

Management of ovarian cysts with percutaneous aspiration and methotrexate injection

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ABSTRACT

Background: To evaluate ultrasonographic-guided cyst aspiration and methotrexate injection in the management of simple and endometriotic ovarian cysts in selected patients. **Subjects and Methods:** This prospective study was conducted in the Department of Obstetrics and Gynaecology in Government Medical College and Hospital, Chandigarh, from November 2007 to October 2009. It included 132 female patients (age range, 15–72 years; mean, 38.7 years) with simple or endometriotic ovarian cysts (3.0–10.6 cm) at ultrasonic examinations. We performed puncture and aspiration followed by methotrexate injection into the cyst. All patients were followed for 12 months. None was lost to follow-up. **Results:** At follow-up ultrasonography, cysts had disappeared in 120 patients (90.90%) and persisted in 12 patients (9%). No major complications were observed in our study population during or after the procedure. Only 10 patients reported mild pelvic pain, and four others reported dizziness or nausea during or after the procedure. Malignant cells were not found in any of the cases at cytologic examination. We did not observe any cases of infection after the procedure. **Conclusion:** Ultrasonography-guided transabdominal aspiration of cyst fluid and subsequent methotrexate injection appears to be an alternative treatment for both simple and endometriotic ovarian cysts in selected cases.

Key words: Aspiration, methotrexate, ovarian cyst, ultrasonography

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INTRODUCTION

Most patients with ovarian cysts are asymptomatic, with the cysts being discovered incidentally during ultrasonography or routine pelvic examination. Some cysts, however, may be associated with severe pain from torsion (twisting) or rupture.^{1,2} Cyst rupture can lead to peritoneal signs, abdominal distention, and bleeding, irregularity of the menstrual cycle and abnormal vaginal bleeding,³ dull, bilateral pelvic pain - This may result from theca-lutein cysts⁴ Cancer antigen 125 (CA-125) - The finding of an elevated CA-125 level is most useful when combined with an ultrasonographic investigation while assessing a postmenopausal woman with an ovarian cyst.^{1,5} Many patients with simple ovarian cysts found through ultrasonographic examination do not require treatment. In a postmenopausal patient, a persistent simple cyst smaller

than 5 cm in dimension in the presence of a normal CA-125 value may be monitored with serial ultrasonographic examinations.^{3,6} Functional cysts do not regress when treated with combined oral contraceptives than they do with expectant management.⁷ However, ovarian cysts can herald an underlying malignant process or, possibly, distract the clinician from a more dangerous condition, such as ectopic pregnancy, ovarian torsion, or appendicitis.^{8,9} Methotrexate cannot suppress fluid production by the cells of the cyst wall. In the current study, we used ultrasound (US)-guided aspiration of ovarian cysts combined with methotrexate injection into the cyst to promote cyst resolution and prevent recurrence. Our purpose was to evaluate this treatment method prospectively in selected patients with simple and endometriotic ovarian cysts.

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SUBJECTS AND METHODS

This prospective study was conducted in the Department of Obstetrics and Gynaecology in Government Medical College and Hospital, Chandigarh, from November 2004 to October 2009. It was approved by the Institutional Medical Ethics Committee. It included 132 female patients (age range, 15–72 years; mean, 38.7 years) with simple or endometriotic ovarian cysts (3.0–10.6 cm) at ultrasonic examinations. A written informed consent was obtained from all the patients. We performed puncture and aspiration followed by methotrexate injection into the cyst.

Inclusion criteria were as follows:

- A unilateral simple ovarian cyst that had persisted for more than 6 months before the procedure
- Cyst diameter more than 30 mm
- No family history of ovarian cancer
- No evidence of renal or hepatic disease
- A normal value (35 IU/mL) of serum CA-125 before the procedure
- No large amount of free fluid in the pouch of Douglas, for fear of starting a torsion of the cyst
- No previous puncture of the cyst
- No lower abdominal or pelvic pain
- At US, a simple cyst was defined as a cyst with no papillary projections, a clearly defined wall, and clear content. Endometriosis was suspected at US when diffuse low-level echoes were observed within a cyst that had persisted for more than 2 months, and the diagnosis was proved by means of cytologic findings after aspiration in all cases. Although color Doppler US was used in many cases to examine the neovascularity of the cyst, specific Doppler studies were not done routinely in every patient; therefore, Doppler indexes were not used for the diagnostic evaluation of benignancy.

