Alexandria University
Faculty of Medicine
Department of Obstetrics and Gynecology

THE EFFECT OF INTRA-UTERINE INSEMINATION ON PREGNANCY RATE IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME TREATED WITH CLOMIPHENE CITRATE

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Mahmoud Mohamed Rezk Hamoudah

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Presented by
Mahmoud Mohamed Rezk Hamoudah

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Examiner's Committee: Approved

Prof. Dr. Adel Hanafi Al Fazzary ....
Professor of Obstetrics and Gynecology
Department of Obstetrics and Gynecology
Faculty of Medicine
Tanta University

Prof. Dr. Ahmed Abd El Aziz Ismail ....
Professor of Obstetrics and Gynecology
Department of Obstetrics and Gynecology
Faculty of Medicine
Alexandria University

Prof. Dr. Emad Abd Elmonim Darwish ....
Professor of Obstetrics and Gynecology
Department of Obstetrics and Gynecology
Faculty of Medicine
Alexandria University

Date / /

Advisors' Committee — Approved

Prof. Dr. Emad Abd Elmonim Darwish ……..
Professor of Obstetrics and Gynecology
Department of Obstetrics and Gynecology
Faculty of Medicine
Alexandria University

Dr. Ashraf Hany Abdel Rahman ……..
Assistant Professor of Obstetrics and Gynecology
Department of Obstetrics and Gynecology
Faculty of Medicine
Alexandria University

CO-SUPERVISOR

Dr. Yasser Saad El Kassar ……..
Lecturer in Obstetrics and Gynecology
Department of Obstetrics and Gynecology
Faculty of Medicine
Alexandria University

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LIST OF ABBREVIATIONS

AES : Androgen Excess Society.

ASRM : American Society for Reproductive Medicine.

BMI : Body Mass Index.

CC : Clomiphene Citrate.

CVD : Cardiovascular Disease.

DHEA : Dehydroepiandrosterone.

DHEA-S : Dehydroepiandrosterone Sulfate.

DNA : Deoxyribonucleic Acid.

E_1 : Estrone.

E_2 : Estradiol.

ESHRE : European Society for Human Reproduction and Embryology.

FAI : Free Androgen Index.

FSH : Follicle Stimulating Hormone.

GnRH : Gonadotropin Releasing Hormone.

hCG : Human Chorionic Gonadotropin.

IGF-1 : Insulin Growth Factor-1.

IGFBP-1 : Insulin Growth Factor Binding Protein-1.

IR : Insulin Resistance.

IUI : Intrauterine Insemination.

IVF : In Vitro Fertilization

IVF-ET : In Vitro Fertilization- Embryo Transfer.

IVM **:** In Vitro Maturation.

LH **:** Luteinizing Hormone.

LOD : Laparoscopic Ovarian Drilling.

NICHD **:** National Institute of Child Health and Human Development.

NIH **:** National Institute of Health.

OHSS **:** Ovarian Hyper- Stimulation Syndrome.

OI **:** Ovulation Induction.

OPKs **:** Ovulation Predictor Kits.

PCO **:** Polycystic Ovary.

PCOS **:** Polycystic Ovary Syndrome.

PRL **:** Prolactin.

SHBG **:** Sex Hormone Binding Globulin.

TIC **:** Timed Intercourse.

TVS **:** Trans-Vaginal Ultrasonography.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders. PCOS is a complex, heterogeneous disorder of uncertain etiology. Both genes and the environment contribute to PCOS. Obesity, exacerbated by poor dietary choices and physical inactivity, worsens PCOS in susceptible individuals.[1]

PCOS produces symptoms in approximately 5% to 10% of women of reproductive age (12–45 years old). It is thought to be one of the leading causes of female subfertility[2]and the most frequent endocrine problem in women of reproductive age.[3]

The cardinal features are hyperandrogenism, ovulatory dysfunction and/or ultrasonographic polycystic ovarian (PCO) appearance. Three major diagnostic criteria for PCO have been proposed by the National Institute of Health (NIH 1990), the Rotterdam European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine sponsored PCOS Consensus Workshop Group (ESHRE/ASRM 2003) and the recent task force of the Androgen Excess Society (AES 2006). The PCO appearance is not a prerequisite in American criteria for the diagnosis of PCOS.[4]

Although an elevated LH value in the presence of low or low normal FSH may be diagnostic, the diagnosis is easily made by clinical presentation alone. About 20-40 % of patients with the condition do not have reversal of LH/FSH ratio, so it is not suggested to routinely measure FSH and LH levels in an-ovulatory patients.[5]

Causes

There is strong evidence that there is a genetic component in many cases. Such evidence includes the familial clustering of cases, greater concordance in monozygotic compared with dizygotic twins and heritability of endocrine and metabolic features of PCOS.[6]

The genetic component appears to be inherited in an autosomal dominant fashion with high genetic penetrance but variable expressivity in females, this means that each child has a 50% chance of inheriting the predisposing genetic variant(s) from a parent, and if a daughter receives the variant(s), then the daughter will have the disease to some extent.[7-9]

The genetic variant(s) can be inherited from either the father or the mother, and can be passed along to both sons (who may be asymptomatic carriers or may have symptoms such as early baldness and/or excessive hair) and daughters, who will show signs of PCOS.[8]The allele appears to manifest itself at least partially via heightened androgen levels secreted by ovarian follicle theca cells from women with the allele.[9] The exact gene affected has not yet been identified.[6, 7, 10]

The clinical severity of PCOS symptoms appears to be largely determined by factors such as obesity.[3, 6]

Table (1): Clinical signs and symptoms associated with PCOS[11]

Symptom	Frequency
Oligomenorrhea	29-52%
Amenorrhea	19-51%
Hirsutism	64-69%
Obesity	35-41%
Acne	27-35%
Alopecia	3-6%
Acanthosis nigricans	<1-3%
Infertility	20-74%
Elevated Serum LH	40-51%
Elevated testosterone	29-50%

In 2003 in Rotterdam, Netherlands, a consensus meeting between the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) redefined PCOS. Affected individuals must have two out of the following three criteria: (1) oligo-ovulation or anovulation, (2) hyperandrogenism (clinical and/or biochemical) and (3) polycystic ovaries on sonographic examination.[4]

Common symptoms of PCOS include:

- Menstrual disorders: PCOS mostly produces oligomenorrhea or amenorrhea, but other types of menstrual disorders may also occur.[3]
- Infertility: This generally results directly from chronic anovulation.[3]
- High levels of masculinizing hormones: The most common signs are acne and hirsutism (male pattern of hair growth), but it may produce hyper menorrhea (very frequent menstrual periods) or other symptoms.[3, 12] Approximately three-quarters of patients with PCOS (by the diagnostic criteria of NIH/NICHD 1990) have evidence of hyperandrogenemia.[13]
- Metabolic syndrome: This appears as a tendency towards central obesity and other symptoms associated with insulin resistance.[3]
- Serum insulin, insulin resistance and homocysteine levels are higher in women with PCOS.[14]

Pathogenesis

Polycystic ovaries develop when the ovaries are stimulated to produce excessive amounts of male hormones (androgens), particularly testosterone, by either one or a combination of the following (almost certainly combined with genetic susceptibility):

- The release of excessive luteinizing hormone (LH) by the anterior pituitary gland.

