

Treatment of ovarian cyst after clomiphene citrate ovulation induction

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Abstract

Infertility is a common problem around the world . About one in six of all couples have some problem in getting pregnant and that includes some trying for a second or subsequent baby⁽¹⁾ . The most common causes of it is ovulation defects and the famous treatment of this cause is by ovulation induction drugs especially clomiphene citrate which used for long period , but this treatment is not without side effects and one of the side effects is ovarian cyst . The aim of this study is to assess the effect of oral contraceptive pills , provera tablets (medroxyprogesterone acetate tablets) and expectant management in the resolution of ovarian cysts induced by clomiphene citrate ovulation induction .Study design : a prospective ,randomized study .Setting: patients complained of ovarian cyst more than 2.5 mm were diagnosed by ultrasound after clomiphene citrate ovulation induction and randomized into 3 groups . Group (1) received oral contraception , group (2) received oral progesterone tablets treatment and group (3) had expectant management. Follow up of patients were done monthly by ultrasound and resolution of cyst was observed as a main out come measure .

علاج أكياس المبايض بعد التحفيز بالكلوميفين سترتيت أثناء فترة الإباضة

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المستخلص

العقم هو مشكلة كبيرة تواجه العالم وحوالي واحد من المتزوجين لديهم هذه الحالة سواء اكانت اولية أو ثانوية ومن اهم اسباب العقم هو ضعف المبيض ومن اشهر علاجات هو كلوميفين سترتيت لعلاج ضعف الإباضة ولكن هذا الدواء لديه مضاعفات كثيرة شأنه شأن أي دواء ومن اهم مضاعفاته هو كيس المبيض .وعلى هذا الاساس تم إجراء هذه الرسالة لمعرفة كيفية علاج هذه الاكياس وهو العلاج بحبوب منع الحمل او حبوب هرمون البروجسترون او بدون علاج هو الافضل لمثل هذه الاكياس .فقسمت المريضاات المصاباات بأكياس المبيض الى ثلاثة مجاميع المجموعة الاولى مستخدم حبوب منع الحمل ومجموعة ثانية تستخدم حبوب هرمون البروجسترون ومجموعة ثالثة لاتستخدم دواء .النتائج لاتوجد فروقات معنوية بين المجاميع الثلاثة وحجم الكيس في المبيض لاعلاقة له بجرعة الدواء (الكلوموفين سترتيت) وومدة زوال الكيس لاعلاقة لها بحجم الكيس ان استعمال الهرمونات غير ضروري لعلاج اكياس المبيض الناتجة عن استعمال (الكلومفين سترتيت) ولكن نتاج الى دراسات اوسع وباعداد اكبر.

Introduction

Episodes of infertility will be experienced by 25 % of women during their reproduction years⁽²⁾ and approximately 10-15% are effected by infertility⁽³⁾. There are many causes of it and ovulation defects will be 40%⁽¹⁾. The first drug of choice in the treatment is clomiphene citrate ovulation induction. It is now more than 40 years ago that Greenblatt first reported a new compound, the anti-estrogen MRL-41, capable of inducing ovulation for anovulatory women. It is an orally administered, non steroidal agent which induce ovulation in an ovulatory women in selected cases⁽⁴⁾. Its chemical structure is 2-[p- (2- chlo - 1,2 - diphy - vinyl) phenoxy] triethylamine citrate (1:1). It has the molecular formula $C_{26}H_{28}ClNO.C_6H_8O_7$ and its molecular weight 598.09. Its action through increasing out put of pituitary gonadotropins, which in turn stimulate of the maturation and increase the activity of the ovarian follicles and subsequent development and function of the corpus luteum. Antagonism of competitive inhibitor of endogenous estrogen play role in the action of clomiphene citrate in the pituitary. Clomiphene citrate is indicated for the treatment of ovarian dysfunction in women desiring pregnancy who meet the conditions described below:

1. Patients who are not pregnant.
2. Patients without ovarian cyst because of further enlargement of ovarian cyst may occur during treatment.
3. Patients without abnormal uterine bleeding.
4. Patients with normal liver function.

