Pregnancy Outcomes in Polycystic Ovary Syndrome Using Different Modules of Ovulation Induction

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Abstract: Polycystic ovary disease is a common endocrine problem related to puberty and menopause. The prevalence of polycystic ovary disease in community based on clinical, endocrinilogical and radiological data was found to be 21-22%. The syndrome is seen in the second and third decade of life. The great majority of polycystic ovary disease patients were first seen between ages of 20 and 30 years, presumably due to the gradual appearance of the clinical manifestation of the polycystic ovary disease in the postpubertal reproductive year This study included 90 women with polycystic ovary syndrome (PCOS). PCOS was diagnosed by (Rotterdam Consensus, 2004), aged between 2 and 3 years. All women were overweight, i.e. BMI Kg/m2, with History of failure of medical induction of ovulation with clomiphene citrate i.e Clomiphene citrate resistance). We compared DAY 3 serum level of (FSH, LH, FSH/LH, E2, PRL and TSH), also ovarian volume and pre antral and small antral follicle count (done by vaginal ultrasound). Medical induction of ovulation is main line of infertility disorder pattern which is usually associate women suffering from poly cystic ovary. Clomiphene citrate (clomid) is the first drug in arsenal medication of pco but 20-25% of patients shows cc resistance, solving of that resistance open the door widely for gonadotrophin aand and aromatase inhibitors treatment for clomiphene resistant women with polycystic ovarian disease. Medical ttt of pco has great role in solving infertility pattern associate pco also has many side effects, ohss is most serious issue as regard side effects. Proper hormonal assay and accurate monitoring of induction proper adjust of suitable doses and proper choice of drugs play a great role in treatment. Must mention that obesity (BMI) also insulin resistance has role in detection of protocol and duration of ttt protocol of ttt and dosage and duration and route of administration play also in cumulative pregnancy rate. The aim of our study to compare efficacy of three different protocols of medical induction in pco patients showing clomiphene citrate resistance. All protocols show results as regard pregnancy rate, ovulation rate and monofollicular and endometrial thickness. These results were similar with no significant difference between the three protocols. We must note that suitable protocol is based on many point duration of infertility also route of administration, financial state of each patient and finally patient capability to continue more than one cycle of induction. Fixed paramters used lead to similar results even with different protocols. Good preparations, proper investigations and definite protocol and close monitoring and continuity lead to acceptable results.

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1. Introducation

Poly cystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. It is characterized by anovulation manifested as oligo- or amenorrhea, elevated levels of circulating androgens, and polycystic ovaries as visualized by ultrasound. The diagnosis is based on the presence of at least two of the described characteristics, as defined by the **(Rotterdam Consensus, 2004)**. The World Health Organization (WHO) classifies anovulatory women into 3 categories. Those for whom the ovaries fail to function properly because of decreased signals from the brain (hypothalamus and pituitary) are in Group I. Typically the pituitary hormone "follicle stimulating hormone (FSH)" is low in these patients. This may be due to excessive exercise, disorders of inadequate weight such as anorexia nervosa, tumors of the hypothalamus or pituitary, or a rare disorder called Kallman's syndrome. Patients with PCOS are in Group II. Finally patients with intrinsic ovarian failure are in Group III. These patients will have an elevated FSH level and may include premature ovarian failure, prior surgery or radiation, or advancing age **(WHO, 2009).**

PCOS encompasses a broad spectrum of clinical and biochemical characteristics, and, although the mechanisms leading to PCOS are still poorly

understood, the common denominator is a disturbance in the selection of the dominant follicle resulting in anovulation. The defective selection mechanism results in an accumulation of small antral follicles, which contribute significantly to the production of AMH. AMH lowers the sensitivity of follicles to FSH **(Durlinger et al., 2002),** possibly contributing to deranged follicle selection. It has been suggested that aromatase activity in PCOS patients might be decreased because follicles from PCOS women do not produce large amounts of E_2. AMH also inhibits aromatase activity so it contributes to the severity of PCOS **(Agarwal et al. 1996)**.

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age. Familial clustering of cases suggests that genetic factors play an important part in its aetiology. A number of studies of families with several cases of PCOS have produced results suggesting an autosomal dominant trait. Detailed analysis of a large number of affected families has, however, cast some doubt about the mode of inheritance. An autosomal dominant trait remains possible but a more complex aetiology seems more likely. The results of recent studies support the concept of an oligogenic disorder in which genes affecting metabolic pathways in glucose homeostasis and steroid biosynthesis are both involved. A review of evidence for an important role for the insulin gene minisatellite in the aetiology of anovulatory PCOS and for the gene coding for P450 cholesterol side chain cleavage (CYP11a) in the mechanism of excessive androgen secretion in women with polycystic ovaries. It is proposed that the heterogeneity of clinical and biochemical features in PCOS can be explained by the interaction of a small number of key genes with environmental, particularly nutritional, factors **(Franks et al., 1997).**