- Through high levels of insulin in the blood (hyperinsulinaemia) in women whose ovaries are sensitive to this stimulus.[9]

Alternatively or as well, reduced levels of sex-hormone binding globulin can result in increased free androgens.[13]

The syndrome acquired its most widely used name due to the common sign on ultrasound examination of multiple (poly) ovarian cysts. These "cysts" are actually immature follicles, not cysts ("polyfollicular ovary syndrome" would have been a more accurate name). The follicles have developed from primordial follicles, but the development has stopped (arrested) at an early antral stage due to the disturbed ovarian function. The follicles may be oriented along the ovarian periphery, appearing as a 'string of pearls' on ultrasound examination. There is also an increase in volume of ovary, especially due to increase in stroma.[15]

A majority of patients with PCOS have insulin resistance and/or are obese. Their elevated insulin levels contribute to or cause the abnormalities seen in the hypothalamic-pituitary-ovarian axis that lead to PCOS. Hyperinsulinemia increases GnRH pulse frequency, LH over FSH dominance, increased ovarian androgen production, decreased follicular maturation, and decreased SHBG.[12]All these steps contribute to the development of PCOS. Insulin resistance is a common finding among patients of normal weight as well as overweight patients.[3, 14]

PCOS may be associated with chronic inflammation,[16]with several investigators correlating inflammatory mediators with anovulation and other PCOS symptoms.[17, 18]

It has previously been suggested that the excessive androgen production in PCOS could be caused by a decreased serum level of IGFBP-1, in turn increasing the level of free IGF-I which stimulates ovarian androgen production, but recent data concludes this mechanism to be unlikely.[19]

Diagnosis

Rotterdam criteria:

An internationally accepted definition was been adopted in 2003 by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine, known as the ESHRE/ASRM Rotterdam consensus. It required the presence of two of the following three diagnostic criteria: [1] oligo-ovulation or anovulation, [2] clinical or biochemical evidence of hyperandrogenism and [3] the presence of polycystic ovarian morphology.[4]

Polycystic ovarian morphology is seen on ultrasound in approximately 22% of women with a prevelance of up to 10%.[4]

Ultrasound diagnosis of PCOS:

At a joint ESHRE /ASRM consensus meeting, a refined definition of the PCOS was agreed, encompassing a description of the morphology of the polycystic ovary (PCO). According to the available literature, the criteria fulfilling sufficient specificity and sensitivity to define the PCO should have at least one of the following: either 9 or more

follicles measuring 3-8 mm in diameter, or increased ovarian volume (>10 cm^3) (Figure 1, 2 and 3). [20]If there is a follicle > 10 mm in diameter, the scan should be repeated at time of ovarian quiescence in order to calculate volume and area. The presence of unilateral PCO (in only one ovary) is sufficient to provide the diagnosis. The distribution of follicles and a description of the stroma are not required in the diagnosis. Increased stromal echogenicity and/or stromal volume are specific to PCO, but it has been shown that the measurement of ovarian volume is a good surrogate for quantification of the stroma in clinical practice. A woman having PCO in the absence of an ovulation disorder or hyperandrogenism (asymptomatic PCO) should not be considered as having PCOS, until more is known about this situation. Three-dimensional and Doppler ultrasound studies may be useful research tools but are not required in the definition of PCO.[20-23]

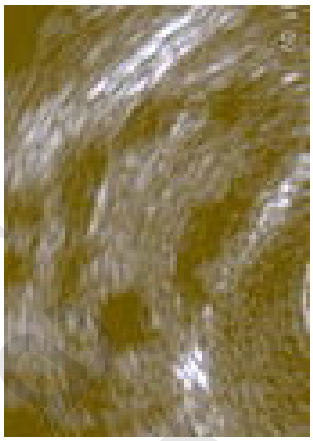


Figure (1): Polycystic Ovary as seen on Sonography

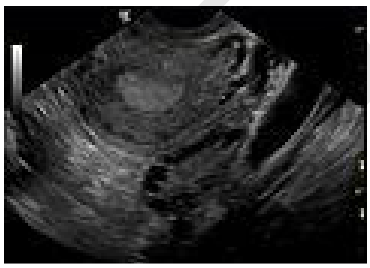


Figure (2): Transvaginal ultrasound scan of polycystic ovary

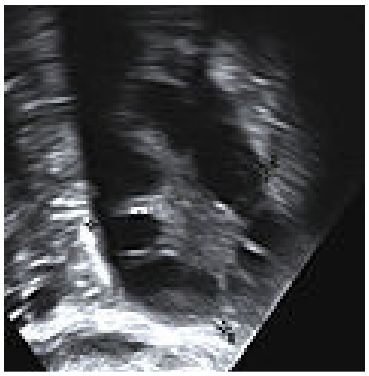


Figure (3): Polycystic Ovary as seen on Sonography

Serum hormone levels

Abnormal LH/FSH ratio is the main issue in the continuation of an-ovulatory state in PCOS subjects. Increased LH and decreased or normal FSH are due to (a) GnRH pulsatile secretion i.e. at hypothalamic level. (b) High estrogen environment i.e. at pituitary level.[24] In PCOS, clinically intense androgenization due to excess androgen production is observed. Hyperandrogenemia induces the increase in testosterone, androstenedione, dehydroepiandrosterone (DHEA), DHEA-S, 17-hydroxyprogesterone and estrone (E_1) (excess androgen converted to E_1 by peripheral fat). Decrease in the sex hormone binding protein in the liver increases in insulin response in the ovary and the effect of high LH induces the increase in androgen secretion in the ovary. After that, follicle growth and maturation are suppressed.[4, 25]

In PCOS patients, excessive androgen secretion results in increased estrogen precursors in granulosa cells. In these patients, luteinizing hormone receptors, in the presence of hyperinsulinemia, appear earlier in granulosa cells, causing activation of aromatase in these cells. This phenomenon results in increased estrogen production, with positive feedback on luteinizing hormone and negative feedback on follicle-stimulating hormone (FSH), and ultimately disruption of folliculogenesis.[26]

Differential diagnosis

Other causes of irregular or absent menstruation and hirsutism, such as hypothyroidism, congenital adrenal hyperplasia (21-hydroxylase deficiency), Cushing's syndrome, hyperprolactinemia, androgen secreting neoplasms and other pituitary or adrenal disorders should be investigated.[4]

Ovulation prediction

Ovulation may be predicted by the use of urine tests that detect the pre-ovulatory LH surge, called ovulation predictor kits (OPKs). However, OPKs are not always accurate when testing on women with PCOS. Charting of cervical mucus may also be used to predict ovulation, or certain fertility monitors (those that track urinary hormones or changes in saliva) may be used. Methods that predict ovulation may be used to time intercourse or insemination appropriately.[27]

While not useful for predicting ovulation, basal body temperatures may be used to confirm ovulation. Ovulation may also be confirmed by testing for serum progesterone in mid-luteal phase approximately seven days after ovulation (if ovulation occurred on the average cycle day fourteen, seven days later would be cycle day 21). A mid-luteal phase progesterone test may also be used to diagnose luteal phase defect. Methods that confirm ovulation may be used to evaluate the effectiveness of treatments to stimulate ovulation.[28]

Management

Management of infertility in polycystic ovary syndrome includes lifestyle modification as well as assisted reproductive technology such as ovulation induction, oocyte release triggering and surgery.