In addition patients selected for clomiphene citrate treatment should be evaluated in regard to the following:

1. Estrogen levels
2. Primary pituitary or ovarian failure.
3. Endometriosis or endometrial carcinoma.
4. Impediments to pregnancy.

5. Uterine fibroids.

Ovulation rate after clomiphene citrate ovulation induction is 80%, pregnancy rate is 30%, multiple pregnancy rate is 7.98%, twin pregnancy rate is 6.9%, triplet pregnancy rate is 0.5%, quadruplets pregnancy rate is 0.3% and quintuplet pregnancy rate is 0.1%.

The possible side effects of clomiphene citrate ovulation induction treatment are:

Dermatologic: acne, allergic reaction, erythema multiforme, erythema nodosum, hypertrichosis, pruritus.

Central nervous system: migraine headache, paresthesia, seizure, stroke, syncope.

Psychiatric: anxiety, irritability, mood changes, psychosis.

Visual disorders: abnormal accommodation, cataract, eye pain, macular edema, optic neuritis, photopia, posterior vitreous detachment, retinal hemorrhage, retinal thrombosis, retinal vascular spasm, temporary loss of vision.

Cardiovascular: arrhythmia, chest pain, edema, hypertension, palpitation, phlebitis, pulmonary embolism, shortness of breath, tachycardia, thrombophlebitis.

Musculoskeletal: arthralgia, back pain, myalgia.

Hepatic: transaminases increased, hepatitis.

Neoplasms: liver (hepatic hama giosarcoma, liver cell adenoma, hepatocellular carcinora); breast (fibrocystic disease and breast carcinoma); endometrium (endometrial carcinoma); nervous system (astrocytoma, pituitary tumor, prolactinoma, neurofibromatosis, glioblastoma multiforme, brain abcess); ovary (luteoma of pregnancy, dermoid cyst of the ovary, ovarian carcinoma); trophoplastic {hydatiform mole, choriocarcinoma}; miscellaneous (melanoma, myeloma, perianal cyst, renal cell carcinoma, hodgkins lymphoma, tongue carcinoma, bladder carcinoma); and neoplasms of offspring (neuroectodermal tumor, thyroid tumor, hepatoblastoma and lymphocytic leukemia).

Genitourinary : endometriosis , ovarian cyst (ovarian enlargement or cyst could be complicated by adnexal torsion) , ovarian hemorrhage , tubal pregnancy and uterine hemorrhage .

Body as a whole : fever , tinnitus , weakness .

Other : leukocytosis , thyroid disorder .

Dose of treatment should begin with 50 mg daily (1 tablet) for 5 days from day 2 of cycle . If no ovulation the dose will increased gradually to 100 mg daily in the second cycle and the total dose should not be more 200 mg / day . It is recommended that the patient be examined for pregnancy , ovarian enlargement , or cyst formation between each treatment cycle .^(5,6,7) One complication of clomiphene citrate ovulation induction is ovarian cyst . The management of it is by follow up with or without treatment but in the practice hormonal therapy is become a wide accepted management especially oral contraception⁽⁸⁾ . Many studies suggest these type of ovarian cyst can be resolved spontaneously and not related to the use of oral contraception or the hormonal treatment is unnecessary in cases with functional ovarian cysts^(9,10). But in the practice its became accepted that progesterone tablets or oral contraceptive pills as a treatment of functional ovarian cysts especially those induced by ovulation induction. The aim of this study is to observe the resolution of ovarian cyst in women who were treated with clomiphene citrate ovulation induction and to find which modalities of treatment such as oral contraception , provera tablets (medroxyprogesterone acetate tablets) and expectant management is effective in the treatment of such type of ovarian cysts .