Ovulation induction is the method for treating anovulatory infertility **(Messinis, 2005)**. For more than 40 years ago clomiphene citrate has been the most commonly used oral agent. Clomiphene Citrate (Clomid, Serophene) 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. Prior to Clomiphene, patients with PCOS who were anovulatory had few options besides weight loss and surgical wedge resection of the ovaries. While wedge resection was successful, it required a major surgical procedure and was associated with a high incidence of tubal scarring, both of which limited its widespread application. Sufficient weight loss has proven difficult for even the most motivated patients **(Cooke et al., 1997).** Now aromatase inhibitors are a new group of drugs to join the arsenal of fertility treatments **(Hananel et al., 2006).** Also gonadotrophin therapy is granted now as an essential component in the routine management of infertility **(Lunenfeld et al., 2004).**

There has been a recent surge of interest in laparoscopic treatment of polycystic ovarian disease (PCOD) that is unresponsive to first-line ovulation-inducing agents. Laparoscopic treatment options include multiple ovarian punch biopsy, ovarian electrocauterization and laser vaporization or photo-coagulation. These procedures are relatively easy to perform, devoid of major complications, and yield satisfactory ovulation and conception rates. Adhesion formation, however, is a potential complication following such procedures. Furthermore, women subjected to laparoscopic destructive ovarian procedures also need to be critically assessed regarding other long-term risks, such as premature ovarian failure **(Timur et al., 1995).**

Aim of the Work

The aim of this work is to compare induction by r-FSH and HP-HMG and aromatase inhibitor role in clomiphene citrate resistant poly cystic syndrome patients.

2. Patients and Methods

This is a prospective cross sectional study performed at the May 2012 till July 2017.

This study included 90 anovulatory women with polycystic ovary syndrome (PCOS).

PCOS was diagnosed by **(Rotterdam Consensus, 2004)** the presence of at least two of the following:

i. Oligomenorrhoea, with eight or fewer menstruations in the previous 12 months, or amenorrhea.

ii. Clinical and/or biochemical signs of hyperandrogenism such as testosterone >2.6 nmol/l (74.9 ng/ml), elevated androstenedione >10 nmol/l or free androgen index (FAI) >4 or hirsutism (>7 on the Ferriman and Gallway scale) or the early follicular phase (defined as days 2-5 of the menstrual cycle) serum LH/FSH ratio was ≥2. The FAI was calculated using the formula testosterone x 100/sex hormone binding globulin (SHBG). In women with severe oligomenorrhoea or amenorrhoea, a random blood sample was accepted.

iii. Polycystic ovaries as visualized by transvaginal ultrasound (evidence of **ovarian** stromal hypertrophy and multiple (≥10), small (2-9 mm) follicles arranged in the periphery).

Methods

In our study we divide 90 patients suffering from infertility due to ovarian factor (pco) in which male shows normal semen analysis according to who criteria. Also female shows normal patent both tubes document by free hsg or laproscopy.

As infertility represent the main complication of pco patient. That survey done in order to evaluate medical ttt in induction of ovulation in which we compare three protocols of induction.

Here we will mention role of cc as it is first drug used in that track. 20-25%of patients treated by cc show resistance i.e failure of ovulation.

Each couple undergo research have accept to participate after full concelling about benefits and hazarads of treatment.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric. Also qualitative variables were presented as number and percentages.

The comparison between groups with qualitative data were done by using **Chi-square test** and **Fisher exact test** instead of the Chi-square only when the expected count in any cell found less than 5.

The comparison between more than two independent groups with quantitative data and parametric distribution was done by using **One Way Analysis of Variance (ANOVA)** followed by post hoc analysis using LSD test.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:

P > 0.05: Non significant

P < 0.05: Significant

P < 0.01: Highly significant

3. Results

Table (1): Comparison between the three studied groups regarding age, infertility and duration

		Group A No. = 30	Group B No. = 30	Group C No. = 30	Test value	P-value	Sig.
Age (Years)	Mean±SD Range	30.83 ± 2.80 24 – 36	31.57 ± 2.78 28 – 38	32.07 ± 3.10 28 – 38	1.377•	0.258	NS
Infertility	Primary Secondary	21 (70.0%) 9 (30.0%)	24 (80.0%) 6 (20.0%)	18 (60.0%) 12 (40.0%)	2.857*	0.240	NS
Duration (years)	Mean±SD Range	4.97 ± 1.94 1 – 9	4.33 ± 2.51 1 – 12	4.23 ± 2.14 1 – 11	0.971•	0.383	NS

NS: Non significant; S: Significant; HS: Highly significant
*: Chi-square test; •: One Way ANOVA test

The previous table shows that there was no statistically significant difference found between the three studied groups regarding age, infertility and duration with p-value > 0.05.

Table (2): Comparison between the three studied groups regarding anthropometric measures

		Group A No. = 30	Group B No. = 30	Group C No. = 30	Test value•	P-value	Sig.
WC	Mean±SD Range	79.07 ± 18.77 51 – 141	75.80 ± 14.08 52 – 110	79.93 ± 20.20 53 – 134	0.446	0.642	NS
Height	Mean±SD Range	155.20 ± 6.41 140 – 168	155.03 ± 5.12 144 – 168	156.47 ± 4.21 148 – 165	0.651	0.524	NS
BMI	Mean±SD Range	32.69 ± 6.55 18.73 – 51.79	31.48 ± 5.34 22.51 – 45.2	32.54 ± 7.45 20.96 – 49.31	0.312	0.733	NS

NS: Non significant; S: Significant; HS: Highly significant
•: One Way ANOVA test

The previous table shows that there was no statistically significant difference found between the three studied groups regarding anthropometric measures with p-value > 0.05.