Lifestyle modification

Obese women with PCOS are more likely than thin women with PCOS to suffer from anovulation.[29] This effect on ovulation may be secondary to insulin resistance, which in turn results in hyperinsulinemia and stimulation of excess androgen production from the ovaries. Intra-ovarian hyper-androgenism in turn inhibits follicular maturation.[30]

It is well documented that modest weight loss (5-14%) via energy restriction improves CVD risk factors, hormonal profile and reproductive function in overweight and obese women with PCOS. Also improvements in menstrual cyclicity, ovulation and fertility, [31-35]reductions in abdominal fat, blood glucose, blood lipids, IR, testosterone levels and free androgen index (FAI)[32-34] and increases in sex-hormone binding globulin (SHBG). [32]Studies have also shown improved self-esteem, depression and anxiety in obese infertile women including those with PCOS following lifestyle modification and/or energy restriction.[31, 35-37]

In women with PCOS, reduction in insulin concentration is considered the primary determinant of most reproductive weight loss benefits, [38]while metabolic improvements are primarily associated with reductions in abdominal fat.[32]

Palomba *et al*. reported that 24 weeks of dieting or exercise improved menstrual cyclicity and ovulation in overweight women with PCOS.[39]

Some Studies also showed that overweight women are less likely to respond to pharmacologic ovulation induction methods.[40]

For obese PCOS patients (BMI $\geq$25 kg/m^2), weight loss and exercise are recommended as a first option. Norman et al. demonstrated that lifestyle modification led to increased insulin sensitivity and resulted in improved ovulation and fertility in obese women with PCOS.[38]This approach of lifestyle modification, which includes weight-reducing diet and exercise, should be the first step in the management of them.[35] Increase in physical activity and loss of at least 10 % of body weight are given in the form of lifestyle modification. Weight reduction causes spontaneous ovulation and dose of stimulation of ovulation is reduced.[41]Lifestyle management should also be used as the primary therapy in overweight and obese women with PCOS for the treatment of metabolic complications.[42]

The combination of exercise and dieting has been extensively reported to increase weight loss compared with dieting or exercise alone.[43]

Ovulation induction

For those who after weight loss still are an-ovulatory or for an-ovulatory lean women, ovulation induction to reverse the anovulation is the principal treatment used to help infertility in PCOS. Clomiphene citrate is the main medication used for this purpose, and is the first-line treatment in sub-fertile an-ovulatory patients with PCOS. Gonadotrophins such as follicle-stimulating hormone (FSH) are, in addition to surgery, second-line treatments. Aromatase inhibitors show promising results.[44]

Clomiphene citrate (CC) is the standard drug used for ovulation induction in women with PCOS.[45, 46] Successful ovulation is achieved in 70–85 % of them and 40–50 % will conceive.[47]Non-obese patients or those obese women who do not ovulate after lifestyle changes are submitted to ovulation induction therapy with CC. CC is anti-estrogenic and it binds with estrogen receptors causing decreased concentration of receptors. So activation of GnRH, increase in FSH and/or LH and growth of the dominant follicle occurs.[24]

Previously considered an anti-estrogen, clomiphene citrate recently was reclassified as a selective estrogen receptor modulator.[48]It is known to be both an estrogen agonist and antagonist, however, its agonist properties manifest only when endogenous estrogen levels are extremely low. In general, its antagonistic effects prevail. Clomiphene citrate administration leads to depletion of estrogen receptors at the level of the pituitary and hypothalamus, interrupting the negative feedback that estrogen normally produces. As a result, GnRH secretion is improved and stimulates pituitary production of follicle-stimulating hormone (FSH), which in turn drives follicular growth and maturation with emergence of one or more dominant follicles.[49]

Many clinicians use doses up to 150 mg and some even up to 250 mg per day for 5 days (commencing between day 2 and 5 of menses), taking into account that alternative treatments such as gonadotropins are more costly and have greater risk.[50]

All cycles of CC should be monitored by ultrasound. To prevent ovarian hyper-stimulation syndrome (OHSS), we should have control over the growing follicle and E_2 levels. Hyperandrogenism and obesity affect the CC response adversely. Failure to ovulate within 3 months of use of CC 150 mg/day for 5 days is called CC resistance, and 20 % of PCOS patients will be CC resistant.[24]

In CC resistant PCOS patients with hirsutism and high androgen concentrations, the combination of dexamethasone and CC is effective, because dexamethasone reduces the levels of androgens.[51] In CC resistant PCOS patients with galactorrhea or hyperprolactinemia, both CC and dopamine agonists should be used.[52]

Common indicators of an ovulatory response are a biphasic pattern on basal body temperature charting and a serum progesterone measurement in the mid-luteal phase of >10 nmol/L if tested 6 to 8 days before the onset of menses. However, in some circumstances, detection of the pre-ovulatory LH surge with urinary kits, and ovarian follicle and endometrial assessment with transvaginal ultrasound during the late follicular phase can be useful. If ovulation cannot be achieved with CC, the patient should be offered further options.[53]

Although 60-85% of patients will ovulate on CC, only about one half will conceive.[46] Approximately 50% of conceptions will occur on 50 mg, with another 20-25% and 10% occurring on 100 mg and 150 mg respectively.[54]

The discrepancy between ovulation and pregnancy rates may be partly explained by the peripheral antiestrogenic effects of CC at the level of the endometrium and cervical mucus or by hypersecretion of LH.[55]

In one study, no pregnancies occurred when the endometrium was < 6 mm at mid-cycle,[56] but others have not found a similar association.[57] Alternatives for ovulation

induction should be considered if the pre-ovulatory endometrium is persistently thin on CC therapy. Similarly, if pregnancy does not occur within 6 ovulatory cycles, another ovulation induction method should be considered.[57]

Combination of metformin and clomiphene citrate (CC) for PCOS with insulin resistance

Numerous articles have been published where insulin sensitizers such as biguanides (metformin)[58, 59] and thiazolidinediones (troglitazone)[60]have been used and proven to improve metabolic abnormalities in PCOS patients. Metformin declines the peripheral glucose level without interfering with pancreatic β-cell function by inhibiting hepatic gluconeogenesis and increasing insulin receptor affinity.[24]Metformin reduces levels of LH, hyperinsulinemia and decrease ovarian levels of androgen.[61] Hyperinsulinemic and hyperandrogenic PCOS patients with thecal hyperplasia are best down regulated with metformin. Several trials were prospective double-blind placebo controlled.[62-65] Each of those trials randomized metformin with placebo in the CC-resistant patient. In one trial there was no difference in the outcome.[64] The other trials had a statistically significant improvement when metformin was added to CC in the CC-resistant patients. Kurabayashi et al. also reported that combination of metformin and CC could improve ovulation rates in CC-resistant infertile Japanese women with PCOS in spite of no effect of metformin treatment alone.[66]Therefore, obese CC-resistant PCOS patients who have impaired glucose tolerance or insulin resistance are treated with a combination of metformin and CC.[67]

Inefficacy of metformin

Previously, metformin was a recommended treatment for anovulation. A systematic review and meta-analysis in 2012 concluded that there is insufficient evidence to establish a difference between metformin and clomiphene citrate in terms of ovulation, pregnancy, live birth, miscarriage and multiple pregnancy rates in women with PCOS and a BMI less than 32 kg/m^2. It emphasized that a lack of superiority of one treatment is not evidence for equivalence.[68]