Material and methods

This study is a prospective ,randomized study and it was performed in infertility clinic of Tikrit Teaching Hospital , through the period between june-2004 to june-2008 . The study protocol was approved by the scientific committee of Tikrit

University – College of Medicine .Ninety patients with ovarian cyst more than 2.5 cm after clomiphene citrate ovulation induction(tab contain 50 mg of clomiphene citrate-Aventis) for ovulation cause of infertility were diagnosed by vaginal ultrasound(Ev6.5MH2/R13 -DP 1100 Plus Ultrasonic diagnostic image-Mindray) by taking the largest cross section and averaging the 2 perpendicular diameter measurements . The ovarian cyst was diagnosed either at monitoring for follicular growth and ovulation at day 12-14 of clomiphene citrate treated cycle⁽⁴⁾ or in the beginning of next cycle when the menstrual period delayed or the cycle became irregular. The involved patients had normal basal ultrasound at day 5 of the cycle to exclude presence of any ovarian cyst ,normal basal serum hormones of FSH(follicle-stimulating hormone), LH(luteinizing hormone), Prolactin (all at day 3 of the cycle) ,normal semen analysis for the husband and normal hysterosalpingogram for the patient more than three years infertility. Informed consent was taken from each patient. Those patients were randomized in three groups .Thirty patients were assigned for group (1) and received oral contraceptive pills(Microgynon ED and ferrous fumarate containing levonorgestrel 0.15 and ethinylestradiol 0.03 mg-Shering) .Thirty patients were assigned for group (2) and received provera tablets (5 mg of medroxyprogesterone acetate- pharmacia) . Thirty patients were assigned for group (3) and managed expectantly (only they were received mefenamic acid on need when there is pain) .We observed the details of cyst such as size ,diameters and which ovary was involved whether left or right or bilateral . Follow up of patients was done for each patient every month at day 5 of the cycle by ultrasound to observe the time needed for the resolution of cyst for each group as the main outcome measure .Statistical analysis: Statistical analysis of data were done using SPSS manager system version 10. The level of significance was 0.05 .

Results

There was no significant differences between three groups in the resolution time of ovarian cyst . The size of cyst was not depend on the dose of ovulation induction and the time of resolution of it was not depend on the size of ovarian cyst .

