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Management of Ovarian Cysts with Aspiration and Methotrexate Injection[1]

PURPOSE: To evaluate prospectively ultrasonography (US)-guided cyst aspiration and methotrexate injection in the management of simple and endometriotic ovarian cysts in selected patients.

MATERIALS AND METHODS: Authors obtained informed patient consent and approval from hospital ethics committee. Study included 162 female patients (aged 15–77 years) with simple or endometriotic ovarian cysts (3.0–10.6 cm) at a tertiary hospital. Criteria for inclusion in the study were *(a)* persistence of the cyst for at least 6 months, *(b)* benign appearance of the cyst at US, and *(c)* normal serum CA-125 level measurement before the procedure. Authors performed transabdominal aspiration of the cysts with direct US guidance and injection of methotrexate (30 mg). Cytologic examination was performed in all cases. Follow-up US was performed at 1, 3, and 6 months. If the cyst persisted, the procedure could be repeated. Main outcome measure was resolution or persistence of cysts. χ^2 Test or Mantel-Haentszel χ^2 tests for univariate analysis and multiple logistic regression were used for multivariate statistical analysis.

RESULTS: Of 162 patients, 148 were available for follow-up. Malignant cells were not found in any of the cases at cytologic examination. At follow-up US, cysts had disappeared in 124 patients (83.8%) and persisted in 24 (16.2%). Cyst diameter proved to be a significant prognostic factor for cyst resolution ($P = .01$). No major complications were observed. Patients received neither analgesia nor antibiotics.

CONCLUSION: US-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.

The frequency of ovarian cysts detected in asymptomatic female patients has increased in recent years with the use of ultrasonography (US) and other imaging methods for evaluation of the abdomen and pelvis. Among healthy women, 6% are found to have adnexal masses, 90% of which are cystic lesions—mostly simple cysts (1). Ovarian functional cysts were also the fourth most common gynecologic cause of hospital admission in the United States in the late 1980s (2). Moreover, the possibility of malignant transformation of ovarian cysts remains unknown, especially in postmenopausal women (3,4). Many of these cysts are managed with laparoscopy or laparotomy. Simple ovarian cysts do not usually become malignant (5), however, and most adnexal cysts removed at surgery are benign or functional (6,7). Thus, surgery may represent overtreatment in these patients, and the cost and risks may outweigh the benefits. Nevertheless, the diagnosis of an ovarian cyst causes anxiety, mainly because of the fear of malignancy (6).

US-guided aspiration of ovarian cysts with cytologic evaluation of the cyst fluid has been proposed by many investigators, but results have been contradictory, with the rate of definite cure ranging from 30% to 80% (4,8–28). The fear of spreading malignant cells in the peritoneal cavity, in case of unrecognized malignancy, has been the case against cyst aspiration for many years (18,29–32). Along with an evolution in US accuracy, multiple attempts have been made to identify characteristics of nonmalignant cysts (33,34). Granberg et al (33) observed that the risk of malignancy in a simple ovarian cyst, as diagnosed

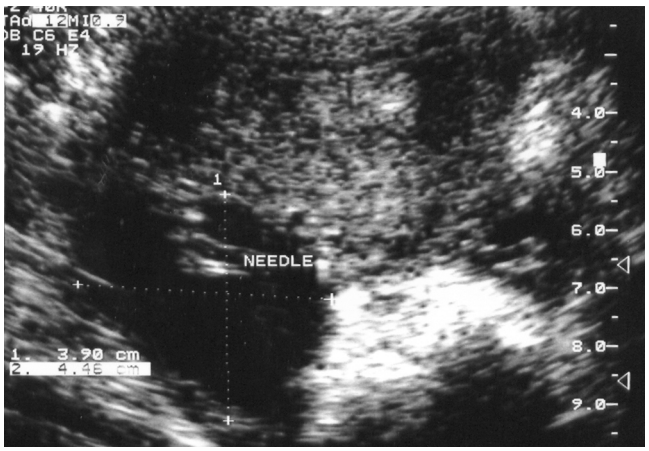

Figure 1. Transverse US section of an ovarian cyst with the needle inside, before aspiration. The abdominal surface is on the top.