Table (3): Comparison between the three studied groups regarding FSH, LH and PRL

FSH	Group A No. = 30	Group B No. = 30	Group C No. = 30	Test value•	P-value	Sig.
Mean±SD Range	4.89 ± 0.93 3.3 – 6.9	5.11 ± 0.84 3.7 – 7.9	5.11 ± 1.03 3.1 – 8	0.558	0.575	NS

NS: Non significant; S: Significant; HS: Highly significant •: One Way ANOVA test

LH	Group A	Group B	Group C	Test value•	P-value	Sig.
	No. = 30	No. = 30	No. = 30			
Mean±SD Range	5.23 ± 1.30 3.3 – 10	6.71 ± 3.39 3.5 – 18	5.38 ± 1.90 3.1 – 12	3.566	0.032	S

NS: Non significant; S: Significant; HS: Highly significant •: One Way ANOVA test

PRL	Group A	Group B	Group C	Test value•	P-value	Sig.
	No. = 30	No. = 30	No. = 30			
Mean±SD Range	17.09 ± 8.20 1.7 – 42	12.66 ± 4.93 4.9 – 26	18.41 ± 8.86 5.7 – 40	4.813	0.010	S

NS: Non significant; S: Significant; HS: Highly significant •: One Way ANOVA test

The previous table shows that there was no statistically significant difference found between the three studied groups regarding FSH level with p-value > 0.05 while there was statistically significant difference found between the three studied groups regarding LH and PRL levels with p-value < 0.05.

Also the table shows that there was no statistically significant difference between CC group and Letro group regarding LH and PRL but the two groups differ from GF group which was higher in LH level and lower in PRL level.

The previous table shows that there was no statistically significant difference found between the three studied groups regarding TSH level with p-value > 0.05 while there was statistically significant difference found between the three studied groups regarding Progestrone with p-value < 0.05.

Table (4): Comparison between the three studied groups regarding number of follicles, dominant follicle, day of tigger and endo thickness

		Group A	Group B	Group C	Test value	P-value	Sig
		No. = 30	No. = 30	No. = 30			
No. of follicles	1.00 2.00	29 (96.7%) 1 (3.3%)	29 (96.7%) 1 (3.3%)	30 (100%) 0 (0.0%)	1.023*	0.600	NS
Dominent Follicle ms.	Mean±SD Range	20.39 ± 1.64 15 – 22.18	18.36 ± 3.50 10 – 22	18.43 ± 3.63 11 – 22	4.235•	0.018	S
Day of tigger	Mean±SD Range	12.59 ± 0.78 11 – 14	12.50 ± 0.68 11 – 14	12.33 ± 1.27 8 – 13	0.545•	0.582	NS
Endo. Thick (mm)	Mean±SD Range	11.42 ± 0.78 10 – 12.5	11.35 ± 1.74 2.8 – 13	11.91 ± 1.51 9.5 – 18	1.430•	0.245	NS

NS: Non significant; S: Significant; HS: Highly significant *: Chi-square test; •: One Way ANOVA test

The previous table shows that there was no statistically significant difference found between the three studied groups regarding number of follicles, day of tigger and Endo thickness while there was statistically significant difference between the studied groups regarding dominant follicle.

Table (5): Comparison between the three studied groups regarding ovulate, number of pregnancy, outcome, number of cycles and pregnancy

		Group A		Group B		Group C		Test value*	P-value	Sig.
		No.	%	No.	%	No.	%			
Ovulate or not	No Yes	4 26	13.3% 86.7%	8 22	26.7% 73.3%	3 27	10.0% 90.0%	3.360	0.186	NS
Single or twins	No pregnancy Single	23 7	76.7% 23.3%	26 4	86.7% 13.3%	24 6	80.0% 20.0%	1.015	0.602	NS
delivered	Delivered No pregnancy	7 23	23.3% 76.7%	4 26	13.3% 86.7%	6 24	20.0% 80.0%	1.015	0.602	NS
no of cycles	1.00 2.00 3.00 4.00	0 21 8 1	0.0% 70.0% 26.7% 3.3%	15 10 5 0	50.0% 33.3% 16.7% 0.0%	1 26 3 0	3.3% 86.7% 10.0% 0.0%	37.803	0.000	HS
Pregnancy	No Yes	23 7	76.7% 23.3%	26 4	86.7% 13.3%	24 6	80.0% 20.0%	1.015	0.602	NS

NS: Non significant; S: Significant; HS: Highly significant *: Chi-square test

The previous table shows that there was no statistically significant difference found between the three studied groups regarding ovulation, number of pregnancy and outcome and pregnancy but there was statistically significant difference between them regarding number of cycles.

4. Discussion

PCOS is a common endocrine disorder that primarily affects women of reproductive age, with prevalence rates ranging from 5% to 10%. In 2004, a consensus panel established a controversial definition (the Rotterdam criteria) for PCOS, to include at least 2 of the following criteria: oligo- or anovulation (menses less than once every 35 days), hyperandrogenism (laboratory-confirmed or clinical symptoms), or polycystic ovaries on ultrasound **(The Rotterdam ESHRE/ASRM–Sponsored PCOS Consensus Workshop Group, 2004).**

Moreover, this definition states exclusion of secondary causes of hyperandrogenism. Given these endocrine abnormalities, infertility is a common complication of PCOS. Studies have reported PCOS as the major cause of infertility in up to 20% of couples. Currently, clomiphene citrate is considered first-line therapy for ovulation induction for women with PCOS and infertility **(The Thessaloniki ESHRE/ASRM–Sponsored PCOS Consensus Workshop Group, 2008)**.