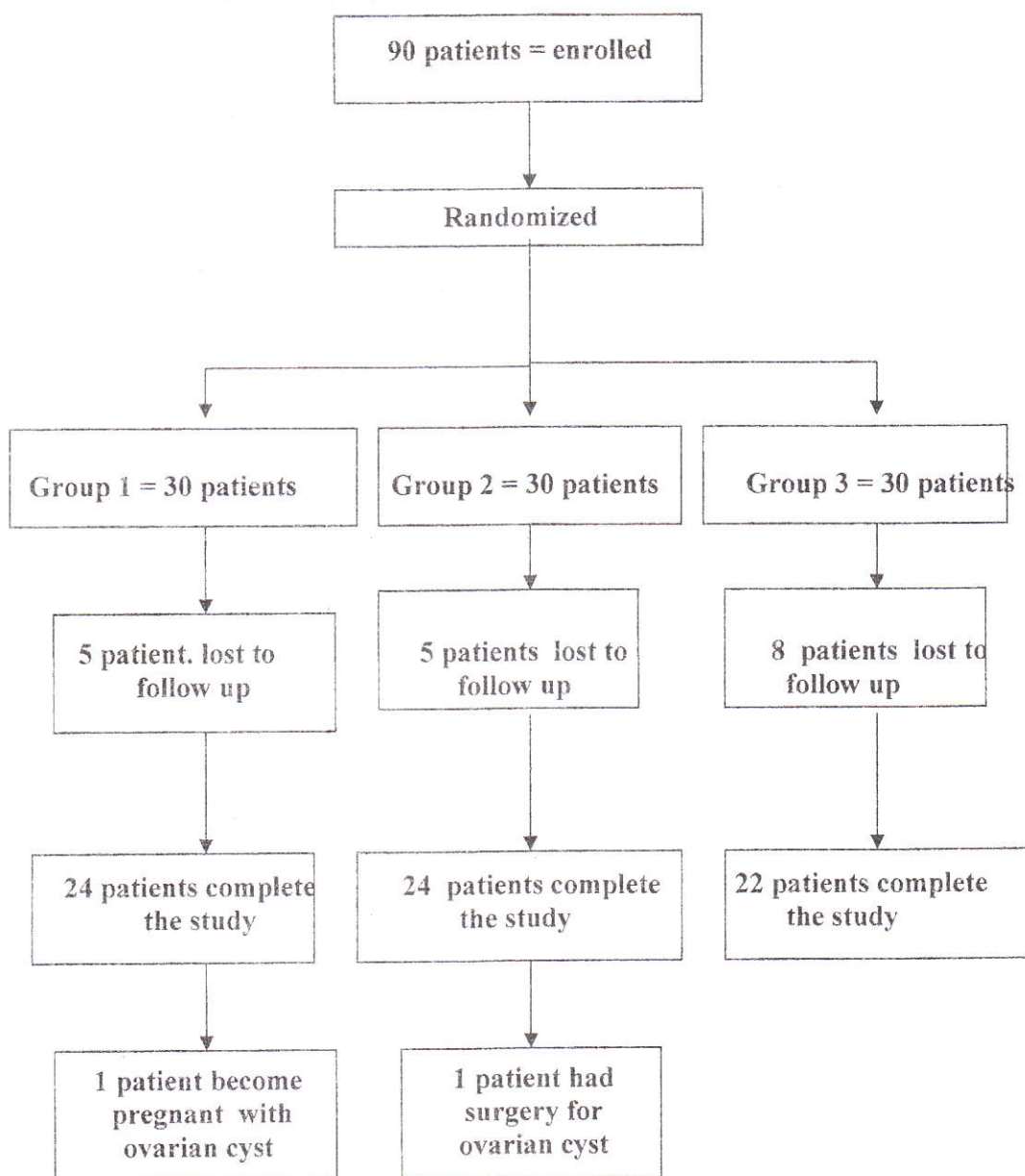
Conclusion

The ovarian cyst induced by clomiphene citrate ovulation induction can be managed by expectant management and the clinical practice of using oral contraceptive pills or provera tablets (medroxyprogesterone

acetate tablets) were not necessary but further larger studies are needed to confirm these results .

Results

From 90 patients initially enrolled in the study only 72 patients were followed up in the study because 5 patients in group (1,2) were lost to follow up and 8 patients were lost to follow up in group (3) and 2 patients were not completed the study in group 1 and 2 . Figure 1 :



Baseline characteristics of women according to treatment allocation are shown in table (1). The mean \pm SD age of group (1,2,3) is (27.28 \pm 7.8), (28.56 \pm 7.7), (27.7 \pm 7.4) years for each group respectively. Job, residency and infertility type are shown in table (1). The mean \pm SD

infertility period for group (1,2,3) is (2.56 \pm 1.9), (2.52 \pm 1.2), (2.3 \pm 1.5) years for each group respectively. All these results were statistically not significant.

Table (1):- Baseline characteristics of women according to treatment allocation.

Characteristics	Group 1		Group 2		Group 3		Total		P value*
	No.	%	No.	%	No.	%	No.	%	
Age									
<20	8	32	5	20	5	22.7	18	25	0.537
21-25	2	8	7	28	5	22.7	14	19.4	
26-30	5	20	2	8	4	18.2	11	15.3	
\geq 31	10	40	11	44	8	36.4	29	40.3	
Job									
house wife	17	68	19	76	15	68.2	51	70.8	0.850
student	4	16	2	8	2	9.1	8	11.1	
worker	4	16	4	16	5	22.7	13	18.1	
Residence									
urban	12	48	8	32	8	36.4	12	38.9	0.489
rural	13	52	17	68	14	63.6	13	61.1	
Type of infertility									
primary	9	36	11	44	10	45.5	30		0.772
secondary	16	64	14	56	12	54.5	42		
No. of Abortion									
0	14	56	18	72	15	68.2	27	65.3	0.269
1	4	16	7	28	4	18.2	15	20.8	
2	5	20	0	0	3	13.6	8	11.1	
3	1	4	0	0			1	1.4	
5	1	4	0	0			1	1.4	
No. of children									
No children	9	36	8	32	10	45.5	27	37.5	0.60
one child	4	16	6	24	2	9.1	12	16.7	
two child	2	8	4	16	1	4.5	7	9.7	
\geq 3 child	10	40	7	28	9	40.9	26	36.1	

*not significant difference among the study groups.

