

Salpingitis, Salpingoliths, and Serous Tumors of the Ovaries: Is There a Connection?

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Summary: We have observed luminal and mucosal calcifications frequently surrounded by a mantle of bland epithelium in the fallopian tubes (“salpingoliths”) of women with serous tumors of the ovaries. These lesions resemble noninvasive peritoneal “implants” in women with advanced stage atypical proliferative serous tumors (APSTs) and micropapillary serous carcinomas (MPSCs). The presence of salpingitis and salpingoliths was prospectively evaluated in 358 women with a variety of non-neoplastic and neoplastic ovarian conditions and compared with 87 previously reported women with APSTs/MPSCs in an effort to determine whether these lesions were specifically associated with serous tumors. The frequency of chronic salpingitis among women without ovarian pathology was 27%, and the frequency of salpingoliths was 4%. Serous epithelial tumors (cystadenomas, APST/MPSC, and carcinomas) were significantly more often associated with chronic salpingitis (53%) and salpingoliths (32%) than all other cases with or without ovarian neoplasms ($p < 0.01$). APSTs/MPSCs were associated with salpingoliths significantly more frequently than all other groups ($p < 0.001$). For patients with APSTs/MPSCs, salpingoliths were found significantly more often in advanced stage (FIGO II and III) patients (51%) than stage I patients (24%) ($p < 0.01$), but salpingitis, present in 60% of these patients, was not stage-dependent ($p > 0.05$). Chronic salpingitis was identified in 66% of women with endometriosis, which was significantly more frequent than those with normal ovaries (27%) ($p < 0.001$). In conclusion, fallopian tube abnormalities may be related to both the high frequency of infertility and the noninvasive peritoneal implants in women with APSTs/MPSCs. Whether the fallopian tubes with salpingoliths are the source of the peritoneal “implants,” the recipient of implants, or are independent is unknown. In addition, the high frequency of salpingitis in women with endometriosis may be related to the mechanism of endometriosis-associated infertility. **Key Words:** Ovarian neoplasms—Fallopian tube—Salpingitis—Endometriosis—Borderline tumor—Atypical proliferative serous tumor.

The pathogenesis of peritoneal “implants” associated with ovarian proliferative noninvasive serous tumors (atypical proliferative serous tumors [APSTs] and micro-

papillary serous carcinomas [MPSCs]) is unknown. We have frequently observed calcifications, often surrounded by a single layer of epithelium and occasionally associated with papillary excrescences (hereafter referred to as “salpingoliths”), in the tubal lumen, epithelium, and lamina propria of patients with APSTs/MPSCs. These salpingoliths bear a resemblance to the noninvasive peritoneal implants associated with APSTs/MPSCs. We have also noted that the peritoneal implants are often associated with inflammation, usually chronic, and that there appears to be a high frequency of salpingitis in these women. To evaluate the significance of the salpingoliths and salpingitis objectively, we ex-

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amed consecutive fallopian tube specimens from a large series of women with a variety of neoplastic and nonneoplastic conditions of the ovaries and compared the findings to those from fallopian tubes from a large series of APSTs/MPSCs from two previous studies (1,2).

