

Incidence of Ovarian Cysts in Patients Taking Ovulation Induction with Clomiphene Citrate

Frequency of Ovarian Cyst in Patients of Induced Ovulation

Abroo Shahnaz¹, Joveria Sadaf¹, Asia Aziz², Tanzila Rafiq¹ and Aslam Mahmood Malik¹

ABSTRACT

Objective: To determine the frequency of ovarian cyst in patients of induced ovulation.

Study Design: Descriptive study

Place and Duration of Study: This study was conducted at the Department of Obstetrics & Gynecology, Shahida Islam Teaching Hospital Lodhran from September 2019 to August 2020.

Materials and Methods: A total of 214 patients with infertility planned for ovulation induction, 20-35 years of age were included. Patients with preexisting ovarian cyst were excluded. To all patients 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 > 30ng/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 was made to a maximum dose of 150 mg per day in 3rd cycle. As part of protocol, in every patient transvaginal ultrasound was repeated before prescribing clomiphene citrate.

Follicular tracking was added for monitoring of ovulation. After 3rd cycle pelvic ultrasound was done to diagnose any ovarian cyst.

Results: Age range in this study was from 20 to 35 years with mean age of 29.27 ± 2.34 years. Majority of the patients 132 (61.68%) were between 20 to 30 years of age. Mean duration of infertility was 3.81 ± 1.63 years. Mean BMI was 28.53 ± 2.59 kg/m². Mean dose of clomiphene citrate was 84.63 ± 21.63 mg. Frequency of ovarian cyst in patients of induced ovulation was found in 22 (10.28%) patients.

Conclusion: This study concluded that frequency of ovarian cyst in patients of induced ovulation is quite high.

Keywords: infertility, ovulation induction, ovarian cyst. Clomiphene citrate

Citation of article: Shahnaz A, Sadaf J, Aziz A, Rafiq T, Malik AM. Incidence of Ovarian Cysts in Patients Taking Ovulation Induction with Clomiphene Citrate. *Med Forum* 2021;32(4):104-107.

INTRODUCTION

Ovarian cysts are commonly found among women all over the world. Women having ovarian cysts may need hospitalization and even the need for surgery. It has been seen that 5 to 10 % women will need surgical removal of adnexal mass. In the United States, Annually more than 250,000 women had diagnosis of ovarian cyst at the time of hospital discharge.¹ Ovarian cysts are divided into two main types, physiological and pathological. Most of the ovarian cysts found in women of reproductive age are physiological in nature.

¹. Department of Obs and Gynae, Shahida Islam Medical Complex Lodhran.

². Department of Community Medicine, Quaid e Azam Medical College Bahawalpur.

Correspondence: Dr. Joveria Sadaf, Assistant Professor, Obs and Gynae Shahida Islam Medical Complex Lodhran.

Contact No: 03001280960

Email: joveriasadaf@gmail.com

Received: November, 2020

Accepted: January, 2021

Printed: April, 2021

Among them, the most common type in reproductive age is functional cysts, which in rare cases enlarge up to 8cm or more. They resolve themselves within 4 to 8 weeks. Follicular cysts are formed when mature follicle fail to rupture and keep on increasing in size. Other type of functional ovarian cyst, a corpus luteal cyst is formed when after ovulation the corpus luteum does not regress.² Pathological tumors are further divided into benign, malignant and borderline tumors. The risk of malignant tumor is increased with ageing. Ovarian cysts are commonly asymptomatic and likely to resolve themselves in premenopausal women, while in postmenopausal women; ovarian cysts lead to the symptoms of pain or pressure and may need surgical removal.

Mostly ovarian cysts are asymptomatic especially when they are smaller in size. But as the size grows symptoms appear that may be abdominal or pelvic pain or discomfort, increased urinary frequency, dysmenorrhea dyspareunia, nausea vomiting or bloating sensation and feeling of fullness or heaviness.^{3,4}