Table (2):- The relation of ovarian cyst appearance with the age and parity

age	No. of children								Total	
	no children		one child		two child		≥ 3 child		No.	%
	No.	%	No.	%	No.	%	No.	%		
≤20	15	55.55	2	16.67					17	23.61
21-25	8	29.63	4	33.33	1	16.7	1	3.8	14	19.4
26-30	2	7.41			1		9	34.6	12	16.6
≥31	2	7.41	6	50	5	83.3	16	61.5	29	40.3
Total	27	100	12	100	7	100	26	100	72	100

P value=0.001 (significant between three groups)

Table(2) shows that the young age patients ≤20 with low parity and patients age ≥31 with ≥ 3 child is associated with significant appearance of ovarian cyst after clomiphene citrate ovulation induction. The mean ±SD of cyst size in group (1,2,3) is

(4.4±1.4),(4.44±1.3),(4.5±1.5) cm respectively and the site of ovary which was involved by the cyst in the three groups are shown in table (3) . All these results were statistically not significant(p value=0.984).

Table(3):- characteristic of ovarian cyst

Characteristics	Group 1		Group 2		Group 3		Total		P value
	No.	%	No.	%	No.	%	No.	%	
Side of the cyst									
Right	13	52	12	48	9	40.9	34	47.2	0.18
Left	12	48	10	40	13	59.1	35	48.6	
Bilateral			3	12			3	4.2	
Diameter of the cyst(cm)									
		Mean ±SD		Mean ±SD		Mean ±SD		Mean ±SD	0.984
	25	4.42±1.43	25	4.4±1.3	22	4.5±1.5	72	4.4±1.4	

Table (4) shows the relation of dose of clomiphene citrate with the diameter of cyst and this shows there is no relation between

them and no statistical differences between three groups .

Table (4):- Relation of ovarian cyst diameter with the dose of clomiphene citrate .

Dose of clomiphene citrate	Diameter of the cyst(cm)					
	Group 1		Group 2		Group 3	
	No.	Mean ±SD	No.	Mean ±SD	No.	Mean ±SD
1 tab.*	2	5.6±1.3	2	5.95±2.3	1	2.8
2 tab.	14	3.9±1.5	16	4±1.1	18	4.7±1.±5
3 tab.	6	4.6±1.1	4	5±0.6	2	3.8±0.7
4 tab.	3	5.5±1	3	4.9±2	1	4.2
Total	25	4.4±1.4	25	4.4±1.3	22	4.48±1.5

P value= 0.981(not significant between group 1,2,3)

*tab.=tablets=50 mg of clomiphene citrate

Table (5) shows the relation of cyst diameter with resolution time and there is

no relation between them, there is no statistical differences between three groups

Table (5):- Relation of cyst diameter with the resolution time.

Resolution time	Cyst diameter(cm)					
	Group 1		Group 2		Group 3	
	No.	Mean \pm SD	No.	Mean \pm SD	No.	Mean \pm SD
1 month	15	4.1 \pm 1.2	14	4.5 \pm 1.4	13	4.6 \pm 1.5
2 month	7	4.5 \pm 1.2	8	4.6 \pm 1.4	8	4.0 \pm 1.2
3 month	2	4.7 \pm 2.6	2	3.6 \pm 1.0	1	6.6
Total	24*	4.3 \pm 1.3	24*	4.4 \pm 1.4	22	4.5 \pm 1.5

one patient not complete the study from group (1 and 2).

