

Risk of Developing Ovarian Cyst in Monitored Versus Unmonitored Ovulation Induction

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Abstract

Objective: To compare the frequency of ovarian cysts in clomiphene citrate ovulation induction cycles among regularly monitored and unmonitored patients.

Study Design: Quasi-experimental study.

Place and Duration of Study: This study was conducted at Combined Military Hospital (CMH) Quetta from 31st March 2010 to 31st March 2011.

Methodology: Sixty women in reproductive age group, with history of primary or secondary infertility, who were unable to conceive after 1 year of unprotected intercourse and were taking clomiphene citrate for ovulation induction, were included in the study. Patients were sampled through consecutive sampling, from outpatient department.

Results: The group without monitoring (group A, n=30) had 12 (40%) patients who developed ovarian cysts while in the regularly monitored group (group B, n=30) only 3 (10%) patients formed ovarian cysts. No difference was observed regarding number of cycles or dose, which took to develop cysts. Out of total 15 patients who developed a cyst, 7(47%) patients developed ovarian cyst(s) at ≤ 3 clomiphene cycles and 8(53%) patients developed cyst(s) at ≥ 3 clomiphene cycles. Seven (47%) patients were found to have ovarian cyst at ≤ 100 mg dose and 8 (53%) patients developed ovarian cyst at ≥ 100 mg dose.

Conclusion: Regular monitoring during ovulation induction reduces the incidence of ovarian cyst formation.

Key words: Infertility, Ovulation induction, Ovarian cyst, Clomiphene Citrate.

Introduction

Infertility is defined as failure to conceive after one year of unprotected intercourse.¹ Approximately 10%

of couples seek health care of infertility.² Clomiphene citrate is in use since the 1960s and is still considered the best initial treatment for the majority

of women with anovulatory infertility.³ Clomiphene has also been widely used among couples with unexplained infertility.⁴ Clomiphene citrate is an orally active synthetic non-steroidal compound with oestrogenic as well as anti-oestrogenic properties. The exact mechanism of action of clomiphene citrate is not known.⁵ It displaces oestrogen from its receptors in the hypothalamic-pituitary axis, reduces the negative feedback effect of oestrogen and encourages GnRH secretion.⁶ The result is an increase in the release of pituitary gonadotrophins, growth of the ovarian follicle and subsequent follicular rupture. Ovulation is expected to occur in 80% and pregnancy in 35-40% women on clomiphene.⁷ Approximately 20-25% of women show no response to clomiphene citrate and are considered to be resistant.⁶

The aim of ovulation induction therapy should be, wherever possible, to correct the underlying disturbance and achieve uni-follicular ovulation to achieve the live birth of singleton babies.⁸ It is very essential for infertility experts to ascertain the complications of the use of fertility agents on a sound basis, particularly in view of the fact that the drugs are becoming increasingly popular. These drugs are being used randomly not only in clinics involved in assisted reproductive technology but also by gynaecologists in general and even by general practitioners. Significant ovarian enlargement occurs in 5% but ovarian hyperstimulation syndrome is rare. The multiple pregnancy rate associated with clomiphene is 7-10%.⁶

The risk of ovarian stimulation is under estimated in our society by both patients and practitioners. Hypothesis of this study was that unmonitored use of clomiphene citrate for ovulation induction may cause

formation of new ovarian cysts or further stimulation in the size of already existing ovarian cysts, which offsets the effects of clomiphene by either with holding the treatment for 2-3 months or further adding oral contraceptive pills for resolution of these cysts. Therefore, the aim of this study was to compare the frequency of ovarian cysts in clomiphene citrate ovulation induction cycles among regularly monitored and unmonitored patients.

Methodology

This study was conducted at Combined Military Hospital (CMH) Quetta from 31st Mar 2010 to 31st Mar 2011. Study design was Quasi experimental study. Women, who were unable to conceive after 1 year of unprotected intercourse and were planned for ovulation induction with clomiphene citrate, were included in the study. Patients were sampled through consecutive sampling, from the gynaecological outpatient department of CMH Quetta. Women with pre-existing ovarian cyst(s) at baseline pelvic ultrasound scan (US), detection of a multilocular septate or complex cyst during the study, or conception ordinary during the study were our exclusion criteria. Seventy four women were initially enrolled in the study after an **informed written consent**. Six women with pre-existing ovarian cysts (size >3 cm) and five women who became pregnant within first three cycles of clomiphene citrate ovulation induction were excluded from the study. Three women who developed ovarian cysts (while on clomiphene citrate) of more than 8 cm in size or with septations or any other associated feature suggesting malignancy were referred for appropriate evaluation and were excluded from the study.