MATERIALS AND METHODS

Fallopian tubes from consecutive surgical pathology accessions over a 2-year period at the Washington Hospital Center (WHC) were reviewed prospectively. To accumulate sufficient numbers of tubal specimens, accrual of cases with ovarian neoplasms and endometriosis was continued after 100 specimens from routine tubal ligations and salpingectomies for ectopic pregnancy, and 100 hysterectomies were examined. In addition, all available sections of fallopian tubes accompanying APSTs/MPSCs from two previous studies were reviewed (1,2). Chronic salpingitis was diagnosed if at least one of the following features was identified: at least three plasma cells in the lamina propria, marked blunting and fusion of plicae, or hydrosalpinx. Acute salpingitis was diagnosed based on neutrophils infiltrating the lamina propria. Neither the severity of salpingitis nor the location of the plasma cells in relation to the salpingoliths was evaluated. The location of salpingoliths, either in the mucosa (lamina propria, epithelium, or both) or in the lumen, was noted. Because tangential sectioning of a mucosal salpingolith could mimic an intraluminal site, and for simplicity of analysis, salpingoliths were considered present or absent for each fallopian tube. For luminal salpingoliths, the presence or absence of an epithelial lining surrounding the calcifications was noted. Patients with endometriosis and a neoplasm, or with two distinct neoplasms, were included in both respective groups (i.e., a patient with ovarian endometriosis and a Brenner tumor would be included twice—once in each group—thus resulting in unequal totals in the tables). Tubal and ovarian lesion laterality was recorded. When possible, the fallopian tubes were evaluated without knowledge of the ovarian pathology, but this was not feasible in many cases including instances in which sections of tube and ovary were on the same slide. Masking was impossible for tubes from postpartum tubal ligations, ectopic pregnancies, and tubes directly involved by endometriosis. Peritoneal implants from patients with advanced stage APSTs were reviewed, and the presence or absence of acute and chronic inflammation was recorded. All fallopian tubes and peritoneal implants were reviewed by one observer (J.D.S.). Approximately 15% of fallopian tubes were reviewed by a second observer (M.S.), and all peritoneal implants were re-reviewed by two observers

(M.S., K.B.). Discrepancies were resolved by consensus review.

Fallopian tubes were reviewed from 445 patients. In 55% of cases, bilateral tubes were reviewed (22% for APSTs/MPSCs, 68% for all other groups). The number of sections reviewed per tube ranged from 1–16, with a mean of 2.3 sections per tube for APSTs/MPSCs and 3.5 sections per tube for all other groups. Ovarian tumors were diagnosed according to WHO criteria, with further subclassification of serous “borderline” tumors into APSTs and micropapillary serous carcinomas (MPSC) (“serous borderline tumor with micropapillary pattern”) (1,3). Staging of APSTs/MPSCs was based on FIGO criteria (4). The chi square test was used to compare groups.

RESULTS

The results are shown in Tables 1–3, and statistical analyses are shown in Table 4.

Salpingitis

Chronic salpingitis was found in 38% of cases, and acute salpingitis in 5%. Approximately 15% of cases with chronic salpingitis had hydrosalpinx. Evaluation of left-right concordance for patients with APSTs/MPSCs for whom bilateral tubes were examined revealed that 83% of tube pairs were concordant for the presence or absence of salpingitis. Similarly, among all other cases, 89% of tube pairs were concordant for salpingitis. In view of this high degree of left-right concordance, no further analyses with respect to laterality were performed.

TABLE 1. *Histological findings in fallopian tubes*

	Total n	Salpingitis		Salpingoliths n (%)
		Chronic	Acute	
		n (%)	n (%)	
Postpartum tubal ligation specimens	85	18 (21)	0 (—)	0 (—)
Tubal pregnancies	15	5 (33)	7 (47)	2 (13)
Normal/nonneoplastic ovaries ^a	100	33 (33)	4 (4)	7 (7)
Endometriosis	35	23 (66)	1 (3)	3 (9)
Nonserous neoplasms in the ovaries ^b	73	17 (23)	1 (1)	4 (5)
Serous ovarian neoplasms ^b	146	78 (53)	11 (8)	46 (32)
Total	454	174 (38)	24 (5)	62 (14)

^a Includes normal ovaries and those with the following conditions: follicular cysts, adhesions, and stromal hyperplasia.

^b See Table 2 for details of subgroups.

TABLE 2. Salpingitis and salpingoliths associated with various types of ovarian tumors

	n	Salpingitis		Salpingoliths (%) n (%)
		Chronic n (%)	Acute n (%)	
Nonserous neoplasms				
Benign	14	5 (36)	0 (—)	1 (7)
Carcinomas	13	1 (8)	0 (—)	0 (—)
Stromal tumors	17	1 (6)	0 (—)	1 (6)
Mature teratomas	14	5 (36)	0 (—)	0 (—)
Metastatic tumors	15	5 (33)	1 (7)	2 (13)
Total	73	17 (23)	1 (1)	4 (5)
Serous neoplasms				
Serous cystadenoma	43	18 (42)	1 (2)	6 (14)
Atypical proliferative serous tumors	76	45 (59)	10 (13)	27 (36)
Micropapillary serous carcinomas ^a	11	7 (64)	0 (—)	7 (64)
Serous carcinomas	16	8 (50)	0 (—)	6 (38)
Total	146	78 (53)	11 (8)	46 (32)

^a Noninvasive type only.

