EFFECT OF CLOMIPHENE CITRATE,TAMOXIFEN AND LETROZOLE ON ENDOMETRIAL THICKNESS IN CYCLES OF OVULATION INDUCTION A RANDOMIZED CONTROLLED TRIAL

Protocol of Thesis

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INTRODUCTION

Infertility is the inability of a married couple to conceive within one year in spite of regular marital life. Globally 10-15% of the married couples are experiencing this problem. ***(Propst and Bates,2012)***.

Anovulation accounts for about 20-25% of causes of infertility as ovulation is a core event for reproduction. Anovulation may be due to problems affecting the ovary, pituitary or hypothalamus. These causes have been organized by the world health organization (WHO) into three main categories based on the site of the lesion and as reflected by gonadotropin production:

- WHO type 1 (hypogonadotropic hypogonadism): caused by any lesion affecting pituitary or hypothalamus and affecting gonadotropin production.

- WHO type 2 (normogonadotropic hypogonadism): the commonest cause of anovulation and is most commonly caused by polycystic ovarian syndrome (PCO).

- WHO type 3 (hypergonadotropic hypogonadism): usually is an indication of ovarian ***failure (Metwally and Ledger,2010 & Propst and Bates,2012)***.

Polycystic Ovarian Syndrome (PCO) is the most common endocrinal disorder in women of reproductive age

and is the primary cause of anovulatory infertility. Its prevalence range from 6-10% in general population. Its diagnostic criteria at least two of the following (Rotterdam criteria): 1- oligo or anovulation 2- hyperandrogenism (laboratory confirmed or by clinical symptoms) 3- polycystic ovaries on ultrasound ***(Metwally and Ledger,2010)***.

Ovulation induction involves the use of medication to stimulate development of one or more mature follicles in the ovaries of women who have anovulation and infertility. These women don't regularly develop mature follicles without help from ovulation enhancing drugs as Selective Estrogen Receptor Modulator (clomiphene citrate and tamoxifen), Aromatase Inhibitors (letrozole), Gonadotropins, etc. Treatment with these drugs has the potential to result in pregnancy if the woman has good quality eggs in her ovaries and if other causes of infertility are absent ***(Messinis, 2005 & Propst and Bates,2012)***.

Clomiphene citrate (CC):

CC is non-steroidal selective estrogen receptor modulator (SERM), has both estrogen agonist and antagonist properties. It binds to estrogen receptors primarily in the hypothalamus, which interrupts the negative feedback of the increasing estrogen level and results in continued production of FSH, which stimulates follicular growth and maturation ***(Brown et al.,2009 & Sedeyoshohadaei et al.,2012).***

Its anti-estrogenic effect causes long standing estrogen receptor depletion due to its long half life (2 weeks), so it has adverse effects on the quality and quantity of cervical mucus and negative impact on endometrial development causing its significant thinning, implantation failure and decreased blood flow during the peri-implantation stage ***(Wang et al.,2010 & Selim and Borg,2012 & Banerjee Ray et al.,2012 & Hussain et al.,2013)***.

It can induce ovulation in 60-80% of anovulatory women but only 20-40% become pregnant ***(Richard et al.,2005 & Sedeyoshohadaei et al.,2012)***.

Tamoxifen:

Tamoxifen is non-steroidal selective estrogen receptor modulator (SERM). Commonly used today as an adjuvant therapy in treatment of breast cancer. It acts primarily by binding to estrogen receptors at hypothalamus, this competitive inhibition results in a perceived drop in endogenous estrogen levels, eventually leading to increased gonadotropins secretion and subsequent induction of ovulation ***(Steiner et al.,2005)***.

It may also improve folliculogenesis by involving a direct action on the ovary without intervention of hypothalamo-pitutary system ***(Dhaliwal et al.,2011).***

It acts as an agonist on estrogen receptors of endometrium and vaginal mucosa, its half life is short (5-7 days) leading to favorable cervical mucus, better endometrial thickness and may be better endometrial blood flow ***(Steiner et al.,2005 & Dhaliwal et al.,2011)***.

It can induce ovulation in about 50-90% of anovulatory women with pregnancy rate 30-50%. This better results due to high score in endometrium, cervical mucus and better functioning corpus luteum ***(Steiner et al.,2005 & Dhaliwal et al.,2011 & Pant et al.,2013)***.

Letrozole:

Letrozole is highly selective Aromatase Inhibitor, prevents conversion of androgen to estrogen, thus releasing the hypothalamo-pitutary axis from the negative feedback, resulting in an increase of FSH secretion from the anterior pituitary. The accumulated androgens in the ovary further increase the follicular sensitivity to ***FSH (Holzer et al.,2006 & Kamath and George,2011)***.

