Summary

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy of women, with aprevalence of 6.5–6.7% among premenopausal women ***(Diamanti-Kandarakis et al.,1999 and Escobar-Morreale et al.,2000)***. In 2006, the Androgen Excess Society provided a contemporary version of the definition of PCOS . The final statement has highlighted hyperandrogenism (clinical or biochemical) in combination with ovarian dysfunction (including both functional and ultrasonographic abnormalities) as the core characteristics of PCOS***(Azziz et al.,2006)*** .

Biochemical and clinical hyperandrogenism in PCOS, of ovarian and/or of adrenal origin, is evident in the majority of patients with PCOS (60–80%) (***Franks,2006 & Azziz,2006)***. Insulin appears to be a triggering factor that aggravates the inherent dysregulation of theca steroidogenesis in PCOS. Insulin seems to act in synergy with LH to stimulate androgen synthesis in PCOS ovarian theca cells ***(Poretsky et al., 1999) .*** PCOS represents the commonest cause of normogonadotropic anovulation. ***(Broekmans et al.,2006)***

Oligomenorrhoea/anovulation is a major clinical concern and is present in 70–80% of women with PCOS ***(Azziz et al.,2006)***. Anovulation in PCOS is attributed to the disturbances of folliculogenesis that characterize the syndrome. The follicular defect in PCOS consists of accelerated early follicular growth and distortion of the subsequent stages towards the selection of the dominant follicle (follicular arrest) ***(Jonard and Dewailly,2004)***.This is combined with The deceleration of atresia, ***(Webber et al.,2007)*.**

Clomiphene citrate has been the front line therapy for ovulation induction (***Holzer et al., 2006).*** Failure to respond to clomiphene citrate occurs in up to 20% of cases which may require the use of injectable gonadotropines as a second line ***(Mitwally and Casper, 2001).***The drawbacks of this approach include its high cost, the potentially life threatening ovarian hyperstimulation syndrome and the significant risk of high order multiple gestations ***(Holzer et al., 2006).***

Recent research has focused on the successful use of aromatase inhibitors (AIs) as letrozole for ovulation induction ***(Mitwally and Casper, 2006).*** Aromatase is a cytochrome P-450 hemoprotein containing enzyme complex (the product of the CYP19 gene) that catalyzes the rate-limiting step in the production of estrogens which is the conversion of androstenedione and testosterone via three hydroxylation step to estrone and estradiol (***Akhtar et al., 1993).***

There are two types of AIs: Steroidal (type I) and non-steroidal inhibitors (type II) ***(; Plourde et al., 1994).*** Type II non-steroidal AIs exert their function through binding to the heme moiety of the cytochrome P450 enzyme ***(Brodie and Njar, 1996).***Letrozole is rapidly absorbed from the gastrointestinal tract and excreted by the kidney. The elimination half-life of letrozole is about 2 days ***(Mitwally and Casper, 2001).***AIs can be applied for ovarian stimulation as its administration early in the follicular phase can induce ovulation by releasing the hypothalamus or pituitary from estrogen negative feedback on GnRH and gonadotropin secretion, leading to an increase in gonadotropin production which would stimulate ovarian follicular development ***(Lidor et al., 2000).***

AIs prevent the Androgen-Estrogen conversion and therefore interfere with the negative feedback at the level of the hypothalamus-pituitary. The increased pituitary gonadotropin out put will in turn stimulate the ovaries ***(Mitwally et al., 2005).***

Therefore, it seems reasonable to consider simpler and inexpensive therapies such as controlled ovarian hyperstimulation (COH) combined with intrauterine insemination (IUI) for first-line treatment in subfertility.

The aim of this study was To evaluate the ovulation and pregnancy rates by COH/IUI useing letrozole among CC-resistant PCOS .

This study was performed as a clinical trial included twenty infertile females with clomiphene citrate resistant PCOS patient attending the infertility clinic. Benha University Hospital between October 2008 and July 2009.

Diagnosis of PCOS according to ***Rotterdam(2004)*** was: oligo- or amenorrhea, ultrasound criteria (if there were 12 or more follicles measuring 2-9 mm in diameter or increased ovarian volume >10cm)and hyperandrogenism (clinical and\or laboratory).

