Clomiphene Citrate Stair-Step Protocol for Ovulation Induction in Women with Polycystic Ovarian Syndrome

A Randomized Clinical Trial (RCT)

Thesis

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By

Nesreen Khairy Abd Elhalim
M.B., B.Ch. (2003)
Resident of Obstetrics and Gynecology
Dar El-Shefa Hospital

Under Supervision of

Prof. Salah Taha Fayed
Professor of Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Ass. Prof. Adel Shafik Salah El-Din
Assistant Professor of Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2015

بِسْمِ اللّهِ الرّحمَنِ الرّحيمِ

[...رَبِّ أَوزِعنِي أَن أَشكُرَ نِعمَتَكَ
الَّتِي أَنْعَمْتَ عَلَيَّ و عَلى والِدَيَّ
وأَنْ أَعْمَلَ صَالِحاً تَرْضَاهُ و أَدْخِلْنِي
بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ]

صدق الله العظيم

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List of Abbreviations

AIDS	: Acquired immune deficiency syndrome
ASRM	: American Society for Reproductive Medicine
BMI	: Body mass index
CC	: Clomiphene citrate
DHEA-S	: Dehydro-epiandrosterone sulfate
ESHRE	: European Society of Human Reproduction and Embryology
FDA	: Food and Drug Administration
FSH	: Follicle stimulating hormone
GnRH	: Gonadotropin releasing hormone
HAIR-AN	: Hyperandrogenic-insulin resistant-acanthosis nigricans
HCG	: Human chorionic gonadotropin
HMG	: Human menopausal gonadotropin
IGF	: Insulin-like growth factor
IGF-BPI	: Insulin like growth factor-binding protein 1
HDL	: High density lipoprotein
IU	: International unit
LH	: luteinizing hormone (LH)
LHTIC	: Luteinizing hormone-theca interstitial cell
NICHD	: National Institute of Child Health and Human Development
PCOS	: Polycystic ovarian syndrome
PPAR	: Peroxisome proliferator-activated receptor
SD	: Standard deviation
SHBG	: Sex hormone-binding globulin
SPSS	: Statistical package for social science
17P-HSD	: 17p-hydroxysteroid dehydrogenase

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Introduction

Infertility – in general – is defined as inability to conceive after one year of unprotected sexual relation, women who don't have regular menstrual cycle or are older than 35 years old and had not conceive during 6 month period of trying also considered infertile ***(CDC, 2013).***

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, with a prevalence of approximately 4-6%. Its cardinal features are hyperandrogenism and polycystic ovaries ***(Laven et al., 2004).***

The Rotterdam conference of 2003, recommended that at least two of the following three features are for PCOS to be diagnosed:

1- Oligo-ovulation or anovulation; manifested as oligomenorrhea or amenorrhea.

2- Hyperandrogenism (clinical evidence of androgen excess) or hperandrogenemia (biochemical evidence of androgen excess).

3- Polycystic ovaries (as defined on ultrasonography as 12 or more follicles in at least 1 ovary measuring 2-9 mm in diameter or a total ovarian volume of >10m3***(Fauser et al., 2004).***

Polycystic ovary syndrome is characterized by an excessive number of small antral follicles in the ovaries that fail to produce a dominant follicle on a regular basis and by dissociation in LH and FSH release ***(Adams et al., 2004).***

Clomiphene citrate is the traditional therapy used for induction of ovulation in this condition. Clomiphene nitrate is a non-steroidal estrogen receptor agonist and antagonist that induce ovulation by blocking the normal negative feedback initialed by estrogens on hypothalamic GnRH release and result in increasing FSH and LH levels ***(Carmina and Azziz, 2006).*** Clomiphene resistance, which refers to persistence of anovulation after standard clomiphene citrate therapy, occurs in 15%-20% of patients ***(Carmia and Azziz, 2006).***