P value= 0.865(not significant between group 1,2,3)

Table (6) shows the resolution time of cyst in group(1,2,3). There was no

significant differences between three groups.

Table (6):- Resolution time of ovarian cyst after treatment among three groups.

Resolution time	Group 1		Group 2		Group 3		Total	
	No.	%	No.	%	No.	%	No.	%
1month	15	62.5	14	58.33	13	59.1	42	60
2 month	7	29.2	8	33.33	8	36.4	23	32.9
3 month	2	8.3	2	8.34	1	4.55	5	7.14
Total	24	100	24	100	22	100	70	100

P value= 0.971(not significant between group 1,2,3)

Discussion

Benign ovarian cysts are common, frequently a symptomatic and often resolved spontaneously. Physiological cyst is a common type of benign ovarian cyst and they are occasional complication of ovulation induction, when they are commonly multiple. (1) Ovarian cyst is one complications of clomiphene citrate ovulation induction and it is a horrible event to the patient who waits for ovulation and pregnancy. So this complication should manage probably because there is a negative effect on ovulation induction especially in IVF and GIFT cycles. (11,12,13) The basal ultrasound is very important to exclude any basal ovarian cyst before ovulation induction because

clomiphene citrate ovulation induction may held as the ovulation chances success will decrease. (11,12,13) Although 50 mg /day is the recommended dose in the first cycle, a meta-analysis of 13 published reports suggest that only 46% with respond to this dose with ovulation, a further 21% will respond to 100mg and another 8% will ovulate with 150 mg/day. So high dose or starting dose with 100 mg/day is unnecessary especially in young age women or multiparous women because the appearance of ovarian cyst is high in these patients in our study and this may be due to high activity of the ovarian hormones. So if there is no ovulation at 50 mg/day we can use a higher dose to decrease the incidence

of ovarian cyst after clomiphene citrate ovulation induction in those patients .
(4) There is different studies about management of functional ovarian cyst and especially those induced by ovulation induction , spanos (1973) found that suppression of pituitary gonadotropins for 6 weeks by hormones was enough to regress physiological ovarian cyst (14) . Regarding progesterone treatment which became an accepted clinical practice by some doctors ,there is few studies about it and most of theses studies depend on natural progesterone cream or intravaginal application of progesterone cream that provides higher doses where needed in cases of endometriosis, fibroids and ovarian cysts. The signaling mechanism that shuts off ovulation in one ovary each cycle is the production of progesterone in the other. If sufficient natural progesterone is supplemented prior to ovulation, LH levels are inhibited and both ovaries think the other one has ovulated, so regular ovulation does not occur. This is the same effect as contraceptive pills. Similarly, the high estriol and progesterone throughout pregnancy successfully inhibit ovarian activity for nine months. Therefore, adding natural progesterone from day 10 through 26 of the cycle suppresses LH and its luteinizing effect. Thus, the ovarian cyst will not be stimulated will very likely shrink and disappear without further treatment (15,16). But other studies found that hormonal treatment is not necessary in cases with functional ovarian cysts after ovulation induction and the rate of disappearance of functional ovarian cyst was not effected by hormonal therapy and disappear spontaneously by either reabsorption of the cyst fluid or silent rupture within 4-8 weeks of initial diagnosis (9,10,17,18), these results agree with our results which showed that the time of resolution of ovarian cyst is the same for three modalities of treatment and its irrespective to the cyst diameter .Two patients were excluded from the completion of the study because the first one needed surgery because the diagnosis was found to

be torsion ovarian cysts and the second one became pregnant. (1,2,3)

Conclusion

Ovarian cysts treatment induced by clomiphene citrate ovulation induction is not affected by hormonal therapy (progesterone treatment) and expectant management and follow up by ultrasound is necessary because resolution of these cyst will occur spontaneously. Further larger studies are needed to confirm that resolution of ovarian cyst induced by clomiphene citrate ovulation induction will occur spontaneously .

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