Group A: Included 30 women already taking Clomiphene Citrate for 3 to 6 cycles prescribed by sources other than the index hospital. No preliminary or interim ultrasound scan or progesterone levels had been recorded.

Group B: Included 30 women, not having any of the exclusion criteria and with history of primary or secondary infertility who were planning to start clomiphene citrate for ovulation induction. A baseline pelvic US was done to rule out preexisting adnexal or follicular cysts. Clomiphene citrate 50 mg was given from day 2 to day 6 of menstrual cycle. Serum progesterone levels were done on day 21 of cycle. If progesterone levels were ≥ 30 ng/dl then same dose of clomiphene citrate was given in next cycle. If day 21 progesterone levels were < 30 ng/dl then 100 mg of clomiphene citrate was given in 2nd cycle. In this cycle serum progesterone levels were done on day 21 and day 24. If progesterone levels were < 30 ng/dl then increments in the dose were made to a maximum dose of 150 mg per day. As part of protocol, in every patient transvaginal ultrasound was repeated before prescribing clomiphene citrate. Follicular tracking was added for monitoring of ovulation. If there was formation of ovarian cyst of >3 cm size, clear and anechoic, then treatment with clomiphene citrate was withheld for next 2-3 cycles or oral contraceptive pills were prescribed for 1-2 cycles.

Ethical Approval was obtained from the Hospital research committee after presenting the detailed proposal Frequency (as percentage) of development of ovarian cysts and their size was calculated in both the groups.

Data was analyzed using SPSS version 15. Descriptive statistics were used to describe the data i.e. mean and standard deviation (SD) for quantitative

variables like age and size of the cyst while frequency and percentages for qualitative variables like cycles, dose and number of cyst. Quantitative variables were compared through independent samples 't-test' and qualitative variables were compared through chi-square test between both the groups. P-value < 0.05 was considered as significant.

Results

Sixty patients in total were included in this study and 30 patients were allocated to each group. Mean age was comparable between the two groups. In Group A mean age was 25.9 years and in Group B it was 24.3 years (p value >0.5). Results showed that 12 cysts were formed in group A and 3 were formed in group B, the difference is statistically significant (Table I).

Table I. Comparison of study variables

Patients characteristics	Group A (n = 30)	Group B (n = 30)	p-value
Age (in years)	25.90 \pm 4.59	24.23 \pm 3.49	0.119 ^{NS}
Number of cyst	12 (40%)	3 (10%)	0.038 [*]
Size of the cyst (cm)	7.20 \pm 0.91	2.2 \pm 0.32	< 0.001 [*]

* = Significant NS= Non significant

In the unmonitored group cyst size upto 7.2 cm was noted while in group B cyst size did not go beyond 2.2 cm (p -value <0.5 -significant).

Cysts had been formed at doses as low as 50-100 mg in group A (unmonitored) and during very initial cycles (Table II) but these women were still taking incremental doses of the drug whereas because of monitoring scans incremental dose was with held in Group B. Cysts were mainly unilocular in both the groups (multilocularseptate cysts were already ex-

cluded). No cyst accidents were noted in either group.

Table II. Variables associated with Cyst formation in either group

Variable	Frequency of Cyst(s)			p-value
	Group A (n=12)	Group B (n=3)	Total (n=15)	
Cycles	05	02	7 (47%)	0.52 ^{NS}
≤3 cycles				
≥ 3 cycles	07	01	8 (53%)	--
Dose	05	02	7 (47%)	0.52 ^{NS}
≤ 100 mg				
>100mg	07	01	8 (53%)	--

NS=non significant

Discussion

In the reproductive age group functional ovarian cysts are still the most common type of ovarian mass. Unilocular cyst may be followed-up conservatively by ultrasound scan. One series showed that 90% of the cysts will resolve or decrease in size. In the past, contraceptive pills have been prescribed, though it has not proven to hasten resolution.⁹ Cyst accidents like torsion, haemorrhage and infection are liable to happen as in any other cyst including risk of malignancy.