Approximately 50-70% of women on clomiphene citrate will ovulate ***(Hass et al., 2003).*** However, the number of pregnancies was lower than expected. This could be due to negative effects of clomiphene citrate on oocytes or granulose cells, or because of prolonged antiestrogenic effects on the endometrium and cervical mucus ***(Hass et al., 2003).***These negative effects are augmented by relatively long half life of clomiphene citrate, which is known to be 5 days. If treatment is started late in the cycle, those negative effects are more likely to extend into the sensitive peri-implantation period ***(Billijan et al., 1999).***

Clomiphene citrate is the drug most commonly used for ovulation induction starting with a daily dose of (50mg) for 5 days beginning on day 3-5 of the menstrual cycle, if ovulation achieved this is usually continued for 6 cycles or until pregnancy occurs. However if the patient fails to ovulate on this regimen, a further increase by (50mg) per day to a maximum of (200-250mg) is used next cycle ***(Abd-Allaet al., 2007).***

A disadvantage with the mentioned traditional protocol is that several months may pass to ultimately determine that patient is non responsive to clomiphene citrate ***(Thessaloniki, 2008).***

Described a novel clomiphene stair-step protocol that is hoped to reduce time to reach ovulation in women with polycystic ovarian syndrome, this stair-step protocols is performed as follows: (50mg) clomiphene citrate for 5 days and transvaginal ultrasound (TVUS) on days 11-14, when there is no response (no follicle >10mm), (100mg) clomiphene is initiated immediately for 5 days, and TVUS is repeated 1 week after the first ultrasound. If there is no response, (150 mg) clomiphene is initiated immediately for 5 days and ultrasound is performed 1 week after the second ultrasound ***(Hurst et al., 2009).***

Using this approach, 52% ovulated in response to (50mg), and 22% ovulated in response to (100mg), and 12% responded to (150mg) ***(Hurst et al., 2009).***

Aim of the Work

To determine the efficacy of clomiphene stair-step protocol in women with polycystic ovarian syndrome compared to traditional protocol in reducing time of having a mature follicle.

Polycystic Ovarian Syndrome (PCOS)

According to the Rotterdam criteria, polycystic ovary syndrome (PCOS) is characterized by two of the following three criteria: oligo-anovulation, ultrasonographically defined polycystic ovaries and clinical or biochemical signs of hyperandrogenism with the exclusion of other androgen excess disorders. Chronic anovulation is one of the most common causes of infertility in women with PCOS. Oocytes quality or endometrial and implantation abnormalities also may contribute to the pathogenesis of infertility in PCOS ***(Deveci et al., 2014).***

Polycystic ovary syndrome is a heterogeneous clinical syndrome, which has been defined as the association of hyperandrogenism with chronic anovulation in women without specific adrenal and pituitary gland disease. A family history of polycystic ovary syndrome may be present in a subset of patients; however, the genetic basis of the syndrome remains unclear. Most often, 7the age of onset is perimenarchal and it is characterized by the appearance of menstrual disturbances, hirsutism, acne, and more rarely, a male pattern of alopecia. Polycystic ovary syndrome is also associated with metabolic disturbances, such as obesity and insulin resistance with hyperinsulinemia ***(Pelusi and Pasquali, 2003).***

Definition:

Difficulties in the diagnosis of PCOS and controversies in definition arise from the heterogeneous nature of the disorder ***(Franks, 2006).*** Even in the classic 1935 report by Stein and Leventhal describing their case series of seven women with amenorrhea associated with bilateral polycystic ovaries treated with wedge resection of the ovaries, only three of these women were obese, only four were hirsute (one obese), and one had acne ***(O'Brien and Emans, 2008).***

There is no consensus on the diagnostic criteria and definitions of PCOS. Recently, two definitions were followed: one is the National Institute of Child Health and Human Development (NICHD) conference Human Reproduction and Embryology (ESHRE) /American Society for Reproductive Medicine (ASRM). The third definition has been proposed recently by the Androgen Excess Society, which takes into account both the criteria existent till date ***(Dasgupta and Reddy, 2008).***

Prevalence:

Ethnic variation in the community prevalence of PCOS has been less forthcoming due to many studies having a high selection bias and not a true reflection of ethnic groups. However, this article highlights the noted differences of population prevalence rates of PCOS based on available data,