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Comparative Study of Clomiphene Citrate and Aromatase Inhibitors (Short and Long Protocols) In Polycystic Ovarian Syndrome

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is a heterogenous disorder and is characterized by excessive androgen production by the ovaries.First line drug for ovulation induction is clomiphene citrate(CC).Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction.

Methods: It was the prospective study of 120 women between 20 -35 years of age who are PCOS with regular follow up in OPD. They were divided into three study groups on the basis of drugs used.

Results: Ovulation was better in women on clomiphene citrate and letrozole 5 mg short protocol as compared to women on letrozole 2.5mg long protocol.

Conclusions: The rate of ovulation with clomiphene citrate (group A) in PCOS patients is 76% and with letrozole short (group B) and long protocols(group C) it is 64% and 28.8% respectively.The endometrial thickness in clomiphene citrate(group A) in PCOS patients is 8.8 mm and with letrozole short(group B) and long protocol(group C) in PCOS patients it is 10 mm and 10.2 mm respectively

Keywords: Clomiphene citrate, Letrozole, PCOS

Introduction

Polycystic ovarian syndrome (PCOS) is a heterogenous disorder and is characterized by excessive androgen production by the ovaries .It affects 7-8 % of reproductive age women[1]. PCOS is a multifactorial condition diagnosed upon presence of any two of following three criteria (ASRM/ESHRE2003)[2]-

oligomenorrhea, hyperandrogenism, polycystic ovaries.

The treatment of infertile women with PCOS is surrounded by many controversies. On the basis of current evidence recommended first line drug for ovulation induction is clomiphene citrate(CC)[3,4].However the use of CC may be associated with poor cervical mucus & endometrial thinning in 15-50% patients[5,6].Letrozole, an Aromatase Inhibitor(AI) has attracted attention for long time as an ovulatory agent with reported ovulation of 70-85% and pregnancy rate of 20-27% per cycle[7]. Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction. Even singleton pregnancies in PCOS are associated with increased health risk for both mother and the fetus[8]. So newer agents like aromatase inhibitors and insulin sensitisers although promising need further evaluation[9]. Moreover there are other potential applications for aromatase inhibitors in infertility

management like improving implantation in assisted reproduction and in vitro maturation[10].As PCOS contains a variety of fertility and general health problems it is of great importance to tailor the specific treatment for individual patient[11].

Materials and Methods

It was the prospective study of women between 20 -35 years of age who are PCOS with regular follow up in OPD.

Design of study: Single centre prospective study.

No. of subjects in the study: 120

Period of study: April 2010 to April 2011.

Inclusion criteria

1. Age between 20-35 years.
2. Patients fulfilling any of two criterias to categorise as PCOS.
3. Patient with anovulatory cycle on follicular monitoring.

Exclusion criteria

Patients with

- Premature ovarian failure
- Thyroid dysfunction
- Hyperprolactinemia
- Male factor infertility

Study Design

All patients coming to opd fulfilling the inclusion criteria were included. Hormone profile on second day of the cycle including serum FSH, LH, Prolactin, FBS was done. These patients underwent follicular monitoring and one showing anovulation were included in the study and grouped as-

Group A-

CC 50mg given from day 5 for 5 days. In case of failure of ovulation largest follicular size and endometrial thickness was noted. Patient who ovulated were advised to have timed intercourse and progesterone in luteal phase.

Group B-

Letrozole 5mg given from day 3 for 5 days. Ovulation was documented on sonography. In case of failure largest follicle size and Endometrial thickness was noted. Patient who ovulate advised to have timed intercourse and progesterone in luteal phase.

Group C-

Letrozole 2.5mg given from day 1 for 10 days. Ovulation was documented on sonography. In case of failure largest follicle size and Endometrial thickness was noted. Patient who ovulated were advised to have timed intercourse and progesterone in luteal phase.

Results-

Table 1 a. The comparison of outcome between three study groups

Outcome	Group A(CC 50mg ; n=25)	Group B(letrozole 5mg; n=50) ; short term	Group C(letrozole 2.5mg; n=59) ;long term
No ovulation	3(12%)	9(18%)	22(37.3%)
Ovulation without pregnancy	19(76%)	32(64%)	17(28.8%)
Ovulation with missed abortion	1(4%)	3(6%)	12(20.3%)
Ovulation with pregnancy	2(8%)	6(12%)	8(13.6%)

Figure 1- The comparison of outcome between three study groups.

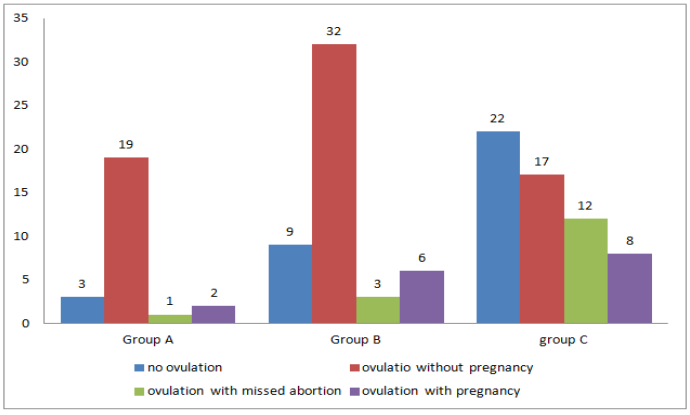

Table 1b- The statistical comparison of outcome between three study groups

Comparison	Chi square value	P value	Statistical significance
Group A vs B	1.103	0.776	Non significant
Group A vs C	16.381	0.001	Highly significant
Group B vs C	15.089	0.002	Significant

Comments-

1. Outcome of ovulation is not significantly different between study groups A and B.
2. Outcome of ovulation is significantly different between study groups A and C.
3. Outcome of ovulation is not significantly different between study groups B and C.
4. Ovulation is better in group A and B compared to C.