It has variable efficacy (20–25% of women are clomiphene citrate resistant), discrepancies between ovulation and conception rates, and a long half-life (~5 days), which may result in negative endometrium and cervical mucus effects **(Messinis, 2005)**.

Although some data exist on use of insulin sensitizers (eg, metformin, thiazolidinediones) in women with clomiphene citrate–resistant PCOS, at present, the consensus for infertility treatment related to PCOS is that there is no advantage to adding these agents to accepted fertility drugs **(The Thessaloniki ESHRE/ASRM–Sponsored PCOS Consensus Workshop Group, 2008)**.

Also gonadotropins and gonadotropin-releasing hormone (GnRH) analogs are accepted alternatives to CC; however, they increase risk of multiples, are associated with ovarian hyperstimulation syndrome, are available only as injectable formulations, and are expensive **(The Thessaloniki ESHRE/ASRM–Sponsored PCOS Consensus Workshop Group, 2008)**.

For these reasons, other therapies are needed for a subset of women with PCOS and infertility **(Eckmann and Kockler, 2009)**.

Third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) are approved adjuvants for treatment of estrogen-receptor–positive breast cancer. Evidence suggests that nonsteroidal aromatase inhibitors, specifically letrozole and anastrozole, have ovulation-inducing effects by inhibiting androgen-to-estrogen conversion.

Centrally, this effect releases the hypothalamic/pituitary axis from estrogenic negative feedback, increases gonadotropin secretion, and results in stimulation of ovarian follicle maturity. Moreover, peripherally, aromatase inhibitors may increase follicular sensitivity to follicle-stimulating hormone (FSH). These aromatase inhibitors have relatively short half-lives (~2 days), so estrogen target tissues (e.g., endometrium) are spared adverse effects **(Mitwally and Casper, 2006)**.

Because of these mechanisms, it is postulated that aromatase inhibitors may have superior ovulation induction properties in terms of follicular growth and endometrium development, which is important for embryo implantation **(Eckmann and Kockler, 2009)**.

The present study was designed to compare efficacy of three regimens of induction. Clomiphene citrate in addition to Highly purified human menopausal gonadotrophin (Fostimon) versus anastrazole (letrozole) versus Recombinent follicular stimulating hormone (Gonal-f).

In this prospective study, we investigate the three regimens of medical induction of ovulation using three different drugs first group (A) clomiphene citrate (clomid 50 mg) plus highly purified FSH (fostimon 75 IU). Second group (B) recombinant FSH (gonal-f 75 IU), third group and finally group (C) anastrazole (letrozole 2.5 mg) on patients suffering of poly cystic ovary syndromre with history of clomiphene citrate resistance.

All patients undergo medical induction shows clomiplane citrate resistance.

The term clomiphene citrate failure refers to the patients who fail to conceive despite of ovulation with clomiphene citrate **(Speroff et al., 2005)**. Whereas the term clomiphene resistance refers to the 15-20% of patients who remain anovulatory with full dose of clomiphene citrate for 3 to 6 months. The patients most likely not to respond to clomiphene citrate are mostly the obese (BMI >30), hyperinsulinemic and hyperandrogenic **(Kelestimur et al., 2000)**.

Study concern on the results as regard ovulation rate, pregnancy rate and outcome either successful delivery or abortion in the three groups.

(The study involved 90 women with PCOS between 28 and 38 years of age. All women BMI 18-26 Kg/m^2. All patients were subjected to medical induction of ovulation.

The hormonal pattern of the studied groups was consistent with the diagnosis of PCOS. FSH levels, LH levels, E2 levels, prolactin and LH: FSH ratio, TSH levels.

PCOS is characterized by an increase in follicle number that has been shown to occur at the earliest stages. **(Pellatt et al., 2010)**.)

In clomphiene citrate group we notice that 26 patients ovulate out of 30 patients i.e 86.7% of patients ovulate. We must mention that 26 women need 70 cycles. Ovulating patients in gonal-f group decline in which only 22 patients in gonal-f ovulate from 30 patients i.e 73.30% of patients ovulate while 26.7% not ovulate. 50 cycles needed by patients in gonal-f group. This precent increase again in letrozole group as only 3 patients only fail to ovulate i.e 10 % which is lowest, while 27 patients ovulate showing 90% which is the highest precent in comparing with other groups.

In letrozole group ovulation rate is 90% which is the highest between comparing groups. As 27 patient ovulate while 3 fail. Patients of these group need 62 cycles divided as follow only one patient proceed for 1 cycle, 26 patients continue for second cycle of induction and finally 3 patients perform 4 cycles of induction.