Serous tumors

Chronic salpingitis was found in 42% of patients with serous cystadenomas, 59% with APSTs, 64% with MPSCs, and 50% of serous carcinomas (Table 2), compared with 34% of nonneoplastic cases (tubal ligations, tubal pregnancies, normal/nonneoplastic, and endometriosis) (Table 1). For patients with APSTs and MPSCs, the salpingitis was not stage-dependent (Table 3). Chronic salpingitis was significantly more common in patients with APSTs/MPSCs than in all nonserous tumors and nonneoplastic cases including all subgroups except patients with endometriosis. Acute salpingitis (Fig. 1) was significantly more common in patients with APSTs than in all other patients with the exception of those with tubal pregnancies. Although chronic salpingitis was found at similarly high frequencies in patients with all serous tumors, acute salpingitis was significantly more common in patients with APSTs than in those with serous cystadenomas, MPSCs, and serous carcinomas (Table 2).

Nonserous tumors and nonneoplastic ovaries

All nonserous tumors, including subgroups, and nonneoplastic ovaries had relatively low frequencies of sal-

TABLE 3. Salpingitis and salpingoliths in noninvasive serous tumors (APSTs and MPSCs) stratified by stage

	Total n	Salpingitis		Salpingoliths n (%)
		Chronic n (%)	Acute n (%)	
Stage I	38	23 (61)	3 (8)	9 (24)
Stage II/III	49	29 (59)	7 (14)	25 (51)
Total	87	52 (60)	10 (11)	34 (39)

TABLE 4. Statistical analysis of various groups

Groups compared	Variable	p value (chi square)
APSTs and MPSCs vs all other cases	Acute salpingitis	<0.01
	Chronic salpingitis	<0.001
Serous vs nonserous primary epithelial neoplasms	Salpingoliths	<0.001
	Salpingitis	<0.01
Stage I vs Stages II/III APSTs and MPSCs	Salpingoliths	<0.01
	Salpingitis	>0.05
APST/MPSC vs serous cystadenoma	Salpingoliths	<0.01
	Salpingitis	>0.05
APST/MPSC vs serous carcinoma	Salpingoliths	>0.05
	Salpingitis	>0.05
Endometriosis vs normal and nonneoplastic cases	Salpingoliths	<0.001
	Salpingitis	<0.001

Note: Salpingitis refers to chronic salpingitis unless otherwise specified.

pingitis (6–36%) except for patients with endometriosis who had a 66% frequency of chronic salpingitis (Tables 1 and 2). Some ovaries included in the normal/nonneoplastic group had focal adhesions, but there was no significant difference in the frequency of salpingitis in these patients with and without adhesions (data not shown).

Salpingoliths

Salpingoliths were identified in 14% of all patients. The salpingoliths were occasionally (6 cases) accompanied by a foreign body giant cell reaction in which the giant cells appeared to be engulfing the calcifications (Fig. 2). Salpingoliths were surrounded by a simple, usually flattened, epithelial layer in 90% of cases (100% for APSTs/MPSCs, 75% for all others) (Fig. 3, A–C).

For patients with APSTs/MPSCs for whom bilateral tubes were examined, 83% of tube pairs were concordant for the presence or absence of salpingoliths. Similarly, among all other neoplasms and nonneoplastic groups, 94% of tube pairs were concordant for salpingoliths.