Another review in 2013 concluded that metformin improves pregnancy rates in women with PCOS when compared with placebo and in addition to clomiphene compared with clomiphene alone. Also, however, it concluded that metformin does not improve live birth rates whether used alone or in combination with clomiphene. It therefore concluded that the benefit of metformin in the improvement of reproductive outcomes in women with PCOS is limited.[69]

The ESHRE/ASRM-sponsored Consensus workshop does not recommend metformin for ovulation stimulation.[27]Subsequent randomized studies have confirmed the lack of evidence for adding metformin to clomiphene.[70]

Gonadotropins

Use of intramuscular gonadotropins began in the 1960s. These preparations, from the purified urine of postmenopausal women, contained both FSH and LH. Over the last decade recombinant human FSH has been the main preparation and it can be self-

administered subcutaneously. Gonadotropins are used when PCOS patients fail either to ovulate or to conceive with oral ovulation induction medications.[71]

Injectable gonadotropins are very expensive and require frequent monitoring with serum estradiol and ultrasound assessments to minimize the risks of excessive follicular growth and development. Because of the high number of antral follicles in women with PCOS, it is not uncommon that treatment is cancelled to minimize the occurrence of multiple pregnancies and also of ovarian hyper stimulation syndrome.[72]Pregnancy rates with gonadotropins are 20% to 25% per cycle.[71]

Aromatase Inhibitors

Aromatase inhibitors have been used for the last decade as adjuvant treatment in breast cancer. They block the conversion of testosterone and androstenedione to estradiol and estrone, respectively, and hence inhibit the estrogen-negative feedback mechanism on the hypothalamic–pituitary axis. This leads to increased gonadotropin secretion, which in turn leads to ovarian follicular growth and development. [73]

The use of aromatase inhibitors in ovulation induction was first introduced in 2001.[74] Ovulation and pregnancy rates with aromatase inhibitors such as letrozole and anastrozole appear to be promising and these agents appear to have less anti-estrogen effect on the endometrium, but the evidence on endometrial effects is conflicting, and most studies show equivalence with clomiphene citrate. [73-76]

In vitro fertilization

If ovulation induction is unsuccessful or conception cannot be accomplished as mentioned above, IVF-ET treatment is indicated. PCOS has been associated with various negative effects on ovulation induction and IVF-ET outcomes.[77, 78]

During ovarian stimulation for IVF-ET, the low-dose step-up regimens of pure FSH preparation are used for women with PCOS to prevent adverse effects.[79]In high OHSS-risk patients, systematic embryo freezing and subsequent frozen embryo transfer cycles are recommended.[80]

Pregnancy rates can approach 40% to 50% per cycle with IVF, but, as with fertility in general, success is significantly influenced by the women's age. PCOS patients achieve pregnancy and live birth rates similar to those of non-PCOS patients during conventional IVF cycles.[71]

Surgery

Surgery can be attempted in case of inefficient result with medications for ovulation induction. Though surgery is not commonly performed, the polycystic ovaries can be treated with a laparoscopic procedure called "ovarian drilling" (puncture of 4-10 small points with electro cautery), which often results in either resumption of spontaneous ovulations or ovulations after adjuvant treatment with clomiphene citrate or FSH.[44]

LOD is indicated in clomiphene resistant cases and as adjuvant therapy before gonadotropin treatment.[81]LOD is an effective procedure in properly selected cases, because drilling appears to be equally effective with lesser chances of multiple

pregnancies.[81, 82] In LOD treatment, high success pregnancy rates of around 60 % are expected after treatment within 6 months of time with a low risk of adverse effects in PCOS, and peak pregnancy rate is seen around 6–9 months after surgery.[83]

Prognosis

PCOS increases the time to pregnancy but does not necessarily reduce the family size. It doesn't appear to increase miscarriage frequency.[44]

With the advance of assisted reproductive technology, a combination of ovulation induction with intrauterine insemination (IUI) has achieved great success in the treatment of infertility. However, the pregnancy rate remains still unstable and depends on the condition of each individual case. To select the appropriate time window for IUI, the common way is to utilize the natural cycle or ovulation induction and monitor the follicular phase. Cycle stimulated or non-cycle-stimulated IUI is considered as the first-line treatment for infertility caused by common etiological factors, including asthenozoospermia, semen abnormal liquefaction, sexual dysfunction, abnormal secretion of the female cervical mucus, and immunological complication.[84, 85]

Intrauterine insemination

Intrauterine insemination (IUI) is the first therapeutic step in assisted reproductive techniques, and is especially appropriate for cases with mild male factor infertility, anovulation, endometriosis with at least one patent tube, and unexplained infertility.[86]

Among the assisted reproductive techniques, IUI is considered a first-line procedure due to its simplicity, easy management, low cost and absence of potentially serious complications. Although the literature reports several factors affecting the likelihood of pregnancy after IUI, among them, age, body mass index (BMI), female etiology, and semen quality, there is little consensus regarding the extent to which these factors affect the likelihood of pregnancy.[87-89]

The more realistic first-line approach of intrauterine insemination (IUI) is proposed when at least one million normal spermatozoa are present,[90] given that this is a more cost-effective method that offers the same likelihood of successful pregnancy as IVF.[91]

The semen collection is strongly recommended after an abstinence period of 3-5 days to maximize the conception rate. A sterile container (non-toxic for the spermatozoa) will be used and the collection of the semen will occur in a private room very close to the laboratory.[92, 93]

Several available sperm separation methods include simple washing, sperm migration into culture medium (swim-up), Sephadex and glass wool columns and density gradient centrifugation.[94]

Renewed interest in IUI is definitely the result of better washing procedures, enhancing the quality of the initial sperm sample. These washing procedures are necessary to remove prostaglandins, infectious agents, antigenic proteins, non-motile spermatozoa, leukocytes and immature germ cells. Current techniques of sperm preparation for IUI such as swim-up and density gradient require the use of centrifugation to separate the sperm

from the seminal plasma. This processing technique provides better sperm quality regarding concentration and motility which may lead to higher success rates after IUI.[95]

All of these techniques are capable of effectively separating sperm from the seminal plasma, but to a varying degree. Recovery rates, motility, morphology and degree of DNA damage vary greatly between procedures.[96]

The methodology of this conventional swim-up is based on the active movement of spermatozoa from the pre- washed cell pellet into an overlaying medium. A yield of very high percentage (>90%) of motile morphologically normal spermatozoa can be obtained with the help of this technique.[97]

In an attempt to improve the sperm yield in oligozoospermic males the "swim-up" can be performed directly from the liquefied semen avoiding the centrifugation and multiple washing steps. During this procedure, several aliquots of liquefied semen are taken from a sample and placed in tubes underneath an overlay of culture medium. Round-bottom tubes or 4-well dishes should be used to optimize the surface area of the interface between the semen layer and the culture medium. The tubes may also be prepared by gently layering culture medium over the liquefied semen. A maximum recovery is obtained by using multiple tubes with small volumes of semen per tube, thus maximizing the combined total interface area between semen and culture medium.[98]

In 1999, it has been shown that the swim-up sperm separation may improve some of the sperm chromatin structure assay–related parameters.[99] Also in 2001, it has been reported that the swim up method does not induce sperm DNA damage.[100]

Patients with PCOS who failed to achieve pregnancy can be treated with Assisted Reproductive Technology. Ovulation induction (OI) with or without intrauterine insemination (IUI) were widely used in managing PCOS related infertility. However, controversies still remain on the issue of the optimal OI plans. In traditional OI protocols, clomiphene citrate (CC) was used as first line agent. In addition, progesterone-induced endometrial withdrawal bleeding before administration with CC is recommended by The American Society of Reproductive Medicine Practice Guidelines.[101]

AIM OF THE WORK

The aim of this work is to study the effect of induction of ovulation with clomiphene citrate and hCG in patients with PCOS with intrauterine insemination compared to timed intercourse.