The exclusion criteria were as follows:

- Presence of US signs that make doubt about the benign character of the cyst (localized parietal thickening, irregularity of the wall, endocystic vegetation, the presence of several partitions, and presence of internal granulation or intracystic tissue mass). Interposition of bowel loops, bladder or uterus
- Absence of informed consent of the patient.

The cysts were punctured transabdominally with a 21-gauge spinal needle. A freehand technique was used, with direct US guidance provided by means of a convex 3.5-MHz probe attached to a US machine. After puncture of the cyst, as much fluid as possible was aspirated and a single dose of methotrexate (30 mg diluted in 3 mL of normal saline) was injected. In all cases, we left a small amount of fluid in the cyst before methotrexate injection to ensure that the needle remained inside the cyst after aspiration. All procedures were performed on an outpatient basis without

administration of general or local anesthesia or antibiotics. The aspirated fluid was sent for cytologic examination in all cases. Although the cyst puncture does not entail much pain, patients were asked to report subjective pain symptoms experienced during the procedure. Furthermore, patients with endometriomas were also asked to report pain symptoms before the procedure and note any difference after it. Pain was reported subjectively, and no questionnaires were used. Patients were instructed to take their temperature at least twice daily for 5 days after the procedure (to assess for infection) and to report any symptoms they experienced. Any complications during or after the procedure were recorded.

Follow-up

All patients were followed up with US at 1, 3, and 6 months after the procedure. In all cases of cyst persistence, a second or – at most – a third aspiration and injection of methotrexate were attempted. The main outcome measure was the disappearance of the cyst and the avoidance of surgery. The cyst was considered resolved if follow-up revealed either no cystic lesion or only a follicle-like cyst no more than 22 mm in diameter. Findings to the contrary were considered to indicate cyst persistence. All patients were followed for 12 months. None was lost to follow-up.

RESULTS

Follow-up ultrasonography was performed at 1, 3, and 6 months.

Complete follow-up was obtained in all the 132 patients. The study group included 110 patients with simple ovarian cysts and 22 with endometriotic cysts. No evidence of malignancy was reported in the cytologic examination in any patient. Overall, cyst resolution was observed in 120 of the 132 patients (90.9%).

The 22 patients with an endometriotic cyst were 20–55 years old (mean, 40 years), and their cysts were 30.0–60.6 mm in diameter (mean, 50.5 mm). The amount of fluid aspirated in this group ranged from 0 to 50 mL (mean, 20.5 mL). Six women underwent a second injection of methotrexate because of cyst persistence, and two others received three injections. Among the 14 remaining women who had one methotrexate injection, the cyst persisted in only three (13.63%). Overall, in this group of patients, the cyst persisted in four patients. Because of the thick nature of the cyst contents, complete aspiration was not achieved in any patient at the first attempt. However, the subsequent aspiration was easier as a result of more dilute contents of the cyst. Six of the 22 women had lower pelvic pain or dysmenorrhea before the procedure. Four reported marked improvement or complete resolution of the symptoms whereas the other two reported persistent (though milder) pain.

The 110 patients with a simple cyst were 15–72 years old (mean, 38.7 years). Their cysts ranged from 30 to 106 mm in diameter (mean, 56 mm), and the aspiration volume ranged from 10 to 250 mL (mean, 80 mL). Six patients in this group underwent a second aspiration with methotrexate injection, and 10 required 3 injections. In one patient receiving two injections and in another two receiving three injections, the cyst persisted despite the repeated procedures. Among the 94 remaining patients who received only one methotrexate injection, the cyst persisted in 5 patients and disappeared in all the others. No malignancy was found in these patients (diagnoses included serous cystadenoma in 6 patients, corpus luteum cyst in three, paraovarian cyst in two, and follicle cyst in one).