The risk factors found for the formation of ovarian cysts are the drugs used in women with sub fertility, tamoxifen use in breast cancer patients, and

hypothyroidism, pregnancy, cigarette smokers and female sterilization. Though the other ovulatory drugs like Aromatase inhibitors, selective estrogen modulators and gonadotrophins are easily available, clomiphene citrate is considered as a first line therapy for ovulation induction in women with sub fertility. Women having ovulation induction may develop the ovarian cyst and several hypotheses have been proposed regarding ovarian cyst formation and its progression. The first hypotheses is Fathalla's tear-and-repair hypothesis states that damage occurred to the ovarian surface due to ovulatory drugs leads to multiple proliferation of the ovarian surface epithelium and DNA replication resulting in the formation of ovarian cyst^{6,7}. A second hypothesis describes the formation of ovarian cysts due to overgrowth of the surface epithelium and the lack in apoptosis of damaged cells mainly caused by gonadotrophins.⁸ Third hypothesis is linked to the inflammatory drugs released after induced ovulation, resulting in cellular proliferation and replication errors due to DNA damage. Another search did by Anwar A and his collaborators have shown the formation of ovarian cysts in 10 % of patients who took ovulation induction,⁹ while Coskmay JM and his team found the incidence of ovarian cysts of about 36.7% in patients with ovulation induction.¹⁰

There is lack of evidence in present research data about this topic. Some studies have been conducted locally but the power of study is not that strong due to smaller sample size⁹ so we decided to research this topic with 214 patients to increase the strength of evidence. My study results will pave the way for future researchers to plan more research in this topic to get more evidence in our local population.

MATERIALS AND METHODS

Descriptive, case series study done in department of Obstetrics & Gynecology, Shahida Islam Teaching Hospital, Lodhran from September 2019 to August 2020

Sample Technique: Non-probability, consecutive sampling

Sample Selection: All women age 20-35 years presented with Infertility in Shahida Islam Teaching Hospital OPD for whom ovulation induction was planned were included in the study. Patients with pre-existing ovarian cyst on ultrasound and patients who had conception during study period on pregnancy test in laboratory were excluded from the study.

Data Collection Procedure: Total 214 patients fulfilling the inclusion and exclusion criteria were included in the study after permission from ethical committee and research department of Shahida Islam Teaching Hospital, Lodhran. Base line demographic information of patients (age, weight, infertility duration) was taken. Informed consent was taken from

each patient, ensuring confidentiality and fact that there is no risk involved to the patient while taking part in this study and the expenses of serum progesterone test would be borne by the researchers. To all patients' initially, 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 > 30ng/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 was made to a maximum dose of 150 mg per day in 3rd cycle. As part of protocol, in every patient trans-vaginal ultrasound was repeated before prescribing clomiphene citrate. Follicular tracking was added for monitoring of ovulation. After 3rd cycle pelvic ultrasound was done to diagnose any ovarian cyst as per operational definition. All ultrasounds were done by a consultant gynecologist of 3-year post fellowship experience. Data regarding ovarian cyst was noted on especially designed proforma.

Statistical Analysis: Data was analyzed with statistical analysis program SPSS version 20. Frequency and percentage were computed for qualitative variables like age groups and ovarian cyst. Mean \pm SD were presented for quantitative variables like age, duration of infertility, dose of clomiphene citrate and BMI. Effect modifiers like age, duration of infertility, dose of clomiphene citrate and BMI were controlled by stratification. Post stratification chi square test was applied $p \leq 0.05$ was considered statistically significant.

RESULTS

Age range in this study was from 20 to 35 years with mean age of 29.27 ± 2.34 years. Majority of the patients 132 (61.68%) were between 20 to 30 years of age as shown in Table I. Mean duration of infertility was 3.81 ± 1.63 years.

Table No.1: Distribution of patients according to age, BMI and dose of clomiphene citrate (n=214)

variable		No of patients	%age	Mean \pm SD
Age in years	20-30	132	61.68	29.27 \pm 2.34 years
	31-35	82	38.32	
BMI (kg/m ²)	≤ 27	73	34.11	= 28.53 \pm 2.59 kg/m ²
	> 27	141	65.89	
Dose of clomiphene	50 mg	41	19.16	103.73 \pm 23.32mg
	100 mg	116	54.21	
	150 mg	57	26.63	

Frequency of ovarian cyst in patients of induced ovulation was 22 (10.28%) patients.

When stratification of ovarian cyst was done on age groups, it was evident that there was significant difference between different age groups as shown in Table II while the stratification of ovarian cyst with respect to duration of infertility which showed no significant difference between different groups. Stratification of ovarian cyst with respect to BMI and dose of clomiphene citrate is also shown in Table II.