In clomiphene citrate group ovulation rate was 86.7% while only 13.3% donot show signs of ovulation i.e 26 patients out of 30 ovulate on the other hand 4 patients fail. These high percent of ovulation need 70 cycles the number which represent the highest between comparing groups. 70 cycles divided as 21 patient proceed for 2cycles of induction, 8 patients continue for third cycle and finally only one patient perform 4 cycles of induction. Pregnancy occurs in 7 patients only out of 30 which represent 23.3%. Those 7 women got singleton pregnancy, also delivered safely with no abortion cases recorded.

Thirdly, Gonal-f group shows 73.3% (22 patient out of 30) ovulation rate while 26.7% (8 out of 30 patients) fail to ovulate. These patient need 50 cycles. In this group only 15 patients proceed for 1 cycle of induction, 10 patients continue for 2 cycle and finally 5 patients perform 3 cycles of induction.

In clomiphene citrate and in gonal-f groups show that 96.7% of patients shows monofollicular pattern, while 100% of letrozole group shows monofollicular pattern.

Dominant follicle range in CC group between 15-22.1 mm, in Gonal-f range between 10-22 mm while in letrozole 11-22mm.

Day of triggering in cc group usually in between 11-14, the same in gf group. But in letro day of triggering occur earlier in between day8 and day13.

Endometrial thickness in cc range between 10-12.5 mm in contrast as we know that bad effect of cc on endo thickness, in gf group range of endometrial thickness was in between 2.8mm (which is very thin)-13mm. letrozole group shows the highest thickness 18mm, while range inbetween 9.5-18mm.

In 2009, Ganesh compere between the same protocols we compare results show the following. In current study ovulation rate in group (A) is 86.7% which is higher than ovulation rate in the same group in study performed by **Ganesh, (2009**), also in group (B) in our study shows 73.3% which is lower than in previous study. And group (C) in own study show higher percent as it is 90% on the other hand in Ganesh 2009 it is 79.3%. As regarding pregnancy rate in group (C) 14.3% in Ganesh which differ than current 23.3%. in group (B) pregnancy rate in Ganesh 17.9% which is higher than current study as it is 13.3%, and in group (c) in Ganesh 23.3% while in current study it is 20%. Ganesh study shows miscarriage rate 16,6%, 13.8% and 14.5% in Clomiphene c citate plus Fsh, letrozole and Rec.fsh groups respectively.

Ganesh study shows cancellation rate while our study donot record any cancellation cases.

In 2013 Ghanem operate new study discuss results of indcution by clomiphene citrate in addition HMG in PCO patients. This study shows ovulation rate 87.8% similar to our study while pregnancy rate 29.2% in this study was higher than our study. Live birth rate is 26.8% **(Ghanem, 2013)**.

Cochrane published new study in 2015 prepared WEISS in this study brief 10 studies comparing Gonal-f with Hp-fsh in this comparsion results.

First study done by BALEN 2007 ovulation rate in Hp-fsh group, Gonal-f 85.2%, 90% respectively, while in our study 86.7%,73.3% respectively.

Pregnancy rate 17.8%, 21.8% respectively in BALEN study, our study 23.3%, 13.3%. In balen study no misscarige as our study. Balen Study shows high percents of bifollicular in both protocols which is differ our study.

Second study prepared by Gereli 2004 which also compare Gonal-f versus Hp-fsh pregnancy rate is 12.6% in Gonal-f while 11.2% in Hpfsh.

Thirdly, Coelingh bennink perform study in 98 in which cumulative ovulation rate in UFSH is 96% which nearly similar but higher to our study (87.6%). in Rec. fsh cumulative ovulation rate 95% which is higher than our study (73.3 %).

On the other hand pregnancy rate in UFSH is 24% nearly equal to our study (23.3%). While in Rec. fsh group pregnancy rate is (27%) which is double our study (13.3%).

Batool hossein at 2016 published research concern effect of gonal-f on 44 pco patients, this study pregnancy rate is coincident with current study as in batool study is 13.6% (6 patients got pregnant out of 44pt).

5patients out of the 6 pt whose pregnant ongo in pregnancy which represent 11.4% which is lower than

our study. Where only 1 patient shows signs of abortion (1 out of 6) (2.3%).

The initial trial evaluating letrozole for infertility in PCOS included 12 women who were considered CC resistant. A 60-day washout period occurred between the last CC cycle and letrozole administration. After a single letrozole cycle, patients exhibited significantly greater endometrium thickness than with prior clomiphene citrate treatment (mean ± SD, 8.1 ± 1.4 vs 6.2 ± 2.5 mm; $p < 0.01$). Ovulation occurred in 9 of 12 (75%) cycles of letrozole, including in 3 of 4 patients who failed to ovulate with clomiphene citrate **(Franks, 1995)**.

While in our study ovulation rate as regard group (C) record 90% which is higher than Frank study.

The same occur in the first clinical study of AIs for ovulation induction, 22 women who had failed to respond to CC were treated with letrozole. Twelve women with PCOS received letrozole 2.5 mg daily for 5 days. Ovulation occurred in 75% of patients and pregnancy was achieved in 25% **(Mitwally and Casper, 2001)**. But the pregnancy rate in our study and in Mitwally was the same.

