Efficacy of Progestins in the Treatment of Functional Ovarian Cyst

Original Article

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ABSTRACT

Background: Ovarian cysts are frequently common in practice at reproductive age.

Aim of the Work: The study aimed to determine the usefulness of use of progestins over expectant management in treatment of functional ovarian cyst.

Cases and Methods: 90 women with ovarian cysts were recruited and subgrouped to either control group or progesterone group. The patients were monitored after 6 to 8 weeks.

Results: The percentage of 50% or more reduction in cyst width in progesterone group was 35.6% while the control group was 17.8%. The percentage of 50% or more reduction in cyst length in progesterone group was 24.4% while the control group was 15.6%. The percentage of 50% or more reduction in cyst depth in progesterone group was 24.4% while the control group was 17.8%. After testing, there no significant difference detected between both treatment modalities regarding cyst length (p = 0.097), cyst width (p = 0.385), cyst depth (p = 0.204). Cysts resolved completely in 26/45 (57.9%) and 17/45 (37.8%) in groups progesterone and control respectively, However, there was no significant difference regarding content (p = 0.059) and cyst disappearance (p = 0.058).

Conclusion: Progestin therapy in functional cysts could be effectively used as expectant management at least among women who are having spontaneous ovulation.

Key Words: Functional ovarian cyst, patient satisfaction progestins.

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INTRODUCTION

The management of the cystic adnexal mass in women of reproductive age remains a common gynecological problem. It is widely accepted that many adnexal cysts represent a persistence of an ovarian follicle or cystic corpus luteum[1-3].

Many patients with simple ovarian cysts diagnosed by ultrasound examination do not require medical treatment. In a postmenopausal patient, a persistent simple cyst smaller than 10 cm in dimension in the presence of a normal CA125 value may be monitored with serial ultrasound examinations[4-6]. However patient seems to be not accepting such modality, also this requires cautious monitoring for complications[7].

Oral contraceptive pills (OCPs) protect against the development of functional ovarian cysts[8]. Here we face other problems, they are drug side effects and patient`s acceptance specially if she is infertile and seeking pregnancy. Persistent simple ovarian cysts larger than 10 cm (especially if symptomatic) and complex ovarian cysts should be considered for surgical removal[9].

Benign featuring cysts are usually managed with oestrogen in combnation with progestin[10].

AIM OF THE WORK

Here we studied whether progestins in the form of dydrogesteron is effective as monotherapy for functional ovarian cyst.

CASES AND METHODS

The present study is randomized controlled trial was conducted with approval of Institutional Review Board (IRB) of Faculty of Medicine with approval number was 17100435.In line with the Declaration of Helsinki, the current work was conducted. All patients signed informed consent. The current study was registered in clinicaltrials.gov with ID: NCT03456570

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This study recruited 130 patients and 90 only completed this study while 40 patients were excluded due different causes (as seen in the flow chart). The included patients were randomized into two groups, 45 patients in group one received progesterone treatment and 45 patients in group two received placebo treatment (Figure 1).

Sample size calculation

Based on previously reported frequency of functional ovarian cyst that was 7%[11] of women have an ovarian cyst at some point in their lives, assuming confidence level 95%, Power 80% a minimum 90 patients was required.

Inclusion criteria

Any menstruating patient with unilocular and unilateral ovarian cyst was enrolled

Exclusion criteria

Ovarian pathology (dermoid, endometriosis or malignancies) or tubal pathology, complicated cyst (rupture, torsion), history of surgical removal of ovarian cyst, comorbidities like uncontrolled DM, hypertension, thyroid problems, and use of hormonal contraception.

All enrolled patients were subjected to

- Full history and examination.
- Transvaginal ultrasound (TVUS) at the proliferative phase of ovarian cycle, full comment was on: Uterus, pelvis, both ovaries and adnexa, Then the cyst included in this study should be 3-10 cm, unilateral, unilocular, clear content thin walled, no papillae or solid parts IOTA criteria of malignancy must be excluded if found, and CA 125 were done to patient with cyst larger than 7 cm patients.