Table No.2: stratification of ovarian cysts with age of the patients their BMI and dose of clomiphene citrate

variable		Ovarian cysts		P value
		yes	no	
Age in years	20-30	07	125	0.006
	31-35	15	67	
Duration of infertility	≤3years	08	109	0.069
	>3years	14	83	
BMI (kg/m ²)	≤27	11	62	0.097
	>27	11	130	
Dose of clomiphene	50 mg	03	38	0.778
	100 mg	13	103	
	150 mg	06	5	
			1	

DISCUSSION

Ovarian cysts are defined as fluid filled sacs that could be simple or complex, unilateral or bilateral. These cysts are found either on physical examination or on ultrasonography.¹¹ Almost 20% of women develop at least one pelvic mass at some point of their life. Women of reproductive age usually experience the formation of physiological cyst due to release of endogenous hormones. In patients who are taking ovulation induction, simple, smooth, thin walled, unilocular cysts commonly develop due to unruptured follicle as the number of developing follicle has increased now with the use of induction. Follicular cysts are usually larger than 2.5cm but very less often they enlarge >8cm. Corpus luteal cysts are formed due to persistence of corpus luteum after 14 days (average life span of corpus luteum). Corpus luteal cysts may be simple or complex and are thick walled with an average size about 3cm or more and they are exclusively found in pregnancy until the end of first trimester and then resolve themselves.^{12,13} So, the management of these functional cysts is expectant especially in women who are trying to be pregnant. Though combined oral contraceptive pills can decrease its incidence by inhibiting ovulation but it is not recommended as a treatment of ovarian cyst.¹⁴ The formation of ovarian cyst is not specific to the patient or her menstrual cycle, Even there is no specific evidence regarding its stimulus which may be central, in the hypothalamus or pituitary or peripheral in the adrenal gland or the ovary. There are limited studies regarding the incidence of functional cysts but two studies were conducted

separately by doing an ultrasound of a large sample of asymptomatic women which showed an incidence of about 6.6%. Some other studies showed that of formation of ovarian cysts is related to the BMI, the onset of menarche, and the pattern of female menstrual cycle.^{15,16,17} Although other ovulatory drugs are widely available but clomiphene citrate is used preferably as a drug of choice initially. But there is a controversy regarding the use of CC in females who already have functional ovarian cysts.

We have conducted this study in 214 cases attending the outpatient department to see the frequency of ovarian cysts in women who took ovulation induction. Age group included in my study was between 20-35 years with a mean age of 29.27±2.34 years. More than half of the patients 132 (61.68%) included the age group of 20 -30 years. Our study demonstrated the development of ovarian cysts in 22 patients making the incidence of 10.28%. Another study conducted by Anwar A and his researchers showed incidence of 10 % in women having ovulation induction.⁹ Study conducted by Csokmay JM and his team found the frequency of ovarian cysts in 36.7% of the females who used ovulatory drugs.¹⁰ The cut-off value defined for the size of an ovarian cyst used in both studies was 10mm though the previous literature marked the follicle to be cystic if it is larger than 3cm because cystic follicle size of 10 mm is difficult to differentiate from follicle and follow-up has no such benefit. Even with this small size of cyst, it is hard to define the nature and blood flow on Doppler ultrasound. The first study found the incidence of basal ovarian cyst of >10mm in almost 5 patients (17.5%) and it was conducted retrospectively.^{11,18,19} While the other study concluded the mean ovarian size of 17.4±5.8mm. Ovulation rate found in patients with ovarian cyst was >80% while the women without ovarian cysts have a higher ovulation rate of 97.6%. Even the comparison of pregnancy rate showed a difference (4.8% versus 11.9% p<0.4). The persistence of ovarian cysts was found in 36.7% patients. The common thing between these studies and my study was that the initial size of the cyst was not used as a predictive indicator for the persistence of cyst.^{20,21}

Though we couldn't find any malignant potential in ovarian cysts, but simple functional ovarian cysts were found by repetitive proliferation of ovaries, induced by clomiphene citrate commonly in overweight women with late reproductive age, and having prolonged subfertility. As a result, we should be more vigilant before starting the infertility treatment and ovulation induction in these high risk cases, increasing the need for frequent trans-vaginal ultrasound, pre-treatment as well as on follow ups after taking ovulation induction with CLOMIPHENE CITRATE.

CONCLUSION

This study concluded that frequency of ovarian cyst in patients of induced ovulation is quite high. So, we recommend that in every women taking ovulation induction, ovarian cyst should be taken into consideration so that the early recognition and management should be initiated to decrease the morbidity of the community.