MATERIAL AND METHODS

The study was conducted upon 60 anovulatory PCOS infertile women defined according to Rotterdam consensus,[4] who were attending El Shatby Infertility Unit, Alexandria faculty of Medicine, Egypt by two out of the following three criteria:

- Oligo- or anovulation.
- Clinical and/or biochemical signs of hyperandrogenism.
- Polycystic appearance of both ovaries on sonographic examination.

The inclusion criteria:

- PCOS infertile women.
- Age group: 18-35 years.
- Occurrence of ovulation in response to previous induction by clomiphene citrate provided that it was more than three months ago.

The exclusion criteria:

- Tubal or uterine factors.
- Male factor infertility.
- History of ovulation induction treatment within the past three months.

All patients were submitted to the following:

1- Informed consent before inclusion in the trial, after the study was approved by the Alexandria University Hospital Research Ethics Committee
2- Estimation of serum prolactin, basal estradiol, basal LH and basal FSH levels (day 2 or 3 after spontaneous or progestin induced cycles).
3- All women received clomiphene citrate (Clomid ^{R}; Global Napi Pharmaceuticals, Cairo, Egypt) 100 mg. / day for 5 days starting from the third day of the menstrual cycle. In the next cycle, the dose was adjusted according to patient's response with a maximal dose 150 mg./ day.
4- Follow up by vaginal ultrasonography was done on days 10, 12 and 14 of the menstrual cycle.
5- HCG (Choriomon; IBSA, Lugano, Switzerland) was given when a leading follicle reached at least 18 mm. in diameter.
6- Patients were randomly allocated into two groups.

The first group was subjected to timed intercourse (TIC) 40-48 hours after hCG administration.

The second group was subjected to intrauterine insemination (IUI) 40-48 hours after hCG administration plus intercourse within the same day.

In IUI group, semen was obtained by masturbation after three to five days of abstinence.

After liquefaction, the ejaculate was placed in 10 ml of warmed (37◦C)Ham's F-10 (Sigma, AldrichChemie, GmbH, Steinheim, Germany) and centrifuged at 1000×*g* for 5

minutes. The supernatant was then discarded and the pellet re-suspended in approximately 500 μl clean sterile medium (swim up technique). Swim up as a procedure is associated with satisfactory IUI outcomes, comparable to density gradient and centrifugation techniques.[9, 10]

A single intrauterine insemination was performed using a flexible intrauterine cannula (Gynetics Medical Products N.V. Harmont, Achel, Belgium) in which the cervix was exposed with a bivalve speculum, the mucus was removed with a cotton swab, and the tip of the catheter was gently introduced into the uterus until it lay about 0.5cm from the top of the uterine cavity in the fundal region. The in vitro-prepared sperm was expelled gently and the catheter subsequently withdrawn.

After insemination, the patient was asked to rest for a short period of time (10-15 minutes) following insemination.

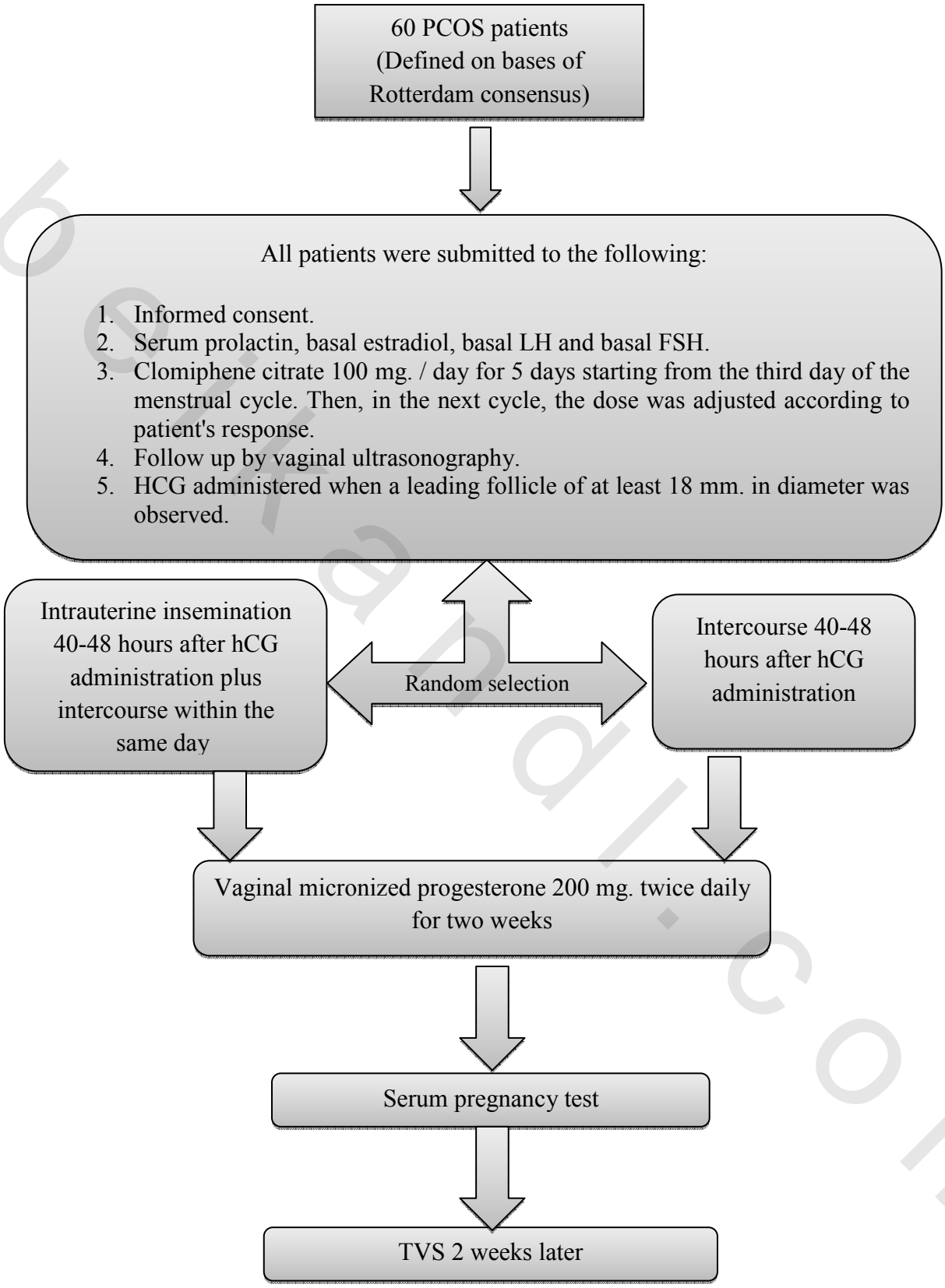
Luteal phase support for the two groups by administration of vaginal micronized progesterone 200 mg. (Prontogest 200; IBSA, Lugano, Switzerland) has been used twice daily for two weeks.