Randomization of the patients into 2 groups

A computer-generated table of random numbers is used to assign the patients in 1:1 ratio to the treatment groups. After consenting to participate at the time of enrolment, patients were assigned in numeric order to the corresponding treatment group. Permuted blocked randomization was done online to generate the randomization list (https://www.sealedenvelope.com https://www.sealedenvelope.com/simple-randomiser/v1/lists). Blocked randomization method was used to balance treatment arms. A permuted block of size of 4 or 6 was used (see CONSORT flow diagram).

- Group 1: were offered dydrogesterone 10 mg twice daily for 10 days
- Group 2: were offered placebo (folic acidv 500 mcg tab).

Then TVUS if

- Complete resolution (another examination after one month), just reduction in size (repeat the course of therapy), no change or increase in size (change to another therapy two cycles later). Complicated cysts were laparoscopically or surgically managed.
- Then patient satisfaction score was calculated according to the presumed module (the SAPS)

Outcome measure: primary outcome of the study was resolution of the cyst as evaluation by the TVUS

Ethical consideration

The study obtained approval of Institutional Review Board (IRB) of Faculty of Medicine with approval number was 17100435.In line with the Declaration of Helsinki, the current work was conducted. All patients signed informed consent. The current study was registered in clinicaltrials.gov with ID: NCT03456570

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 23, 64 bit. Symmetrically distributed parameters were presented as mean and standard deviation. For ordinal categorical data median and range in square brackets were indicated. Student's t-tests were used to compare symmetrically distributed parameters whereas continuous variables of a skew distribution were compared by means of the Mann-Whitney-Wilcoxon rank-sum test (for unrelated samples) and the Wilcoxon signed-rank test (for related samples). The Chi-square test was applied to analyze categorical data. In general, 0.05 was set as level of significance.