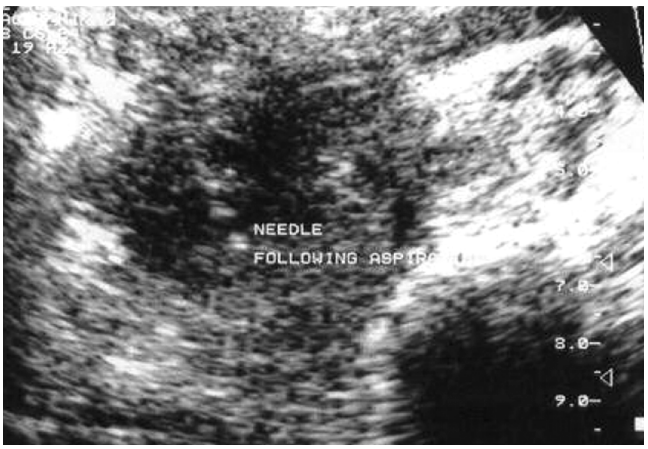

Figure 2. Same US section of the cyst shown in Figure 1, after aspiration and with the needle in place. Again, the abdominal surface is on the top.

at US, is less than 0.5%. The cyst wall seems to be responsible for fluid production and the subsequent persistence of the cyst (4).

Methotrexate is a well-known folate antagonist and is the classic antimetabolite prototype. It is frequently used in the conservative management of ectopic pregnancy, in medical abortion in early pregnancy, and in the treatment of gynecologic malignancies. We thought that it might suppress fluid production by the cells of the cyst wall (35). In the current study, we used 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.

MATERIALS AND METHODS

Patients

This prospective study was conducted during 1997–2002. It included 162 female patients (age range, 15–77 years; mean, 38.7 years) who were referred to our department after detection of an adnexal cystic mass at US examination. In all cases, after obtaining the patient's informed consent for the study, we performed puncture and aspiration followed by methotrexate injection into the cyst. We obtained approval from the hospital ethics committee.

Inclusion criteria were as follows: *(a)* a unilateral simple ovarian cyst that had persisted for more than 6 months before the procedure; *(b)* cyst diameter more than 30 mm; *(c)* no family history of ovarian cancer; *(d)* no evidence of renal or hepatic disease; *(e)* a normal value (<35 IU/mL) of serum CA-125 before the procedure; *(f)* no large amount of free fluid in the pouch of Douglas, for fear of starting a torsion of the cyst; *(g)* no previous puncture of the cyst; and *(h)* 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.

Procedure

The procedure was performed by one of several authors (S.M., G.D., A.P., N.P., P.K., A.A.). Four of them (S.M., N.P., P.K., A.A.) had had more than 4 years of experience in cyst puncture when the study started, and two (G.D., A.P.) were less experienced. All authors have been performing cordocentesis for the diagnosis of thalassemia, most of them (S.M., N.P., P.K., A.A.) since 1977 and during the 1980s (approximately 600 procedures per year).

The cysts were punctured transabdominally with a 21-gauge spinal needle (Fig 1). A freehand technique was used, with direct US guidance provided by means of a convex 3.5-MHz probe attached to a US machine (ATL-9 HDI; Advanced Technology Laboratories, Bothell, Wash). 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 (Fig 2).

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. Follow-up images were interpreted by at least two of the authors (S.M., G.D., A.P., N.P., P.K.) for each patient. In all cases of cyst persistence, a second or—at most—a third aspiration and injection of metho-

TABLE 1
Distribution of Patients according to Outcome and Study Variable

Variable	Cyst Persistence	Cyst Resolution
Patient age (y)*		
<25	4/24 (16.7)	22/124 (17.7)
25–34	4/24 (16.7)	28/124 (22.6)
35–44	4/24 (16.7)	38/124 (30.6)
45–54	8/24 (33.3)	22/124 (17.7)
>55	4/24 (16.7)	14/124 (11.3)
Cyst size (mm)†		
<40	0.0	16/124 (12.9)
41–50	4/24 (16.7)	38/124 (30.6)
51–60	6/24 (25.0)	26/124 (21.0)
61–70	6/24 (25.0)	16/124 (12.9)
71–80	2/24 (8.3)	16/124 (12.9)
>80	6/24 (25.0)	12/124 (9.7)
Aspiration volume (mL)‡		
<30	2/24 (8.3)	34/124 (27.4)
30–59	4/24 (16.7)	32/124 (25.8)
60–89	10/24 (41.7)	20/124 (16.1)
>90	8/24 (33.3)	38/124 (30.6)
Cyst composition§		
Simple	20/122 (16.4)	102/122 (83.6)
Endometriotic	4/26 (15.4)	22/26 (84.6)

Note.—Data are numbers of patients, with percentages in parentheses.
* $P = .22$ (Mantel-Haentszel χ^2 test).
† $P = .01$ (Mantel-Haentszel χ^2 test).
‡ $P = .06$ (Mantel-Haentszel χ^2 test).
§ $P = .90$ (χ^2 test).

trexate 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.