Serum pregnancy test was done two weeks after IUI or timed intercourse.

Chemical pregnancy was considered to have occurred when serum β- hCG was 50 mIU/ml or more 2 weeks after either IUI or TIC.

Trans-vaginal ultrasonography (TVS) was done two weeks later to confirm clinical pregnancy.

Materials and methods are summarized in the following diagram.



RESULTS

A total of 60 couples met the criteria of PCOS with a normal semen analysis were included. Thirty (30) couples were studied by CC and IUI and the other thirty (30) couples were studied by CC and TIC.

There were no statistically significant differences between the two groups as regards age, duration of infertility, type of infertility and body mass index as shown in Table (2).

Table (2): Patient Demographic Data.

	CC/IUI group (n 30)	**CC/TIC group (n 30)**	**p-value**
Age	26.0 ± 3.9	25.3 ± 4.5	0.260
Type of infertility Primary Secondary Relative	 21 (70.00%) 4 (13.33%) 5 (16.66%)	 20 (66.67%) 9 (30.00%) 1 (3.33%)	0.099
Period of infertility	4.1 ± 2.2	3.3 ± 2.4	0.100
BMI	27.07+2.92	27.47+2.58	0.285

Values are mean ±SD or numbers (percentages) of women.
None of the differences was statistically significant (p>0.05).

There were no statistically significant differences between the two groups regarding basal FSH, basal LH, basal E_2 and prolactin levels as shown in table (3) and figure (4).

Table (3): Hormonal Levels.

	CC/IUI group (n 30)	**CC/TIC group (n 30)**	**p-value**
Basal FSH	5.2 ± 1.4	5.7 ± 2.0	0.126
Basal LH	6.64 ± 2.96	7.1 ± 3.3	0.197
Basal E_2	40.11 ± 9.03	38.43± 7.65	0.098
PRL	13.9 ± 6.6	13.8 ± 6.0	0.466

Values are mean ±SD or numbers (percentages) of women.
None of the differences was statistically significant (p>0.05).

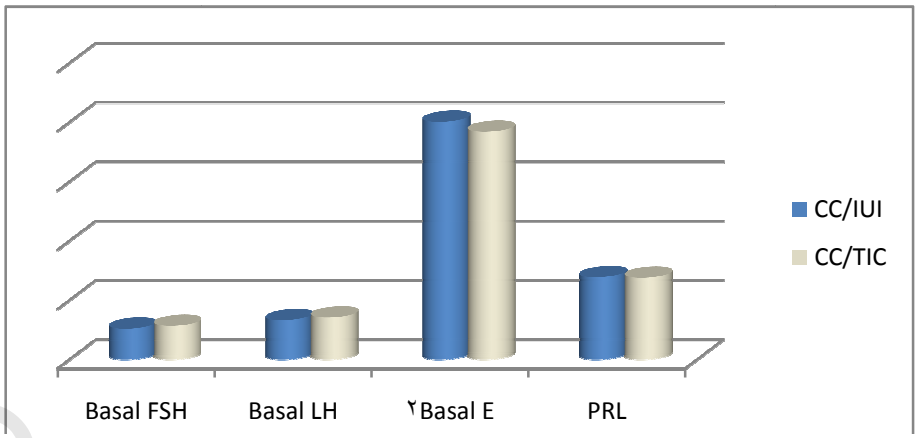


Figure (4): Comparison between the two studied groups regarding hormonal levels.

There was no significant difference between the two groups regarding the clinical pregnancy rate. The pregnancy rate was 16.67% (5 pregnant cases) in CC/IUI group and 13.33% (4 pregnant cases) in CC/TIC group; this difference was not statistically significant (p-value 0.821), (Figure 5).

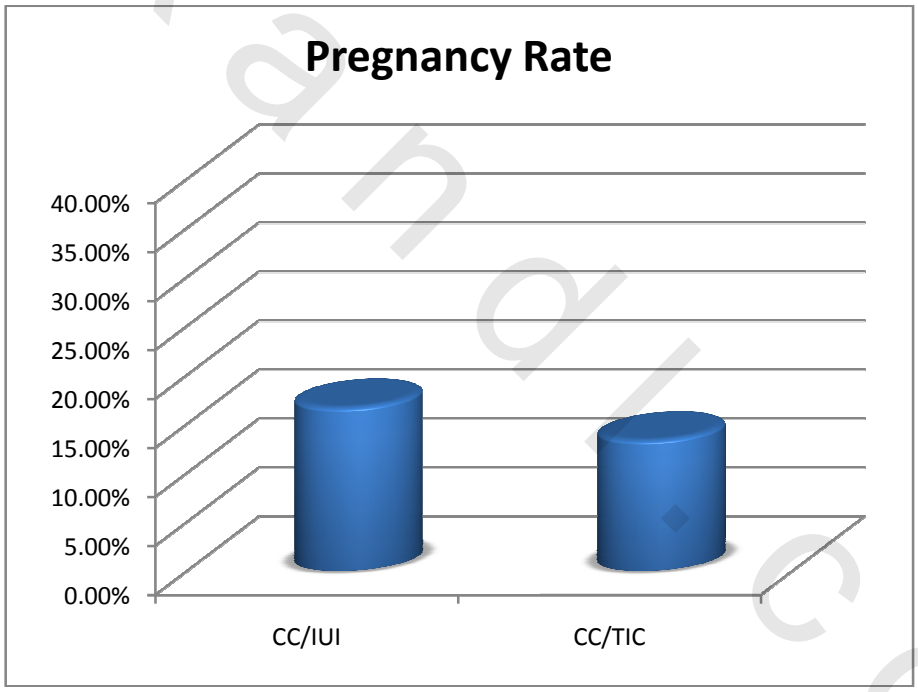


Figure (5): Comparison between the two studied groups as regarding pregnancy rate.