After these initial positive results for letrozole and ovulation induction, **Elnashar and colleagues** in 2006 evaluated letrozole in 44 women with clomiphene citrate–resistant PCOS and characterized responders and nonresponders. Letrozole was administered 60 days after the last cycle of CC to allow for CC washout. Mean endometrium thickness was considered adequate (10.2 ± 1.31 mm) for implantation. More than half (24/44) of the women ovulated, resulting in 6 clinical singleton pregnancies. Which is lower than our results as regard ovulation or pregnancy rates.

Different studies have assessed the efficacy of AIs for ovulation induction compared with CC. Findings of four prospective randomized studies deserve to be commented on **(Atay et al., 2006; Bayar et al., 2006; Sohrabvand et al., 2006; Badawy et al., 2007)**.

In all studies, 2.5 mg letrozole **(Atay et al., 2006; Bayar et al., 2006; Sohrabvand et al., 2006)** or 5 mg letrozole **(Badawy et al., 2007)** was administered daily for 5 days. Human chorionic gonadotrophin (hCG) at a dose of 10 000 IU was administered when at least one follicle with a mean diameter >18 mm was observed using transvaginal ultrasound. Which is similar to our methodology.

Differences among these studies are mainly related to the selection of patients.

In the study of Atay and colleagues in 2006, 106 women with oligoamenorrhea and PCOS were enrolled (55 received CC and 51 letrozole). Results were more favorable in the letrozole group than in the CC group regarding the percentage of ovulatory cycles (82.4% versus 63.6%), pregnancy (21.6% versus 9.1%), monofollicular cycles (1.2 versus 2.4 follicles >18 mm on the day of hCG administration) and endometrial thickness (8.4 mm versus 5.2 mm) Which agree to our results in which letrozole group results were morebetter versus clomiphene citrate plus Hp-hmg results as regard ovulation rate (90% versus 86.7% respectively). But, pregnancy rate shows more increase in group (A) than group (C) in which (23.3% versus 20%) which differ than Atay study.

In the study of Bayar and colleagues in 2006, 36 patients (95 cycles) were given CC and 38 patients (95 cycles) were given letrozole. Differences regarding ovulation rates (74.5% versus 65.7%) these results was lower than our study but no differ as cc group in our study and Bayer were higher than letrozole group. pregnancy rates were (7.4% versus 9.1%) differing from our study as cc group in our study is the best as regard pregnancy rate. Although the percentage of monofollicular cycles was higher in letrozole-treated women in relation to significantly lower estradiol levels on the day of HCG.

In the study of Sohrabvand and colleagues in 2006, 59 women with PCOS resistant to CC were treated with the combination of letrozole and meftormin (53 cycles) or CC and metformin (67 cycles). Differences between the study groups included higher endometrial thickness in women treated with letrozole and metformin (8.2 versus 5.5 mm) and higher total estradiol level on day of hCG administration and mean estradiol level per mature follicle in the CC group.

Badawy and colleagues in 2007 studied 438 infertile women (1063 cycles) with PCOS. Patients were randomized to treatment with 5 mg of letrozole daily (218 patients, 540 cycles) or 100 mg of CC daily (220 patients, 523 cycles). In this study, advantage to the use of letrozole over CC as a first-line treatment for induction of ovulation in women with PCOS was not observed as significant differences in ovulatory cycles, pregnancy rates or miscarriage rates were not found. In contrast to previous studies and current study endometrial thickness at the time of HCG administration was significantly greater in the CC group (9.2 versus 8.1 mm).

It is remarkable that in none of the above mentioned studies, hyperstimulation syndrome or multiple gestations were reported.

In one trial, Begum and colleagues in 2008 evaluated the efficacy of high-dose letrozole in 64 women with PCOS who were diagnosed by Rotterdam criteria. If ovulation did not occur when women took CC 100 mg/day for 2 consecutive cycles, they were randomized to receive high-dose letrozole 7.5 mg/day or high-dose CC 150 mg/day. Similar to previous studies, letrozole therapy resulted in

significantly greater endometrium thickness compared with clomiphene citrate (10.37 ± 1.2 vs 9.03 ± 0.89 mm; $p < 0.001$) as our study. Although ovulation occurred in a higher percentage of letrozole-treated patients (62.5% vs 37.5%; $p < 0.05$), pregnancy rates were not significantly different (40.62% vs 18.75%; $p > 0.05$) similar to our study (20% versus 23.3%).

A meta-analysis including the four randomized-controlled studies comparing letrozole and clomiphene was done **(Atay et al., 2006; Bayar et al., 2006; Sohrabvand et al., 2006; Badawy et al., 2007)**. The overall effects of letrozole in comparison with CC in PCOS was neither significant for ovulatory cycles (OR =1.17; 95% CI 0.66–2.09), nor for pregnancy cycle rate (OR = 1.47; 95% CI 0.73–2.96) and for pregnancy patient rate (OR =1.37; 95% CI 0.70–2.71) similar to our study.

In **2009, (Ganesh)** apply similes study in which 3 protocols used in induction of ovulation. 23.3% is the pregnancy rate in Ganesh study as regard induction by CC in addition to Hp-hmg and letrozole. This percent is the same to current study.

Also in letrozole group is (20%) the same result. In Ganesh study results as regard Gonal-f was higher as in Ganesh (17.9%) but our was (13.3%).

Ovulation rate in **Ganesh, (2009**) in letrozloe group was 79.3% while in our is 90% in our study.

