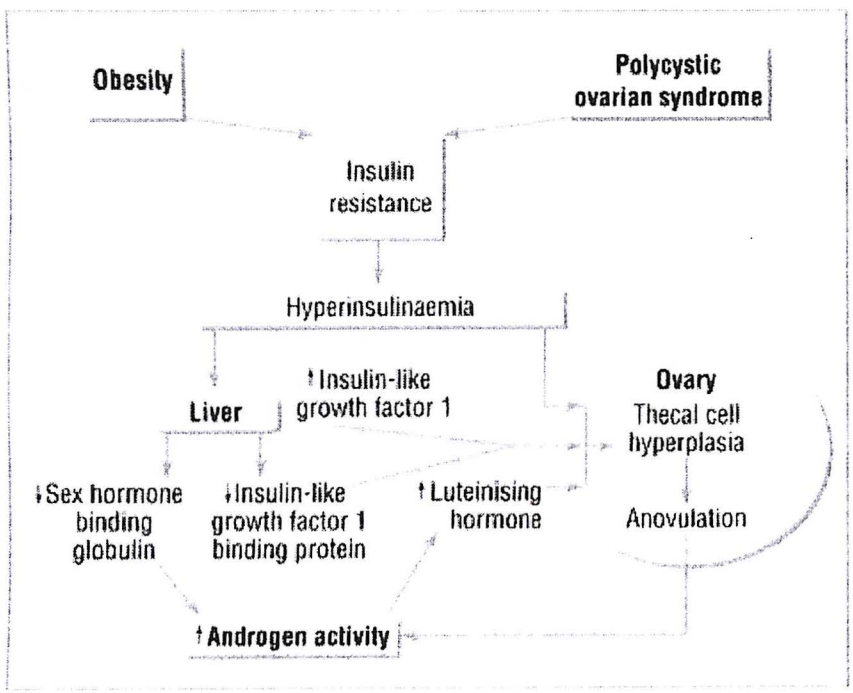

Figure 2.1: Probable mechanisms whereby defects in insulin metabolism promote increased androgen activity at the level of the ovary

Insulin also acts on the liver to inhibit the production of sex hormone binding globulin and insulin-like growth factor 1 binding protein. A reduction in sex hormone binding globulin leads to an increase in the biologically available free testosterone. Thus, insulin

resistance not only increases secretion of ovarian androgens but also promotes an increase in the proportion of free (active) hormone. Similarly, inhibition of production of insulin-like growth factor 1 binding protein results in an increased concentration of circulating free insulin-like growth factor 1, further enhancing ovarian androgen production (Cataldo NA, 1997).

Current consensus suggests that the ovary is the principal site of excess androgen production, but some women with polycystic ovarian syndrome may have an adrenal contribution to the increased androgen production. The mechanisms for this remain obscure and are almost certainly multifactorial (Gonzalez F, 1997).

2.3 Diagnosis of PCOS

It is interesting to note that despite the wide acceptance of the insulin resistance hypothesis in PCOS, it does not feature in past and current diagnostic criteria. Traditionally, there were two schools of thought on the ideal diagnostic criteria for 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 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).

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 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.

2.4 PCOS and infertility

It has been well accepted that the infertility in PCOS patients is caused by anovulation. It is one of the end product 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.

2.5 Methods of restoration of ovulation and fertility

2.5.1 Weight control

As I stated above, infertility in PCOS is more commonly seen in women who are obese or overweight. Weight reduction, as a first line treatment, can be very successful in restarting spontaneous ovulation. Including weight reduction in the treatment of PCOS might be able to restore the ovulation of the patients. Changes in body weight (loss of as little as 5% of the initial weight) have been shown to improve the metabolic and reproductive abnormalities in PCOS. Weight loss also has been associated with improved ovulation and pregnancy rate in women with this syndrome.

Few studies support the benefits of high protein diet for women with PCOS, and there are concerns about the adverse effects that the diets has on renal function and lipid. Although data on the effect of exercise on PCOS is limited, for an obvious reason, it is reasonable to assume that a regular exercise programme would have a positive effect.

However, in women who continue to have problems with ovulation and menstruation but wish to get pregnant, treatment is available. Ranging from fertility drugs to surgery, a variety of options may need to be tried before the pregnancy hopes are realised.

2.5.2 Drug therapy

a. Clomiphene citrate (CC)

There are many ways of inducing ovulation in PCOS patients, among which the use of clomiphene citrate (Clomid, Serophene) is the easiest way and carry the least complications to the patients.

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.

CC is an anti-oestrogen (50–100 mg) which is taken from second to sixth day of a natural or artificially induced bleed. It competes with estradiol for binding to estrogen nuclear receptor protein in a variety of estrogen– dependent tissue including the hypothalamic pituitary axis, ovaries, endometrium and vaginal epithelium. CC is successful in inducing ovulation in over 80% of women while pregnancy occurs in about 40% of them. The prolonged anti– oestrogenic effect of CC on other oestrogen– sensitive tissue in the endometrium and cervical mucus may explain the lower pregnancy rate compared with high successful ovulation rate. CC should only be prescribed in a setting where ultrasound monitoring is available (and performed) in order to minimize the 10% risk of multiple pregnancy and to ensure that ovulation