DISCUSSION

PCOS is a common endocrine disorder in women of childbearing age (6.8%).[3] Several medications and regimens have been used for induction of ovulation in PCOS, but none has had a significant outcome. Examples of such treatments include clomiphene citrate, letrozole, metformin, gonadotropins, gonadotrophin-releasing hormone agonists, cauterization, wedge resection of the ovaries and assisted reproductive technology.[102-104]

Clomiphene is still considered to be a first-line treatment for induction of ovulation in PCOS, [105, 106] and can cause ovulation in 73%–80% of cases.[67, 106]

Generally, women with a high body mass index, amenorrhea, severe hyper-androgenemia, and insulin-resistance are resistant to clomiphene.[107]

It is frustrating that the restoration of ovulation by CC does not produce a much higher pregnancy rate, as only 50% of those who ovulate will conceive.[11] This may be explained by the peripheral anti-estrogenic effects of CC at the level of the endometrium and cervical mucus.[55, 56, 108]The rational of using IUI is to enhance the pregnancy rate by increasing the number of motile sperms to reach the oocyte. In the past, IUI has been used as a treatment for couples with poor post coital tests by bypassing the hostile mucus of the cervix.[109]

However, the main cause of infertility in women with PCOS is ovulatory disorder and the treatment is induction of ovulation.[110] It appears reasonable to combine induction of ovulation with IUI in women with PCOS specially if associated with male factor but here we were interested in assessing the benefits of adding IUI to couples with normal semen analysis. We questioned the value of IUI in those couples. The first randomized trial comparing the addition of IUI to CC in women with PCOS and normal semen analysis was reported recently.[111]

In some women, CC blocks endometrial estrogen receptors and suppresses pinopode formation, both essential for implantation, to such an extent that implantation may be impeded. This suppression of endometrial proliferation is a non-dose-dependent, idiosyncratic action that recurs in repeated cycles in the same woman. It indicates a poor prognosis for conception if the endometrial thickness on ultrasound scanning does not reach 8mm at ovulation.[55, 112]

In the present study, a timed vaginal intercourse or intrauterine insemination was carried out 40-48 hours after hCG injection when the leading follicle reaches 18 mm in diameter or more. The semen was prepared utilizing a swim up technique, isolating the most motile spermatozoa prior to insemination. A systematic review and a recent meta-analysis reported that double IUI offers no clear benefit for the overall clinical pregnancy rate in stimulated cycles for sub-fertile couples.[113, 114] Furthermore, there is insufficient evidence for recommending any specific semen preparation technique.[115]

Also, a recent Cochrane review showed no significant differences between the different timing methods for IUI, including hCG administration (urinary or recombinant), detection of LH surge and GnRH agonist administration.[116]

Theoretically speaking, performing IUI could overcome the depression of the cervical mucus. In the present study, with 30 PCOS infertile patients who were managed by CC/IUI, we found five (5) pregnant cases with a clinical pregnancy rate about 16.67%. Custers et al. agreed with our results as they reported a 5–7% pregnancy rate per cycle following CC/IUI, even after seven cycles. So, performing IUI did not translate into significantly higher clinical pregnancy rates.[117]

Our findings matched that reported by Abu-Hashim H et al. who worked upon 93 infertile PCOS patients with CC/IUI over 259 cycles of which 135 cycles were ovulatory and reported 22 pregnant cases with a clinical pregnancy rate about 16.3% per ovulatory cycles, about 8.49% pregnancy rate per cycle (22 pregnant cases over 259 cycles) and 23.6% pregnancy rate per woman.[111]

Wiser A et al. also agreed with our study. They studied CC/IUI in 53 PCOS infertile patients and reported 4 pregnant cases with a clinical pregnancy rate about 7.5%.[118]

TIC is the usual control treatment in trials of IUI. This choice appears to be founded on a belief that a credible comparison of IUI with intercourse requires that intercourse should be timed in a manner similar to the timing of IUI.[119]

As regard to CC/TIC in our study, we studied 30 PCOS infertile patients that resulted into four (4) pregnant cases with the pregnancy rate about 13.33%. We agreed with Badawy et al. who reported 17.9% pregnancy rate with 438 women (1063 cycles) using CC and timed intercourse.[120]

Our findings matched that reported by Abu-Hashim H et al. who worked upon 95 infertile PCOS patients by CC/TIC over 266 cycles of which 137 cycles were ovulatory and reported 21 pregnant cases with a clinical pregnancy rate about 15.3% per ovulatory cycles, about 7.89% pregnancy rate per cycle (21 pregnant cases over 266 cycles) and about 22.1% pregnancy rate per woman.[111]

Wiser A et al. also agreed with our study. They studied CC/TIC in 85 PCOS infertile patients and reported 12 pregnant cases with a clinical pregnancy rate about14.1%.[118]

In some other studies which compare between the effects of clomiphene citrate and other therapeutic lines in patients with PCOS suffering from infertility but with expectant management (ordinary intercourse) without IUI or TIC, Legro RS et al. studied clomiphene citrate versus letrozole and found that of 376 PCOS patients that received CC, 81 cases became pregnant with a pregnancy rate about 21.5%.[121]

Zain MM et al. compared clomiphene citrate with metformin or combination of both in PCOS infertile patients. The study was conducted on 115 PCOS patients with 39 cases received clomiphene citrate at a dose of 50 mg/day on days 2-6 of the menstrual cycle, with only 6 cases became pregnant with a pregnancy rate about 15.4%.[122]

Karimzadeh MA et al. compared clomiphene citrate with metformin or combination of both versus life style modification in PCOS infertile patients. Three hundred forty-three (343) infertile PCOS patients were included in this study. By the clomiphene citrate, 90 patients were stimulated and resulted in 11 pregnant cases with a pregnancy rate about 12.2%.[123]

Kar S compared between the effects of clomiphene citrate and letrozole in 130 PCOS infertile females with IUI or TIC according to patient requirement. Fifty one (51) patients received clomiphene citrate for induction of ovulation. The study resulted in 4 pregnant cases with a pregnancy rate about 7.84%.[124]

Palomba S et al. compared between the effects of clomiphene citrate and metformin in 92 non-obese primary infertile an-ovulatory women with PCOS in which 47 cases received CC over 221 cycles and demonstrated that the cumulative ovulation rate over 6 months period was 67%(148 of 221), whereas the pregnancy rate was only approximately 7.2% per ovulatory cycles (16 of 221), while the cumulative pregnancy rate after 6 months treatment was 34%.[125]

Many mechanisms have been proposed to explain these figures, such as the anti-estrogenic effects on the endometrium, cervical mucus, uterine blood flow, the influences on tubal transport and oocyte quality and maturity, and the increased risk in subclinical pregnancy loss.[126]

SUMMARY

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders. It produces symptoms in approximately 5% to 10% of women of reproductive age (12–45 years old). It is thought to be one of the leading causes of female subfertility. [1, 2]

The cardinal features are hyper-androgenemia, ovulatory dysfunction and/or ultrasonographic polycystic ovarian appearance (two out of these three features are diagnostic). [4]

Clomiphene citrate (CC) is the standard drug used for ovulation induction in women with PCOS. Successful ovulation is achieved in 70-85 % of cases and only 40–50 % will conceive. [45-47]

The discrepancy between ovulation and pregnancy rates may be explained by the peripheral anti-estrogenic effects of CC at the level of the endometrium and cervical mucus or by hyper-secretion of LH. [55]

Intrauterine insemination (IUI) is the first therapeutic step in assisted reproductive techniques due to its simplicity, easy management, low cost and absence of potentially serious complications. [87-89]

The aim of this work was to study the effect of induction of ovulation with clomiphene citrate and hCG in patients with PCOS with intrauterine insemination compared to timed intercourse.

The study was conducted upon 60 an-ovulatory PCOS infertile women, 18-35 years age group, who were attending El Shatby Infertility Unit, Alexandria faculty of Medicine by two out of the previous three criteria.

Patients were randomly allocated into two groups and received clomiphene citrate 100mg. /day for 5 days starting from day 3 of the cycle.

HCG was administered when the leading follicle reached 18 mm. or more.

The first group was subjected to timed intercourse (TIC) 40-48 hours after hCG administration.

The second group was subjected to intrauterine insemination (IUI) plus intercourse within the same day, 40-48 hours after hCG administration.