Irrespective of the number of methotrexate injections, the cyst resolved in 81.8% of patients with endometriotic cyst (18 of 22) and 92.72% of those with a simple ovarian cyst (102 of 110). No major complications were observed in our study population during or after the procedure. Only 10 patients reported mild pelvic pain, and four others reported dizziness or nausea during or after the procedure. These minor complications were managed with bed rest, and they all subsided spontaneously within 1–2 h. No hospital admission was required. We did not observe any cases of infection after the procedure. Endometriotic cyst persisted in 18.18% (4/22) patients, and simple cyst persisted in 7.27% (8/110) patients.

DISCUSSION

The management of ovarian cyst is still a challenge to gynecologists due to the inherent character of these cysts; the recurrence which imposes its burden on the psychological status of patients and so affects their quality of life and endanger their fertility especially in case of endometrioma. Our study clearly indicates that conservative management of ovarian cysts with aspiration and methotrexate injection is a safe alternative to the currently used methods for managing such cases. We observed complete cyst resolved in 81.8% of patients with endometriotic cyst (18 of 22) and 92.72% of those with a simple ovarian cyst (102 of 110). These results are among the best reported so far, and we attribute the improvement to methotrexate administration. Another important finding is that the size of the cyst is an independent factor for the final result whereas the patient's age and the aspiration volume, though contributing factors, are not statistically significant. There are, however, some important cautions regarding needle aspiration of ovarian cysts. The best way to exclude malignancy in an ovarian cyst is to perform a histologic examination, but this requires surgery. Accurate prediction with nonsurgical methods of whether a cyst is benign or malignant requires a combination of clinical examination, US, and measurement of the serum

concentration of CA-125.¹⁰ US is probably the most reliable method, with a diagnostic accuracy of 90–100% for transvaginal scanning.¹⁰ In a recent study that included 2763 asymptomatic women over 50 years of age with a unilocular ovarian cyst <10 cm in diameter, no woman developed ovarian cancer unless she developed another morphologic abnormality.¹¹ Our study focused on simple cysts with no papillary projections, a clearly defined smooth cyst wall, and clear cyst content; endometriotic cysts had diffuse low-level echoes within, but the other characteristics of simple cysts usually applied. Thus, we thought the chance of malignancy was relatively low in all cases, even when ovarian volume, morphology, and Doppler indexes were considered in addition to patient age.¹¹ Cytologic examination of the cyst content is not considered reliable in excluding malignancy, however, mainly because of the inadequate number of cells in the specimen. Nevertheless, we did employ cytologic examination, mainly to reinforce US and clinical findings and to minimize the risk of misinterpreting malignancy. Our patients were informed that this method of prediction (US characteristics, with serum CA-125 level measurement and cytologic examination) was accurate enough but not faultless. There were no cytologic findings of malignancy in our series. Although the seeding of the needle tract and the spreading of malignant cells in the peritoneal cavity after cyst aspiration are exceedingly rare, they remain a theoretical risk and have caused a great deal of concern about this method among clinicians.