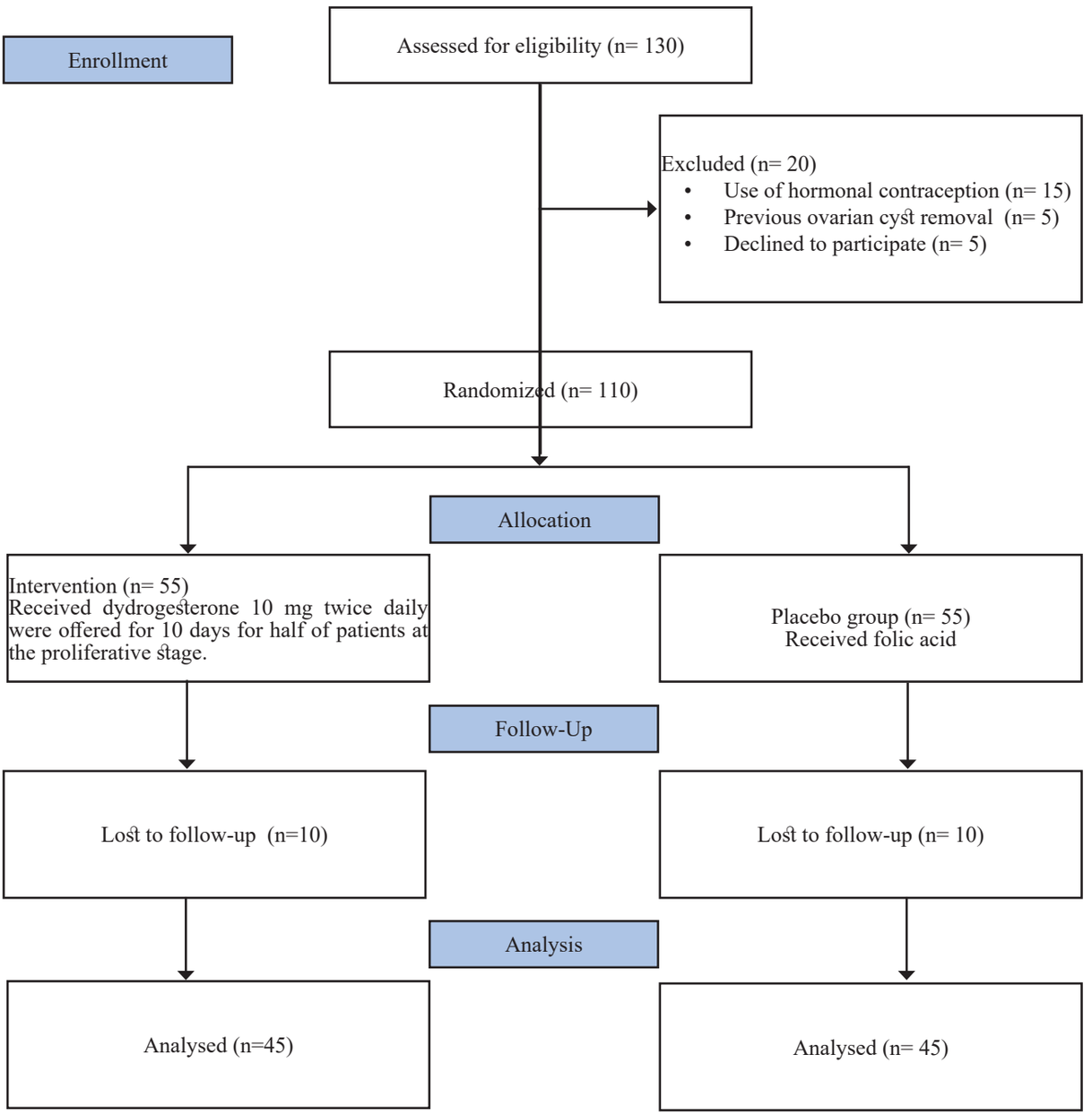

Fig. 1: CONSORT Flow Diagram of the current study

RESULTS

There was no significant difference detected between both treatment modalities regarding cyst length, cyst width, cyst depth, and end-thick as seen at (Tables 1,2).

After 6 to 8 weeks for both treatments, there was no significant difference regarding content and cyst disappearance (Table 3).

The overall patient satisfaction score was significantly higher in progesterone group (25.0 ± 3.13) than placebo group (22.13 ± 3.72) (Table 4).

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In (Table 5), in terms of patient's satisfaction, progesterone group reported higher satisfaction scores than control group in regarding effect of treatment, the choices of decision described by the health care provider, the amount of time the patient feel respected, time you had with your health professional, and the care received. Other data showed no significant differences.

Table 1: Demographic characters of the study cohort

Parameters	Progesterone group (n= 45)	Placebo group (n= 45)	*P value*
	N (%)	N (%)	
Age, year, mean (±SD)	31 (±4.96)	31.29 (±4.88)	0.734
Residence			
Rural	15 (33.3)	19 (42.2)	0.384
Urban	30 (66.7)	26 (57.8)	
Weight, Kg, mean (±SD)	65.53 (±9.30)	68.4 (±6.69)	0.199
Education			
High (college)	32 (71.1)	28 (62.2)	0.658
Medium (high school or institute)	12 (26.7)	16 (35.6)	
Low (preparatory)	1 (2.2)	1 (2.2)	
Gravity			
Nullipara	6 (13.3)	3 (6.7)	0.292
Multipara	39 (86.7)	42 (93.3)	
Mode of delivery			
Cesarean section	25 (55.6)	23 (51.1)	0.787
Normal vaginal delivery	15 (33.3)	19 (42.2)	
Period regularity			
Regular	20 (44.4)	24 (53.3)	0.399
Irregular	25 (55.6)	21 (46.7)	
Pattern of irregularity			
Hypomenorrhea	4 (8.9)	4 (8.9)	0.122
Menorrhagia	5 (11.1)	8 (17.8)	
Metrorrhagia	16 (35.6)	9 (20.0)	
Previous surgery			
Appendicitis	6 (13.3)	3 (6.7)	0.774
Open cholecystectomy	1 (2.2)	2 (4.4)	
Lap cholecystectomy	2 (4.4)	1 (2.2)	
Myomectomy	2 (4.4)	2 (4.4)	
None	34 (75.6)	37 (82.2)	

Data expressed as frequency (percentage), mean (SD) as appropriate. *P value* was significant if < 0.05