It is devoid of any anti-estrogenic peripheral actions so doesn't deplete estrogen receptors ***(Badawy et al.,2009 & Kamath and George, 2011)***. It has short half life (48 hours) thus has no adverse effects on the quality and quantity of cervical mucus and has positive impact on endometrial development causing its significant thickening, better implantation and increase blood flow during the peri-

implantation stage (***Wang et al.,2010 & Selim and Borg,2012& Banerjee Ray et al.,2012 & Hussain et al.,2013)***.

It can induce ovulation in about 80% of anovulatory women with high pregnancy rate ***(Richard et al.,2005 & Sedeyoshohadaei et al.,2012 & Kar et al.,2012 & Roy et al.,2012).***

In Badawy and Gibreal,2011 study shows that CC is superior to tamoxifen for ovulation induction as a first line therapy. In **Dhaliwal et al.,2011 and Pant et al.,2013** studies show that tamoxifen is superior to CC. In **Kar et al.,2012 and Roy et al.,2012** studies show that letrozole is superior to CC. These studies were done to detect the effect of these drugs on ovulation induction and their relation to pregnancy rate and the results were not the same. In **Selim and Borg,2012 and Wang et al.,2010** studies show that endometrial blood flow and thickness during ovulation induction may have a role in improving pregnancy results. So this study will be held to detect if these drugs have positive or negative impacts on endometrial blood flow and thickness during ovulation induction, which may affect the pregnancy rate.

AIM OF THE WORK

The aim of the study is to compare the effect of the following 3 drugs during induction of ovulation:

1-Clomiphene citrate 2-Tamoxifen 3-Letrozole

Regarding:

1- Impact on endometrial thickness

2- Impact on endometrial blood flow

In women with anovulatory infertility.

REVIEW OF LITERATURE

Chapter 1- PHYSIOLOGY OF OVULATION

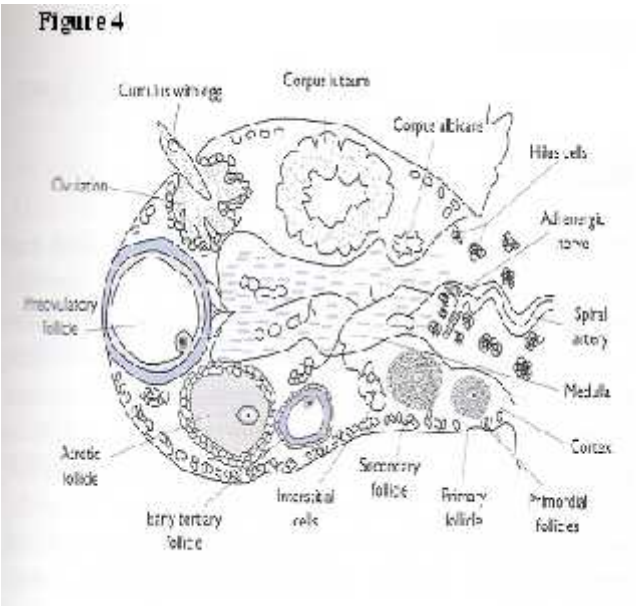
Definition:

Ovulation is the process in a female's menstrual cycle by which a mature ovarian follicle; which is the basic unit of the female reproductive biology contain a single immature ovum. These ovarian follicles rupture and discharge an ovum. This ovum is periodically initiated to grow and develop. This ovum is only developed once every menstrual cycle. ***(Smitz et al ., 2010)***. The process of ovulation is controlled by the hypothalamus and by the release of hormones, FSH and LH, secreted by the anterior lobe of pituitary gland ***(Baewald et al ., 2004)***.

Physiology:

At 6-8 weeks gestation intrauterine life, the first signs of ovarian differentiation are reflected in the rapid mitotic multiplication of germ cells, the number of oocytes peaks in the fetus to 6-7 million by 20 weeks of gestation. Simultaneously, atresia of oogonia occurs. At birth, only 300,000 of the original 6 to 7 million oocytes are available, of these only 400 to 500 will be released during ovulation. At menopause the ovary will be composed of dense stromal tissue with only rare interspersed oocytes remaining ***(Speroff & Marca , 2005)***.

The ovarian cortex at puberty contains hundreds of thousands of primordial follicles. In response to unknown signals, independent of gonadotropins a cohort of primordial follicles is recruited to grow ***(Gougeon et al ., 1998)***. During this early follicle development, the oocyte enlarges and the granulosa cells proliferate to form an antral follicle. Over 3-6 months of the early follicular development, the follicle develops FSH receptors in the granulosa cells and LH receptors in the theca cells, and the follicle forms a fluid-filled space called an antrum. At this stage, antral follicles become acutely dependent on FSH for further development ***(Gougeon et al ., 1998)***.



(Fig. 1) Stages of ovulation