Follow-up was not performed in 14 patients, all of whom had undergone the first procedure successfully but did not come to the follow-up appointment. Five of them had moved to another address and were not contacted. Three patients reported that a follow-up US scan obtained elsewhere had showed resolution of the cyst, and they declined to undergo further scanning in our department. Six others underwent surgery in another hospital and were unable to give specific information about the surgical findings. All 14 of these patients were excluded from the study.

Statistical Analysis

Statistical analysis was performed with the data from the 148 patients in whom complete follow-up was obtained. Univariate analysis was performed with the χ^2 test for the variable "composition" or the Mantel-Haentszel χ^2 test for trend, with one degree of freedom for the remaining variables.

Multivariate analysis was performed with multiple logistic regression from the SAS statistical package (SAS Institute, Cary, NC). Logistic analysis was chosen because the dependent variable is dichotomous, and no further examinations have been performed on the model assumption. Possible correlations and interactions between the independent variables were examined. Statistical significance was defined as a P value of less than .05.

RESULTS

Complete follow-up was obtained in 148 of 162 patients; the other 14 were excluded from the study. The study group included 122 patients with simple ovarian cysts and 26 with endometriotic cysts. No evidence of malignancy was reported in the cytologic examination in any patient. Overall, cyst resolution was observed in 124 of the 148 patients (83.8%).

Endometriotic Cysts

The 26 patients with an endometriotic cyst were 22–50 years old (mean, 33.9 years), and their cysts were 31.0–63.6 mm in diameter (mean, 50.8 mm). The amount of fluid aspirated in this group ranged from 0 to 50 mL (mean, 22.7 mL). Four women underwent a second injection of methotrexate because of cyst persistence, and two others received three injections. Among the 20 remaining women who had one methotrexate injection, the cyst persisted in only two (10%). 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 the more dilute contents of the cyst. Nine of the 26 women had lower pelvic pain or dysmenorrhea before the procedure. Six reported marked improvement or complete resolution of the symptoms, while the other three reported persistent (though milder) pain.

Simple Cysts

The 122 patients with a simple cyst were 15–77 years old (mean, 39.7 years). Their cysts ranged from 30 to 105 mm in diameter (mean, 58.1 mm), and the aspiration volume ranged from 12.5 to 250 mL (mean, 85.8 mL). Eight patients in this group underwent a second aspiration with methotrexate injection, and eight required three injections. In two patients receiving two injections and in another two receiving three injections, the cyst persisted despite the repeated procedures. Among the 106 remaining patients who received only one methotrexate injection, the cyst persisted in 16 patients and disappeared in all the others. The sixteen patients with cyst persistence after the first procedure and the two with cyst persistence after the second procedure decided to undergo surgery rather than receive another injection, mainly as a result of anxiety. These procedures were performed in various hospitals. Telephone communication with these patients confirmed that no malignancy was found (diagnoses included serous cystadenoma in 10 patients, corpus luteum cyst in five, paraovarian cyst in two, and follicle cyst in one).

Outcomes and Complications

Table 1 shows the distribution of patients according to the outcome and the study variable. Table 2 presents the patient characteristics according to cyst composition and outcome. Overall, regardless of the number of methotrexate injections, the cyst resolved in 84.6% of patients with a endometriotic cyst (22 of 26) and 83.6% of those with a simple ovarian cyst (102 of 122). No major complications were observed in our study

TABLE 2
Patient and Cyst Characteristics according to Cyst Component and Outcome

Parameter	Simple Cysts		Endometriotic Cysts		All Cysts	
	Resolution	Persistence	Resolution	Persistence	Resolution	Persistence
Patient age (y)	38.9 ± 1.98	42.9 ± 4.84	34.6 ± 2.92	30.0 ± 0.81	38.2 ± 1.74	41.9 ± 4.31
Cyst size (mm)	57.3 ± 2.28	61.5 ± 5.45	46.5 ± 4.43	74.4 ± 21.00	55.4 ± 2.10	66.5 ± 5.30
Aspiration volume (mL)	88.0 ± 9.34	76.4 ± 12.20	21.4 ± 5.35	30.0 ± 5.00	76.3 ± 8.47	76.7 ± 11.89

Note.—Data are given as means ± standard errors.

population during or after the procedure. Only six patients reported mild pelvic pain, and three 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 hours. No hospital admission was required. We did not observe any cases of infection after the procedure. Multiple logistic regression showed that cyst size was a statistically significant factor in the persistence of the cyst ($P < .05$), while age was a contributing but not a significant factor ($P = .2$). Moreover, aspiration volume was a favorable but nonsignificant factor for cyst disappearance ($P = .12$) (Table 3). Univariate analysis showed that the mean age was 38.7 years ± 13.8 (standard deviation), mean size was 56.9 mm ± 17.0, and mean aspiration volume was 75.0 mL ± 62.7. There were no significant differences in the results when possible interactions between the variables were included in the model.