Inclusion criteria included delayed conception for at least 1 year, age between 18-35years, primary infertility≥ 2years, documented history of CC administration for at least 3 consecutive cycles with no response (no follicular maturation) (CC stopped for at least 6 weeks), bilateral patent tubes (normal HSG or laparoscopy), no male factor for infertility (normal semen analysis), normal renal and Liver fnctions, Basal FSH<10 mIu/ml and normal prolactin.

The protocol of ovarian stimulation was conducted by letrozole which was given orally in adose of 5 mg /d started from the third day of the cycle for 5 days. Ovarian follicular response was monitored by transvaginal sonography starting on the next day after finishing Letrozole and thereafter according to the growth of the follicles (usually every other day). Good response was achieved when at least one mature follicle becomes> 18 mm in diameter . When the optimal follicle size was reached the endometrial thickness was assessed and 10,000 IU of hCG injection was given intramuscular. Insemination was performed 34 ±4 hours later.

Sperm processing was done by the buoyant density gradient kits for sperm preparation (Sil –Select Plus). Sperm media was Earle's balanced salt solution. 0.5 ml of the supernatant containing active sperms is used directly for IUI by ***Seminor R*** catheter.

Diagnosis of pregnancy: Clinical pregnancy was defined as the detection of at least one gestational sac on transvaginal ultrasound examination starting one week after the missed period.

In this study mean age of studied group was 26.91 ± 3.21 y.The patient were infertile due to PCOS proved clinically by amenorrhea 30 % and oligomenorrhea 70 % and evidence of hyperandrogenism as hirsutism and acne, and ultrasound feature of PCOS

In this study, the mean (±SD) day of HCG administration was **15.14 ± 1. 34 days .** the mean (±SD) number of days between completion of treatment with Letrozole and the day of HCG administration was **7.14 ± 1. 34** days.

In this study, the mean number of mature follicles ≥ 18 mm on the day of HCG administration was 1.28 (range 1-2) where 5 patients (71%) developed one mature follicle and 2 patients (28%) developed 2 mature follicles. This limited number of mature follicles (range 1-2) with Letrozole will decrease the risk of multiple pregnancy and ovarian hyperstimulation syndrome(OHSS).Therefore, Letrozole treatment does not need intensive monitoring compared to gonadotropins.

In this study, the mean endometrial thickness on the day of HCG administration was **9.85 ±1.46** mm. Thus the endometrium was of adequate thickness to allow implantation. Letrozole induces ovulation but without estrogen receptors down- regulation.

In this study, ovulation occurred in 7 cases (35%)., pregnancy occurred in 2 patients; thus the percent of pregnancies per induced ovulatory cycle is 28.5% . All these pregnancies were single.

Comparing both groups of Letrozole responders and non-responders as regards clinical and laboratory characteristics it was found that, there were no significant differences as regards age ,period of infertility, BMI(kg/m^2) , hirsutism and total testosterone (ng/ml). Thus Letrozole can be given to all patients with CC-resistance, as its efficacy is not limited to a specific abnormality.

In the present study letrozole was well tolerated and no patient required discontinuing letrozole therapy.

In this study IUI was performed for 7 patients up 6 cycles unless pregnancy occurred. The total number of cycles was 33 cycles, the

pregnancy rate was 28.57% per patient and 6.06 % per cycle. the higher pregnancy rate occurred in the first three cycles (15.38%).

This study shows non significant difference between pregnant and non pregnant group rgarding sperm characters (total number of sperm, sperm concentration /ml and sperm motility) before and after processing.

In this study, IUI side effects was reported in 6 cases. 3 cases with difficult application, 2 cases with sperm reflux and 1 case with abdominal cramp.

In conclusion; induction of ovulation with Letrozole in CC-failure PCOS is associated with limited number of mature follicles, no adverse effect on endometrium, ovulation and pregnancy in a significant number of patients .

Induction with Letrozole is not dependent on age, period of infertility, BMI and total testosterone level.

COH/IUI is an alternative to gonadotropins with IVF in mangment of CC resistant PCO.