Collectively, aspiration only showed a significantly higher recurrence rate (65%) compared to aspiration and instillation (18.8%), irrespective of the sclerosant used. These findings indicated the success of the decision to use sclerotherapy as an adjuvant therapeutic line to aspiration for the management of ovarian cyst. However, such effect was more pronounced with endometrioma, which hampers patients' fertility, where recurrence rate of endometrioma was significantly higher in patients received aspiration only compared to patients receive combined aspiration and sclerosant instillation. In line with the obtained results, Noma and Yoshida¹² reported a recurrence rate of 14.9% after more than 6 months follow-up after aspiration and ethanol instillation. Koike *et al.*¹³ also reported an ovarian cyst recurrence rate of 13.3% in women who had endometrioma after ethanol instillation. Messalli *et al.*¹⁴ reported that US-guided alcoholic sclerotherapy of the endometriotic ovarian cysts is effective and safe with a recurrence rate of 10% after a mean follow-up period of about 20 months and concluded that this procedure could be indicated in patients refusing standard surgical therapy. In the same concern, Hsieh *et al.*¹⁵ found the 1-year recurrence rate was significantly lower in patients who had aspiration and ethanol instillation of endometrioma versus aspiration alone; 32.1% versus 13.3%, respectively. Yazbeck *et al.*,¹⁶ Kumbak and Sahin,¹⁷ and Yazbeck *et al.*¹⁸

investigated the efficacy of ethanol sclerotherapy (EST) for recurrent endometriotic cysts, before ovarian stimulation in infertile patients with an adequate ovarian status and found that ovarian cysts recurred in 12.9% of cases; at a mean time of 10 months after EST, ovarian reserve and ovarian response to stimulation were better in the EST group than in the control group with consequently higher clinical and cumulative pregnancy rates in EST group than the control group, and concluded that EST may be a good alternative to surgical management of recurrent endometriotic cysts before assisted reproductive treatment. Wang *et al.*¹⁹ tried to determine the effectiveness of US-guided interventional therapy in the treatment of postoperative recurrent chocolate cysts using simple aspiration in one group of patients and ethanol instillation in the other group and found that the chocolate cyst cure rate was significantly higher in the ethanol retention group (96%) whereas no case was cured in the first group (saline washing) and concluded that US-guided injection and 95% ethanol retention are an effective therapy for the treatment of postoperative recurrent chocolate cysts. The current study reported a nonsignificantly lower recurrence rate with ethanol versus tetracycline solution instillation; 17.5% versus 20%; a finding indicating the efficacy of both modalities as a form of sclerotherapy after cyst aspiration. In line with these data; Fisch and Sher²⁰ reported complete resolution in 75% of patients at follow-up examination and repeat aspiration of watery fluid was required in 25% of patients before resolution with repeat tetracycline treatment was needed in 6% of patients, but only 2% of patients did not ultimately respond and concluded that sclerotherapy with 5% tetracycline is a simple and effective alternative to surgical intervention for treatment of endometriomas before *in vitro* fertilization. Kars *et al.*²¹ and Thummalakunta and Panditi²² investigated the value of tetracycline sclerotherapy for the management of recurrent or persisting nonneoplastic ovarian cysts in comparison to the aspiration without sclerotherapy and reported a 12-month recurrence rates of 14.6% with tetracycline and 50% in aspiration without sclerotherapy and based on the recurrence rates, suggested transvaginal aspiration together with tetracycline sclerotherapy rather than only simple transvaginal aspiration as the management of nonneoplastic ovarian cysts. The rates of persistence or recurrence after cyst aspiration reported in the literature range from 11% to 65% [Table 1]. Our study showed considerably lower persistence for endometriosis; only 18.18% (4/22) of our patients had an endometriotic cyst 12 months after the procedure and simple cyst persisted in 7.27% (8/110) patients. We used the transabdominal route for US-guided puncture of the cyst in all cases, as we have not had a great experience with other possible routes for accessing these lesions. We do not believe that percutaneous needle puncture of cystic contents poses a serious risk of bowel or blood vessel perforation. It is extremely unlikely for the needle to hit a small ovarian