Table 2: Functional ovarian cyst baseline data for the treatment groups

Parameters	Progesterone group (n= 45)	Placebo group (n= 45)	*P value*
	N (%)	N (%)	
Cyst length, Cm, mean (±SD)	4.07 (±1.47)	4.18 (±1.14)	0.497
Cyst width, Cm, mean (±SD)	4.11 (±1.63)	3.91 (±1.06)	0.994
Cyst depth, Cm, mean (±SD)	3.34 (±1.06)	3.52 (±0.92)	0.250
Cyst volume, Cm, mean (±SD)	39.76 (±49.6)	35.24(±29.71)	0.525
Content Clear	45 (100)	45 (100)	-
Echogenicity Anechoic	45 (100)	45 (100)	-
End-thick, Cm, mean (±SD)	7.11 (±1.32)	6.93 (±1.34)	0.510

Data expressed as frequency (percentage), mean (SD) as appropriate. *P value* was significant if < 0.05

Table 3: Functional ovarian cyst data after finishing treatment course (6 to 8 weeks)

Parameters	Progesterone group (n= 45) N (%)	Placebo group (n= 45) N (%)	*P value*
Cyst length, Cm, mean (±SD)	1.85 (±2.44)	2.56 (±2.21)	0.097
Cyst width, Cm, mean (±SD)	4.43 (±1.89)	3.80 (±1.09)	0.385
Cyst depth, Cm, mean (±SD)	3.17 (±1.20)	3.50 (±0.99)	0.204
Cyst volume, Cm, mean (±SD)	45.93 (±52.79)	35.14 (±29.43)	0.374
≥ 50 % reduction in cyst length	11 (24.4)	7 (15.6)	0.292
≥ 50 % reduction in cyst width	16 (35.6)	8 (17.8)	0.061
≥ 50 % reduction in cyst depth	11 (24.4)	8 (17.8)	0.438
≥ 50 % reduction in cyst volume	12 (26.7)	8 (17.8)	0.32
Content			
Clear	12 (26.79)	23 (51.1)	0.059
Turbid	7 (15.69)	5 (11.1)	
Disappeared	26 (57.89)	17 (37.8)	
Disappearance			
Yes	26 (57.89)	17 (37.8)	0.058
No	19 (42.29)	28 (62.2)	

Data expressed as frequency (percentage), mean (SD) as appropriate. *P value* was significant if < 0.05

Table 4: Patient satisfaction score of the study cohort in both treatment modalities.

Parameters	Progesterone group (n= 45)	Placebo group (n= 45)	*P value*
Patient satisfaction score, mean (±SD)	25.02 (±3.13)	22.13 (±3.72)	< 0.001

Data expressed as mean (SD). *P value* was significant if < 0.05

The overall patient satisfaction score was significantly higher in progesterone group (25.0 ± 3.13) than placebo group (22.13 ± 3.72) (Table 4).

Table 5: Items of patient satisfaction score of the study cohort in both treatment modalities

Parameters	Progesterone group (n= 45)	Placebo group (n= 45)	*P value*
1. How satisfied are you with the effect of your (treatment/care)? mean (±SD)	3.71 (±0.66)	2.93 (±0.99)	< 0.001
2. How satisfied are you with explanations the (doctor/other health professional) has given you about the results of your (treatment/care)? mean (±SD)	3.18 (±0.68)	3.16 (±0.67)	0.877
3. The (doctor/other health professional) was very careful to check everything when examining you? mean (±SD)	3.27 (±0.62)	3.22 (±0.67)	0.744
4. How satisfied were you with the choices you had in decisions affecting your health care? mean (±SD)	3.49 (±0.51)	3.22 (±0.60)	0.025
5. How much of the time did you feel respected by the (doctor/other health professional)? mean (±SD)	3.60 (±0.54)	3.27 (±0.62)	0.008
6. The time you had with the (doctor health professional) was too short. mean (±SD)	3.73 (±0.50)	3.38 (±0.61)	0.003
7. Are you satisfied with the care you received the (hospital/clinic)? mean (±SD)	3.76 ± 0.53	3.40 ± 0.58	0.003

Data expressed as mean (SD). *P value* was significant if < 0.05

DISCUSSION

In our cohort, the mean age of progesterone and control groups was 31 ± 4.96 and 31.29 ± 4.88 years, respectively and majority of the studied groups came from urban areas. Abduljabbar *et al*.[12] found that the mean ± standard deviation [SD] age of patients with functional ovarian cyst was 35.35±12.849 years. Similarly Rofe *et al*.[13] found that ovarian cyst is common with mean age of 33 years old.