Our study shows ovulation rate in group (A) higher than Ganesh but group (B) ovulation rate is lower Ganesh group.

Capelo et al., 2003 based that CC treatment has been reported to induce ovulation in 60–80% of properly selected candidates which is lower than our study. More than 70% of those who ovulate respond at the 50- or 100-mg dosage level. Cumulative conception rates up to 70% were observed after up to three successfully induced ovulatory cycles i.e three times our results as regard pregnancy rate**.**

In another study by **Imani et al., 1999** cumulative conception rate of 73% was achieved within nine CC-induced ovulatory cycles. It is important to realize that these figures apply to young women in whom anovulation is the sole reason preventing them from conceiving.

It is generally believed that these effects are most apparent at higher doses or after longer durations of treatment. The endometrium is believed to be one of the most important targets of the antiestrogenic effect of CC and may explain a large part of the lower pregnancy rate and the possible higher miscarriage rate with CC. A reduction in endometrial thickness below the level thought to be needed to sustain implantation was found in up to 30% of women receiving CC **(Check et al., 1995).**

Ovulation is restored in approximately 80% but will result in pregnancy in only about 35–40% of patients who are given clomiphene **(Imani et al., 2002).**

The initial trial evaluating letrozole for infertility in PCOS included 12 women who were considered CC resistant. Patients were considered CC resistant if they were anovulatory (10 cycles) or if endometrium thickness was 5 mm or less (23 cycles) while CC 50–100 mg/day was given for 5 days of each cycle. A 60-day washout period occurred between the last CC cycle and letrozole administration. After a single letrozole cycle, patients exhibited significantly greater endometrium thickness than with prior CC treatment (mean ± SD, 8.1 ± 1.4 vs 6.2 ± 2.5 mm; $p < 0.01$). Ovulation occurred in 9 of 12 (75%) CC. Clinical pregnancy occurred in 3 patients after letrozole therapy, resulting in 2 singleton births. Negative endometrium effects were not reported with letrozole. Study limitations included its small sample size, open-label design, and use of a single cycle of letrozole **(Mitwally and Casper, 2001).**

In one trial, Begum and colleagues in 2007 evaluated the efficacy of high-dose letrozole in 64 women with PCOS who were diagnosed by Rotterdam criteria. If ovulation did not occur when women took CC 100 mg/day for 2 consecutive cycles, they were randomized to receive high dose letrozole 7.5 mg/day or high-dose CC 150 mg/day.

Similar to previous studies, letrozole therapy resulted in significantly greater endometrium thickness compared with clomiphene citrate (10.37 ± 1.2 vs 9.03 ± 0.89 mm; $p < 0.001$). Although ovulation occurred in a higher percentage of letrozole-treated patients (62.5% vs 37.5%; $p < 0.05$), pregnancy rates were not significantly different (40.62% vs 18.75%; $p > 0.05$). Multiple pregnancies were not reported in either group. Two miscarriages occurred with letrozole, while none occurred with clomiphene citrate. In this trial, patients were not technically classified as CC resistant since higher doses of clomiphene citrate were used for one study arm. Additionally, a washout period was not stated, making it difficult to isolate the effects of letrozole alone. Since pregnancy occurrence is multifactorial, the study sample size may have been too small to reflect a difference between groups. Additionally, mean BMIs neared 23 for both groups, which limits the study's external validity, as the mean BMI in PCOS is greater than 30 **(Yildiz et al., 2008).**

Badawy and colleagues in 2007 published trial comparing letrozole with clomiphene citrate in 438 anovulatory treatment-naïve women with PCOS (diagnosed with Rotterdam criteria). Although letrozole-treated patients had significantly decreased endometrium thickness compared with CC–treated patients (8.1 ± 0.2 vs 9.2 ± 0.7, respectively; $p = 0.021$), the ovulation, pregnancy per cycle, and

miscarriage rates were not significantly different between groups. Three twin pregnancies occurred with CC therapy. One unexpected difference in this study was greater endometrium thickness in clomiphene citrate–treated patients compared with letrozole-treated patients. This effect may be from the greater number of follicles plus higher estrogen and progesterone levels noted with CC. This larger, well-designed trial provides additional evidence that letrozole has efficacy similar to that of CC for ovulation induction in treatment-naïve women with PCOS.

Therefore, the 3r generation aromatase inhibitors (AIs) in comparison with other anitestrogenic drugs used for ovulation induction (AS CC) has more advantages with no apparent side effects on endometrial thickness or quality of cervical mucous which cause decrease in abortion rates & increase in full term pregnancies with letrozole.

Transient inhibition of aromatase activity in the early follicular phase with the aromatase inhibitor letrozole results in stimulation of ovarian folliculogenesis similar to that seen with clomiphene citrate with no apparent adverse effect on endometrial thickness or pattern at midcycle **(Stephanie et al., 2002).** Eventually, ovulation induction can sometimes be successful in women documented to be resistant to clomiphene using a combination of clomiphene citrate and letrozole. This is probably worth trying before proceeding to ovarian cautery or gonadotropins **(American Society for Reproductive Medicine 2005).**

In a series describing outcomes using the low-dose step-up regimen 225 women with PCOS were treated over a 10-year period, ovulation and pregnancy rates of 72 and 45% respectively were reported **(White et al., 1996).** The low-dose step-up protocol is associated with a lower incidence of multiple fplliculogenesis and hyperstimulation compared with the standard protocol **(Hamburg and Howles, 1998).** A study comparing the conventional with the low-dose step-up regimen using r-FSH confirmed higher rates of mono-follicular development employing the latter approach **(Hedon et al., 1998).** Pregnancy rates appear similar **(White et al., 1996; Hedon et al., 1998).** More recent studies focusing on further reducing the starting dose have reported the feasibility of commencing with 50 IU **(Hayden et al., 1999)** or 37.5 IU **(Balasch et al., 2000),** although outcomes were similar to those reported with standard doses. While ovulation can be achieved with this approach, the stimulation period may be further extended.