Table 1: Studies of ultrasound guided cyst aspiration

Authors	Method	Number of patients	Cyst persistence percentage
Montanari <i>et al.</i> , 1987 ^[23]	Aspiration	15	53
Ron-El <i>et al.</i> , 1991 ^[24]	Aspiration	30	40
Bret <i>et al.</i> , 1992 ^[22]	Aspiration and alcohol sclerosis	7	30
Lipitz <i>et al.</i> , 1992 ^[21]	Aspiration	41	54
Bret <i>et al.</i> , 1992 ^[20]	Aspiration	48	48
Caspi <i>et al.</i> , 1993 ^[49]	Aspiration	18	11
Dordoni <i>et al.</i> , 1993 ^[48]	Aspiration	204	65
Bonilla-Musoles <i>et al.</i> , 1993 ^[47]	Aspiration	101	25
Giorlandino <i>et al.</i> , 1993 ^[46]	Aspiration	34	53
Lee <i>et al.</i> , 1993 ^[45]	Aspiration	18	11
AbdRabbo and Atta, 1995 ^[25]	Aspiration and tetracycline sclerotherapy	25	4
Caspi <i>et al.</i> , 1996 ^[43]	Aspiration	107	60
Zanetta <i>et al.</i> , 1996 ^[44]	Aspiration	135	54
Morelli <i>et al.</i> , 1996 ^[46]	Aspiration	175	32
Balat <i>et al.</i> , 1996 ^[48]	Aspiration	19	25
Brunner <i>et al.</i> , 1997 ^[42]	Aspiration	26	35
Troiano and Taylor, 1998 ^[41]	Aspiration	41	27.5
Guariglia <i>et al.</i> , 1999 ^[47]	Aspiration	9 (pregnant)	44
Caspi <i>et al.</i> , 2000	Aspiration	10 (pregnant)	50
Petrovic <i>et al.</i> , 2002 ^[9]	Aspiration	72	44
Mesogitis S <i>et al.</i> , 2000 ^[25]	Aspiration and methotrexate injection	148	16.2
Present study	Aspiration and methotrexate injection	132	12

vessel, as it is inserted directly into the cyst and not through the healthy ovary. The other pelvic vessels are quite obvious with US, especially when color Doppler US is used. In almost all cases, the bowel loops are moved away by the pressure exerted from the needle. We never observed hemorrhage or peritonitis caused by puncture of the bowel. Similarly, no such complications were reported in a large series of 878 transabdominal US-guided punctures of gynecologic lesions, including 183 endometriotic cysts.²³ We also did not observe any complication from the methotrexate or from inadvertent spillage of methotrexate into the peritoneum. The methotrexate dose we used was 30 mg, less than half that given in intramuscular injections (1 mg/kg). The absence of side effects is probably due to this reduced dose. In several studies of local methotrexate administration in ectopic pregnancies, no side effects were observed.²⁴ Methotrexate is an antimetabolite of the folic acid analog type. We used methotrexate injections to suppress the cystic wall cells. In endometriomas, these cells show a high mitotic index and are not governed by the control mechanism that regulates normal uterine endometrial glands.²⁵ We chose to focus on cystic wall cells and not on the content of the cyst because the former produce the fluid and are thus

responsible for the growth and persistence of the cyst. A previous study of methotrexate injection in ovarian cysts had already shown promising preliminary results.²⁵ Our study is definitely a controversial approach for management of ovarian cyst, US-guided transabdominal puncture can be recommended for such management, as long as all other preoperative investigations suggest that the cyst is benign, and puncture is followed by methotrexate injection. The shorter treatment period, the avoidance of general anesthesia, and the absence of side effects should also be considered. Nevertheless, patients should be informed that preoperative investigations are not faultless, and histologic diagnosis remains the reference standard for the exclusion of malignancy. The methotrexate dose was chosen arbitrarily. We do not know whether lower or higher doses would alter the outcome of our study or whether the dose should be adjusted according to cyst size. Although larger randomized studies are required to prove the effectiveness of our method, aspiration and methotrexate injection of ovarian cysts may provide an alternative treatment modality in selected patients with no evidence of malignancy.

CONCLUSION

Ultrasonography guided transabdominal aspiration of cyst fluid and subsequent methotrexate injection can be an alternative approach for treatment for both simple and endometriotic ovarian cysts in selected cases with no evidence of malignancy. Although larger randomized studies are required to prove the effectiveness of our method.

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Conflicts of interest

There are no conflicts of interest.

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