The average diameter of our study cyst was 4.11 ± 1.63 in the progesterone group and 3.91 ± 1.06 in the placebo group. These measurements were in comply with Steinkampf *et al*.[14] baseline measurements of the cysts as their larger cysts measures was the mean diameter of the largest cyst (group A: 3.0 cm, group B: 2.9 cm). Our study was in line with Mackenna *et al*.[15].

Our results come in contrary with Steinkampf *et al*.[14] who stated no differences were found as regard size and

patients having received gonadotropins in the previous menstrual cycle were not significantly different among the two groups. Another study was consistent to our findings done by

Moreover, Mackenna *et al*.[15] reported complete resolution in all recruited patients but this wasn't in line with our study and Steinkampf *et al*.[14] and Ben-Ami *et al*.[16], who found that other cysts that wasn't resolved, had another diagnosis as endometriosis, hydrosalpinx, dermoid cysts and para-ovarian cysts.

In the current study after 6 to 8 weeks for both treatments, regarding the disappearance rate, the 57.89% of the progesterone group disappeared and 37.8% of the placebo group disappeared with tendency to found significant difference (p=0.058).

Our finding is in agreement with that of Sanad *et al*.[17] who found that after one cycle of therapy, resolution was observed in 44.4% of control group and 55.5% of patients received oral contraceptive. Complete resolution of the cysts was observed in 66.6% and 72.2% of control and those revived oral contraceptive, respectively after two cycles.

Another prospective study similar to the study of Ayline *et al*.[18] was carried out by Naz *et al*.[19] in which 47 patients with functional ovarian cysts were included. Overall, 22 patients (46.80%) received counseling for expectant management (group A) and oral contraceptives (group B) were prescribed in 25 patients (53.19%). Cyst resolution at 2 months by ultrasound was observed in 72.72% of the women in group A and in 80.0% of the women in group B. There was no statistically significant difference in cyst resolution in the two groups. These results were in agreement with those of our study.

The studies by Mackenna *et al*.[15] are two earlier randomized-controlled trials on the effect of combined oral contraceptive pills on the resolution of functional ovarian cysts compared with that of expectant management; they found that a similar number of functional ovarian cysts had resolved within 1 month. Moreover, all the remaining cysts resolved after 2 months; this is not in agreement with the finding of the present study.

Our findings are in agreement with those of a randomized-controlled trial conducted by Sanersak *et al*.[20]. This study included 70 women. The remission rates after 2 months were 24\33 (72.2%) in the combined oral contraceptive group and 23\34 (67.6%) in the expectant group; there were no statistically significant differences. However, our study detected significant difference between two groups regarding the patient satisfaction score after the end of both treatment modalities. Progesterone was superior to the placebo group regarding the overall satisfaction score.

To our knowledge, we are the first study to assess the patient's satisfaction during functional ovarian cyst treatment. The patient reported scores on different aspects in their lifestyles during both treatment approaches including pain relive. Surprisingly, patients with progesterone treatment were more satisfied during their life. The patients in progesterone modality were satisfied to have a clear expectation of the period time. Also, there were no side effects including spotting and other menstrual abnormalities in this group. Therefore, they were comfortable and satisfied with progesterone treatment.

Also, a strong point in our study is related the management. Most of the previous studies in the literature used combined oral contraceptive pills as the included women were infertile. However, our study only used progesterone as a single treatment for the functional ovarian cyst with no

However, this work pointed out the need for further research regarding the pathophysiology of functional ovarian cysts, which represent a significant health problem among reproductive-age women. The main study's limitations; relatively small sample size and being from a single center which may limit the possibility that the study's results can be generalized to the general population.

CONCLUSION

The findings of our study indicate that progestin therapy is as effective as expectant management for the treatment of functional ovarian cysts, at least among women who are having spontaneous ovulation. The patients were more satisfied with progesterone as modality for functional ovarian cyst treatment. However, studies with a larger number of cases are still needed to confirm our findings.

Conflict of interests

There are no conflicts of interest.

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