In a prospective randomized comparison of low-dose step-up and step-down regimens **(Van Santbrink and Fauser, 1997),** the respective incidence of monofollicular cycles was 56 and 88%. Those treated with the step-down regimen required a mean duration of treatment of just 9 days, as opposed to 18 days in women treated with the low-dose step-up regimen.

A recent multicentre randomized study comparing the step-up versus step-down protocol using r-FSH reported a shorter duration of stimulation when the step-down protocol was used. The cumulative rate of clinical gestations did not differ between the two groups, but in this study the step-up protocol was associated with a higher rate of mono-follicular development and a lower rate of ovarian hyper stimulation **(Christin-Maitre and Hugues, 2003).** The differences in outcomes between these randomized controlled trials may reflect the necessity for increased skill and care in monitoring step-down stimulation cycles, which is easier to ensure in a single-centre setting.

The classical approach to ovulation induction represented by clomiphene citrate as first line and gonado-trophins as second-line agents is associated with high cumulative pregnancy rates. In a study of 240 normo-gonadotrophic anovulatory women in whom this treatment algorithm was followed, cumulative pregnancy rates after 12 and 24 months were 50 and 71% respectively **(Eijkemans et al., 2003).** Recently, a randomized studj^ comparing clomiphene citrate with r-FSH as a first line treatment for anovulation in association with PCOS showed higher cumulative pregnancy rates observed after r-FSH **(Lopez et al., 2004).** However, the increased costs and risks associated with r-FSH treatment mitigate against its use as a first-line treatment.

The complications of ovulation induction with gonadotropbins are primarily related to excessive ovarian stimulation. While the aim of therapy is monofollicular growth, multiple follicular development may occur, causing symptoms of OHSS. Moreover, the development of multiple follicles raises the real risk of multiple pregnancy. In order to increase the chance of therapeutic success and reduce the risks of complications, careful monitoring of treatment is required. Ovarian response to gonadotrophin therapy is monitored using transvaginal ultrasonography to measure follicular diameter. The scans, usually performed every 2 or 4 days, should be focused on identifying follicles of intermediate size. hCG (5000-10.000 IU intramuscularly) is given on the day that at least one follicle measures >18 mm. If more than three follicles larger than 15 mm are present, stimulation should be stopped, hCG withheld, and use of a barrier contraceptive advised in order to prevent multiple pregnancies and ovarian hyperstimulation. Measurements of serum oestradiol may also be useful.

Pre-ovulatory concentrations far above the normal range may predict the onset of OHSS. It is unclear to what extent oestradiol concentrations add to information generated by ultrasound alone, as large quantities of oestradiol can be produced by small or intermediate-sized follicles, particularly in PCOS patients **(Schoot et al., 1995).**

Ovarian stimulation with gonadotrophins has not been shown to be associated with long-term risks. Urinary-derived FSH is associated with a theoretical risk of transmission of prion proteins, which have been identified in human urine. Although in 40 years of use no such infections have been identified, the risk of prion disease such as new variant Creutzfeldt-Jakob disease has been deemed by some to be sufficient as to advise against the use of u-FSH. However, others consider the risk to be minimal and not in itself a reason to prescribe r-FSH over u-FSH **(Balen, 2002).**

Adam balen et al. (2007) compare rfsh vs hp fsh in inducing ovulation in 151 pcos patients dividing them into two groups ovulation rate in rfsh group 90.9% while in hpfsh 85.2% with no significant differance between both groups. The same in percents of pregnancy rate as in rfsh group 12 out of 78 patients get pregnant while in hpfsh group 11 out of 73 patients also there is no significant difference **(Balen et al., 2007)**.

Other study performed by Alberto revelli et al., in 2006 in which they recruited patients shows clpmiphene citrate resistant patients. they use rfsh in group for 37 cycles where hpufsh in 39 cycles. Results shows monofollicular ovulation in 33.3% in hpfsh with no SD in rfsh group as only 40.5% shows monofollicular ovulation. Four cases delivered in hpufsh group on the other hand seven cases delivered in rfsh **(Alberto revelli et al., 2006)**.

Finally, Cochrane published in 2001 prof. **Van wely et al. (2007)** based on that review compare rfsh vs hpfsh as they compare results of six studies some of them in multicentric centeres. These studies will be discussed later, we briefly shows that in all six studies there is no differ in pregnany rate as in loumaye et al., in 1996 in which 30% in rfsh group vs 28% in hpfsh.

The same in coelingh bennink et al., study in 1998 pregnany rate 50% in rfsh while 37% in hpfsh group **(Cochrane 2001)**.

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