TABLE 3
Multiple Logistic Regression–derived Risk Ratios and 95% Confidence Intervals for Cyst Persistence according to Patient and Cyst Variables

Variable	Increment	Risk Ratio	95% Confidence Interval	*P* Value
Patient age	10 years or more	1.39	0.80, 2.41	.23
Cyst size	1 standard deviation	3.28	1.30, 8.30	.01
Aspiration volume	1 standard deviation	0.44	0.15, 1.30	.13
Composition			0.17, 13.36	.72
Endometriotic cysts		Baseline		
Simple cysts		1.49		

DISCUSSION

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 resolution in 102 of 122 patients (83.6%) with simple cysts and 22 of 26 (84.6%) with endometriotic cysts. 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, while 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 a 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 (36). US is probably the most reliable method, with a diagnostic accuracy of 90%–100% for transvaginal scanning (33,36).

In a recent study that included 2763 asymptomatic women over 50 years of age with a unilocular ovarian cyst less than 10 cm in diameter, no woman developed ovarian cancer unless she developed another morphologic abnormality (37). Our study focused on simple cysts with no papillary projections, a clearly defined smooth cyst wall, and a 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 (37,38). 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 (3). 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 (18,29–32,39). However, data from studies addressing this risk (40,41) showed that 5- and 10-year survival rates after aspiration were not worse than those for women with nonaspirated cysts. A retrospective study has shown that abdominal wall metastasis developed in the entry site in 10% of patients who underwent paracentesis before primary debulking for ovarian cancer (39). Nevertheless, metastasis occurred only in patients with advanced-stage disease and ascites present and not in those with stage I or II disease and no ascites.

The rates of persistence or recurrence after cyst aspiration reported in the literature range from 11% to 65% (Table 4). Our study had an overall persistence rate of 16.2%, which shows the effectiveness of our method. While Zanetta et al (4) reported that plain observation is as effective as aspiration in the treatment of simple cysts, we treated only patients with cysts persisting longer than 6 months. Troiano and Taylor (11) reported a recurrence rate of 66% after aspirating endometriotic cysts, while Mo-

TABLE 4
Studies of US-guided Cyst Aspiration

Authors	Method	No. of Patients	Cyst Persistence (%)
Montanari et al, 1987 (24)	Aspiration	15	53
Ron-El et al, 1991 (23)	Aspiration	30	40
Bret et al, 1992 (22)	Aspiration and alcohol sclerosis	7	30
Lipitz et al, 1992 (21)	Aspiration	41	54
Bret et al, 1992 (20)	Aspiration	48	48
Caspi et al, 1993 (19)	Aspiration	18	11
Dordoni et al, 1993 (18)	Aspiration	204	65
Bonilla-Musoles et al, 1993 (17)	Aspiration	101	25
Giorlandino et al, 1993 (16)	Aspiration	34	53
Lee et al, 1993 (15)	Aspiration	18	11
AbdRabbo and Atta, 1995 (25)	Aspiration and tetracycline sclerotherapy	25	4
Caspi et al, 1996 (13)	Aspiration	107	60
Zanetta et al, 1996 (4)	Aspiration	135	54
Morelli et al, 1996 (26)	Aspiration	175	32
Balat et al, 1996 (8)	Aspiration	19	25
Brunner et al, 1997 (12)	Aspiration	26	35
Troiano and Taylor, 1998 (11)	Aspiration	41	27.5
Guariglia et al, 1999 (27)	Aspiration	9 (Pregnant)	44
Caspi et al, 2000 (28)	Aspiration	10 (Pregnant)	50
Petrovic et al, 2002 (9)	Aspiration	72	44
Present study	Aspiration and methotrexate injection	148	16.2

relli et al (26) reported a recurrence rate of 53% for the same group of patients. Our study showed considerably lower persistence for endometriosis; only 15.4% of our patients had an endometriotic cyst 6 months after the procedure.

We used the transabdominal route for US-guided puncture of the cyst in all cases, as we have not had great experience with other possible routes for accessing these lesions (eg, transvaginal, transrectal, or transgluteal). 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 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 (42).

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 (43,44).

Methotrexate is an antimetabolite of the folic acid analog type (35). 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 (45). 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 (4). A previous study of methotrexate injection in ovarian cysts had already shown promising preliminary results (45).

Although we accept that our method is a controversial approach to the management of ovarian cysts, we challenge the dogma that US-guided transabdominal puncture cannot be recommended for such management (32), 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.

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