A starting dose of 50 mg of clomiphene should be given for 3 months, but may be increased upto 100 mg if needed. Once an ovulation dose has been reached, the cumulative conception rate continues to increase for up to 10-12 cycles. It is recommended that use of clomiphene be limited to 12 lifetime cycles.¹⁰

Women using infertility drugs must be counseled regarding the risks and benefits. Alice Whittemore¹¹ summarized that there was a high risk of carcinoma in females diagnosed as infertile after 1970 than

those before 70's. Her argument was that fertility drugs like clomiphene citrate and human menopausal gonadotrophins were introduced in USA between 1967-69. These drugs were originally brought out for the purpose of usage in anovulation as a cause of infertility. The tendency today is to treat even ovulating women in order to induce superovulation. Superovulation certainly multiplies the number of ovarian ruptures in each month thus multiplying the age of ovaries by the number of follicles produced and similarly the quantum of trauma, repair, formation of inclusion cysts and the amount of steroids being produced.

In the UK, the Committee of Safety of Medicines recommends that the use of clomiphene citrate should be restricted to 6 months per patient.⁵ If patients are to continue beyond 6 months limit, further counseling of patient is mandatory because of the suggested increased risk of ovarian cancer with prolonged use. Rossing et al. reported a significant association of clomiphene citrate use for 12 cycles or more and the diagnosis of ovarian tumors.¹² Some studies suggest no association of ovarian cancer with clomiphene treatment^{13,14} whereas a recent study suggested increased risk of borderline ovarian tumors after clomiphene treatment.¹⁵ Risk of other malignancies is also increased with injudicious use of clomiphene citrate. Uterine cancer risk increases with number of cycles of clomiphene¹⁶ and high dose clomiphene citrate therapy may have an elevated risk for breast cancer.¹⁷

The risk of ovulation inducing agent producing a malignancy is thought to be less than 1:5000.¹⁸ Therefore, such a risk is not likely to be taken notice of seriously by average infertile female who is suffering

from social and mental stress which can only be relieved with pregnancy. Although no case of cyst accident was recorded in our study, but the emotional trauma of delaying fertility treatment and using contraceptive pills while to conceive, due to injudiciously use of clomiphene, had a significant negative effect on patients. Moreover, we observed during the study, that infertility is already an “issue” for the affected couple and over and above the stigma of ovarian cyst had a further demoralizing impact on the mental wellbeing of infertile women.

In our study we did not find age as a significant factor for early development of cysts. We did not observe any cumulative effect of clomiphene citrate as far as number of induction cycles and dose was concerned. Even at doses as low as 50-100 mg, 17% (5/30) patients had developed cysts in the unmonitored group. Once cysts are detected further infertility treatment had to be with held in these patients for 4–6 months. Whereas, in group with regular monitoring, only 07% (2/30) patients developed ovarian cyst at doses less than 100mg. Due to early detection, the size of cyst was less than 3 cm in these patients and delay in further treatment was only for 1-2 months. Out of total 15 cases of cysts, one third cysts (05=33%) actually developed in less than 3 cycles in group A only. However in the un-monitored group possibility of pre-existing cysts cannot be ruled out because they had denied the opportunity of having a formal baseline ultrasound scan.

The risk of developing ovarian cysts in response to ovulation induction is being under estimated in our society. One important policy that the practitioners should enforce on themselves is to reduce the quantities of ovarian stimulants administered. No ovulation enhancing agents should be prescribed to pa-

tients for use over several months without monitoring the ovarian performance in each cycle. In fact, before starting ovulation induction with clomiphene citrate, pre-existing ovarian cyst(s) should be ruled out by ultrasound. Simple ovarian cysts significantly reduce ovulatory events in patients treated with clomiphene citrate.¹⁹ A reduction in follicular number would also protect the patients against multiple pregnancies and ovarian hyper stimulation syndrome.

Conclusion

Regular monitoring during ovulation induction reduces the incidence of ovarian cyst formation whereas use of clomiphene citrate without any monitoring increases the risk of cyst formation and may further delay infertility treatment. The optimal form of monitoring is with ultrasound, for at least one cycle, to assess follicular growth, to measure endometrial thickness, and to time the intercourse appropriately around ovulation. Without ultrasound monitoring, the number of clomiphene cycles should probably be limited to three, and early referral to a specialist clinic should be considered before several of the patient's lifetime cycles have been used up.

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