In IUI group, semen was obtained by masturbation after three to five days of abstinence then preparation was done by swim up technique then IUI was done. The patient was asked to rest for10-15 minutes following insemination.

Luteal phase support for the two groups by use of vaginal micronized progesterone 200 mg. has been used twice daily for two weeks.

Serum pregnancy test was done 2 weeks after hCG administration and if positive trans-vaginal ultrasound was done 2 weeks later to confirm clinical pregnancy.

Study results: Pregnancy rate was about 13.33 % in CC/TIC group while it was about 16.67 % in CC/IUI group.

Conclusion: timed intercourse compared to intrauterine insemination after ovulation induction by clomiphene citrate in PCOS patients showed no significant difference in pregnancy rate.

CONCLUSION AND RECOMMENDATIONS

This trial suggests that timed intercourse compared to intrauterine insemination after ovulation induction by clomiphene citrate in PCOS patients showed no significant difference in pregnancy rate.

It is not recommended to do intrauterine insemination as a first choice for PCOS cases suffering from infertility.

We recommend that this study should be conducted on a larger number of PCOS infertile patients to asses our results.

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الملخص العربى

تعد متلازمة تكيسات المبيض المتعددة من الأمراض الشائعة والتي تصيب السيدات في عمر ١٢- ٤٥ سنة بنسبة تتراوح بين ٥-١٠% كما تعد من الأسباب الرئيسية لتأخر الإنجاب.

يتم تشخيص المرض عن طريق وجود علامتين علي الأقل من الثلاث علامات الآتية:
١- زيادة في هرمونات الذكورة.
٢- اضطراب بالتبويض.
٣- وجود تكيسات بأحد المبيضين أو كليهما (بالموجات فوق الصوتية المهبلية).

يعد عقار الكلوميفين سترات أحد الخطوات الأولي لعلاج ضعف التبويض في مرضي متلازمة تكيسات المبيض المتعددة، ويؤدي إلي حدوث التبويض بنسبة ٧٠-٨٥ % إلا أن معدل حدوث الحمل هو ٤٠-٥٠ % فقط.

هذا الفرق بين معدل التبويض والحمل قد يكون بسبب تأثير الكلوميفين سترات السلبي على بطانة الرحم وعلى الإفرازات الموجودة بعنق الرحم وأيضا قد يكون بسبب زيادة في إفراز هرمون LH.

يعد التلقيح داخل الرحم الخطوة الأولي من وسائل الإخصاب المساعدة وذلك لأنه يتميز بالسهولة وقلة التكلفة وقلة المضاعفات الخطيرة المصاحبة.

الهدف من الدراسة: المقارنة بين التلقيح داخل الرحم والجماع محدد الزمن في مرضي متلازمة تكيسات المبيض المتعددة بعد إعطاء عقار الكلوميفين سترات و هرمون hCG.

تم إجراء هذا البحث علي ٦٠ سيدة تعاني من تأخر الإنجاب نتيجة لإصابتهم بمتلازمة تكيسات المبيض المتعددة(حسب العلامات السابق ذكرها) في الفئة العمرية بين ١٨-٣٥ سنة، واللاتي يترددن علي عيادة العقم بمستشفي الشاطبي الجامعي. تم التأكد من عدم وجود أي سبب آخر للعقم في كلا الزوجين وبعد تقسيم الحالات عشوائياً لمجموعتين تم إعطائهم عقار الكلوميفين سترات ١٠٠مجم/يوميا لمدة ٥ أيام بداية من اليوم الثالث للدورة.

المجموعة الأولي: خضعت للجماع محدد الزمن ٤٠-٤٨ ساعة بعد إعطاء هرمون hCG.

المجموعة الثانية: خضعت للتلقيح داخل الرحم ٤٠-٤٨ ساعة بعد إعطاء هرمون hCG بالإضافة إلي الجماع في نفس اليوم.

تم إعطاء هرمون hCG عند وصول حجم البويضة إلي ١٨مم أو أكثر.

تم إحضار عينة السائل المنوي بالمعمل عن طريق الاستمناء(بعد امتناع عن الجماع لمدة ٣-٥ أيام) لتحضيرها ثم عمل التلقيح. ننصح الحالة بالاستلقاء لمدة ١٠-١٥ دقيقة بعد التلقيح.

تم إعطاء الحالات بالمجموعتين ٢٠٠مجم من البروجستيرون عن طريق المهبل مرتين يوميا لمدة أسبوعين.

بعد أسبوعين تم عمل تحليل حمل بالدم، وبعد أسبوعين آخرين تم عمل موجات فوق صوتية مهبلية للتأكد من حدوث الحمل.

نتائج البحث: بعد الدراسة تبين أن معدل الحمل في المجموعة الأولي حوالي ١٣,٣٣% أما بالنسبة للمجموعة الثانية كان معدل الحمل حوالي ١٦,٦٧% وتم تأكيد النتائج بالمقارنة مع الأبحاث السابقة.

خلاصة البحث: الجماع محدد الزمن مقارنة بالتلقيح داخل الرحم لم يُظهر فرقاً كبيراً في معدل الحمل في مرضي متلازمة تكسيات المبيض المتعددة بعد إعطاء عقار الكلوميفين سترات.

جامعة الإسكندرية
كلية الطب
قسم التوليد وأمراض النساء

تأثير التلقيح داخل الرحم على معدل حدوث الحمل عند السيدات المصابات بمتلازمة تكيسات المبيض المتعددة واللاتى تعالج بعقار الكلوميفين سترات

رسالة مقدمة

لقسم التوليد وأمراض النساء ـ كلية الطب ـ جامعة الإسكندرية
ضمن متطلبات درجة

الماجستير

فى

التوليد وأمراض النساء

مـــن

محمود محمد رزق حموده
بكالوريوس الطب والجراحة ، الإسكندرية
كلية الطب، جامعة الإسكندرية

[٢٠١٥]

جامعة الإسكندرية
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رسالة مقدمة من

محمود محمد رزق حموده

للحصول على درجة

الماجستير

فى

التوليد وأمراض النساء

لجنة المناقشة والحكم على الرسالة	التوقيع
أ.د/ عادل حنفي الفزاري أستاذ التوليد وأمراض النساء قسم التوليد وأمراض النساء كلية الطب جامعة طنطا	.....
أ.د/ أحمد عبدالعزيز إسماعيل أستاذ التوليد وأمراض النساء قسم التوليد وأمراض النساء كلية الطب جامعة الإسكندرية	.....
أ.د/ عماد عبدالمنعم درويش أستاذ التوليد وأمراض النساء قسم التوليد وأمراض النساء كلية الطب جامعة الإسكندرية	.....

التاريخ / /

لجنة الإشراف **موافقون**

أ.د/ عماد عبد المنعم درويش .....

أستاذ التوليد وأمراض النساء
قسم التوليد وأمراض النساء
كلية الطب
جامعة الإسكندرية

د/ أشرف هانىء عبد الرحمن .....

أستاذ مساعد التوليد وأمراض النساء
قسم التوليد وأمراض النساء
كلية الطب
جامعة الإسكندرية

المشرف المشارك

د/ ياسر سعد الكسار .....

مدرس التوليد وأمراض النساء
قسم التوليد وأمراض النساء
كلية الطب
جامعة الإسكندرية