Author's Contribution:

Concept & Design of Study: Joveria Sadaf
 Drafting: Abroo Shahnaz, Asia Aziz
 Data Analysis: Tanzila Rafiq, Aslam Mahmood Malik
 Revisiting Critically: Joveria Sadaf, Abroo Shahnaz
 Final Approval of version: Joveria Sadaf

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

- Grimes DA, Jones LB, Lopez LM, Schulz KF. Oral contraceptives for functional ovarian cysts. *Cochrane Database Syst Rev* 2014;4:CD006134.
- Hongqian L, Xiangao W, Donghao L, Zhihong L, Gang S. Ovarian masses in children and adolescents in China: analysis of 203 cases. *J Ovarian Res* 2013;6:47.
- Rofe G, Auslend R, Dirnfeld M. Benign ovarian cysts in reproductive-age women undergoing assisted reproductive technology treatment. *Open J Obstet Gynecol* 2013;3:17-22.
- Farghaly SA. Current diagnosis and management of ovarian cysts. *Clin Exp Obstet Gynecol* 2014;41:609-12.
- Fathalla MF. Incessant ovulation--a factor in ovarian neoplasia? *Lancet* 1971;2:163.
- Burdette JE, Kurley SJ, Kilen SM, Mayo KE, Woodruff TK. Gonadotropin-induced superovulation drives ovarian surface epithelia proliferation in CD1 mice. *Endocrinol* 2006;147:2338-45.
- Murdoch WJ, Townsend RS, McDonnell AC. Ovulation-induced DNA damage in ovarian surface epithelial cells of ewes: prospective regulatory mechanisms of repair/survival and apoptosis. *Biol Reprod* 2001;65:1417-24.
- Murdoch WJ. Ovulatory factor in ovarian carcinogenesis. *Adv Exp Med Biol* 2008;622:119-28.
- Anwer A, Aziz S, Bano I. Risk of developing ovarian cyst in monitored versus unmonitored ovulation induction. *J Soc Obstet Gynaecol* 2011;1(4):221-26.
- Csokmay JM, Frattarelli JL. Basal ovarian cysts and clomiphene citrate ovulation induction cycles. *Obstet Gynecol* 2006;107(6):1292-6.
- Chene G, Penault-Llorca F, Bouedec GL, Mishellany F, Dauplat P, Jaffeux P, et al. Ovarian epithelium dysplasia after ovulation induction. *Human Reprod* 2009;24(1):132-138.
- Smith-Bindman R, Poder L, Johnson E, Miglioretti DL. Risk of Malignant Ovarian Cancer Based on Ultrasonography Findings in a Large Unselected Population. *JAMA Intern Med* 2018.
- MacKenna A, Fabres C, Alam V, Morales V. Clinical management of functional ovarian cysts: a prospective and randomized study. *Hum Reprod* 2000;15(12):2567-9.
- Glanc P, Brofman N, Salem S, Kornecki A, Abrams J, Farine D. The prevalence of incidental simple ovarian cysts P3 cm detected by transvaginal sonography in early pregnancy. *J Obstet Gynaecol Can* 2007;29(6):502-6.
- Sanersak S, Wattanakumtornkul S, Korsakul C. Comparison of low-dose monophasic oral contraceptive pills and expectant management in treatment of functional ovarian cysts. *J Med Assoc Thai* 2006;89(6):741-7.
- Seoud M, El-saghir N, Salem Z, Shamseddine A, Awwad J, Medawar W, Khalil A. Tamoxifen and ovarian cysts: a prospective study. *Eur J Obstet Gynecol Reprod Biol* 2001;100(1):77-80.
- Qublan HS, Amarin Z, Tahat YA, Smadi AZ, Kilani M. Ovarian cyst formation following GnRH agonist administration in IVF cycles: incidence and impact. *Hum Reprod* 2006;21(3):640-4.
- Christensen JT, Boldsen JL, Westergaard JG. Functional ovarian cysts in premenopausal and gynecologically healthy women. *Contraception* 2002;66(3):153-7.
- Borgfeldt C, Andolf E. Transvaginal sonographic ovarian findings in a random sample of women 25-40 years old. *Ultrasound Obstet Gynecol* 1999;13(5):345-50.
- Altinkaya SO, Talas BB, Gungor T, Gulerman C. Treatment of clomiphene citrate-related ovarian cysts in a prospective randomized study. A single center experience. *J Obstet Gynaecol Res* 2009;35(5):940-5.
- Frattarelli JL, Dempsey MS. Characteristics of baseline ovarian cysts in clomiphene citrate ovulation cycle. *Fertil Steril* 2004;82:979-81. The Practice Committee of the American Society for Reproductive Medicine. The clinical relevance of luteal phase deficiency. *Fertil Steril* 2012;98:1112-7.