Table 2a- The comparison of endometrial thickness between three study groups

Endometrial thickness (mm)	Group a(CC 50mg ; n=25)	Group B(letrozole 5mg; n=50) ; short term	Group C(letrozole 2.5mg; n=59) ;long term
Cycle 1	8.5 ± 0.97	9.8 ± 1.23	10.1 ± 0.91
Cycle 2	8.8 ± 0.91	10 ± 0.89	10.1 ± 0.78
Cycle 3	9.2 ± 0.77	10.3 ± 0.84	10.4 ± 0.82
Average	8.8 ± 0.71	10 ± 0.75	10.2 ± 0.57

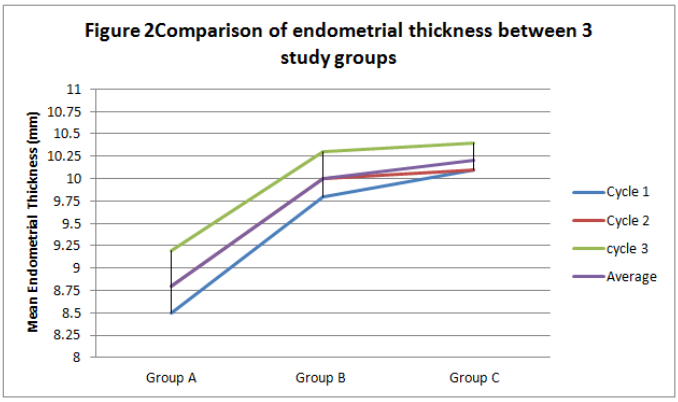

Table 2b- The statistical comparison of endometrial thickness between three study groups

Comparison	P value				Statistical significance
	Cycle 1	Cycle 2	Cycle 3	Average	
Group A vs B	0.001	0.001	0.001	0.001	Highly significant
Group A vs C	0.001	0.001	0.001	0.001	Highly significant
Group B vs C	0.267	0.765	0.750	0.343	Non significant

Comments-

1. Average Endometrial thickness is significantly higher in study groups B and C compared to A.
2. Average endometrial thickness is not significantly different between study groups B and C.

Discussion

Fisch et al[12] and coworkers in 1989 commented that the rate of ovulation in clomiphene citrate in PCOS patient is 57- 91% while in our study we found that CC has rate of ovulation around 76% which is similar to the above study.

As per Holzer et al(2006)[13] the rate of ovulation in Letrozole short protocol in PCOS patients is 70-80% while our study quoted it as 64%.

None of the studies previously compared Clomiphene citate and aromatase inhibitors(Letrozole) as done by our study.

Mitwally MF et al(2001)[14], the endometrial thickness with Clomiphene citrate in PCOS patients is approximately 8 cm which is similar to our study which quoted it as around 8.8cm.

Holzer et al (2006)[13], the endometrial thickness in Letrozole short protocol and long protocol in PCOS patients is 9.9 – 11.2 mm.The result of my study is comparable to the above study.

None of the studies compared endometrial thickness between clomiphene citrate and letrozole short and long protocols in PCOS patients.

As per Ashalatha Ganesh et al(2008)in Clomiphene citrate in PCOS patients rate of missed abortion was 16% while in our study it was only 1%.

Badawy et al (2007)[15,16,17] rate of missed abortion in letrozole short protocol is 17.9 % and in long protocol in PCOS patients is around18.4%.

The rate of missed abortion is very less in our study which may be due to age group differences, racial differences or extra care and progestational supports in our set up.

According to Mosammat Rashida Begum et al (2009)[18] with clomiphene citrate in PCOS patients the pregnancy rate is 16% while in our study it is very low (only 2%).

As per Badway et al(2008)[15,16,17] the rate of pregnancy by letrozole short protocol in PCOS patients is 12.4% and by letrozole long protocol in PCOS patients is 17.4 % which is high comparing our data showing 6% and 8% respectively.

These differences may be due to age group and racial differences.

Conclusion

The rate of ovulation with clomiphene citrate (group A) in PCOS patients is 76% and with letrozole short(group B) and long protocols(group C) it is 64% and 28.8% respectively.

The endometrial thickness in clomiphene citrate(group A) in PCOS patients is 8.8 mm and with letrozole short(group B) and long protocol(group C) in PCOS patients it is 10 mm and 10.2 mm respectively.

The rate of miscarriage in clomiphene citrate(group A) and letrozole short(group B) and long(group C) protocol in PCOS patients is 1%,3% and 12% respectively.

The rate of pregnancy in clomiphene citrate(group A) and letrozole short(group B) and long(group C) protocol in PCOS patients is 2%,6% and 8% respectively.

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