Serous tumors

Salpingoliths were found at similar frequencies in patients with APSTs, MPSCs, and serous carcinomas and at significantly greater frequencies than that in serous cystadenomas (Table 2). Salpingoliths were significantly more common in patients with APSTs and MPSCs than in all cases with nonserous tumors and nonneoplastic conditions (Tables 1 and 2). Advanced stage APSTs and MPSCs were associated with salpingoliths significantly more frequently than stage I APSTs and MPSCs (Table 3). Of note, calcifications surrounded by cytologically

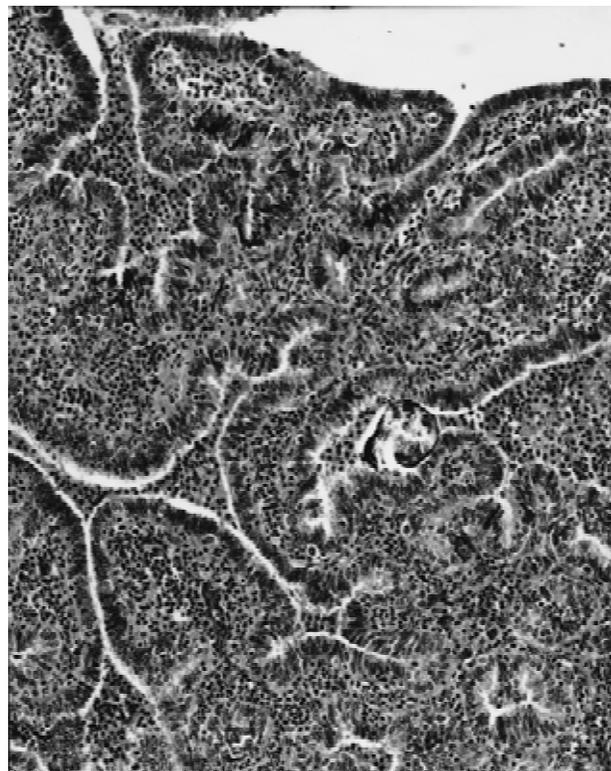


FIG. 1. Acute salpingitis with a luminal salpingolith in a patient with an atypical proliferative serous tumor.

malignant epithelium were seen only in the tubal lumen in patients with serous carcinomas. These had an identical appearance to the ovarian tumors and were considered “floaters.” Only calcifications surrounded by benign epithelium were considered salpingoliths in these patients (as well as all others).

Nonserous tumors and nonneoplastic ovaries

All nonserous tumors and nonneoplastic cases had similarly low frequencies of salpingoliths (0–13%) (Tables 1 and 2).

Relationship of Salpingitis to Salpingoliths

Salpingoliths were present significantly more frequently in tubes with chronic salpingitis (26%) and acute salpingitis (29%) than in those without salpingitis (5%) (data not shown).

Relationship of Salpingitis to Inflammation in Noninvasive Implants

Chronic inflammation was found in 65% of noninvasive peritoneal implants. For tubes matched with implants from the same patient, 60% were concordant for the presence or absence of inflammation, and 40% were concordant for the presence and type of inflammation

(acute or chronic). Chronic inflammation was found in the implants in 58% of patients with advanced stage APSTs and chronic salpingitis compared with 75% of advanced stage APSTs without salpingitis ($p>0.05$). Similarly, acute salpingitis did not correlate with acute inflammation in the implants (data not shown). There were too few invasive implants available for meaningful analysis.

Relationship of Salpingitis to Endometriosis

Among 35 patients with endometriosis, 23 had salpingitis (66%) (Table 1). Although 12 patients (34%) had endometriosis directly involving the fallopian tube, the frequency of chronic salpingitis in patients with tubal endometriosis (75%) was not significantly different from the frequency of chronic salpingitis in patients with non-tubal endometriosis (61%) ($p>0.05$).

DISCUSSION

The main finding of this study is that of all types of ovarian tumors, serous epithelial tumors (serous cystadenomas, APSTs/MPSCs, and serous carcinomas) are most strongly associated with salpingitis. This relation-



FIG. 2. Intraluminal and intraepithelial salpingoliths. A multinucleated giant cell in the center has engulfed several calcifications. Note plical fusion forming gland-like structures.

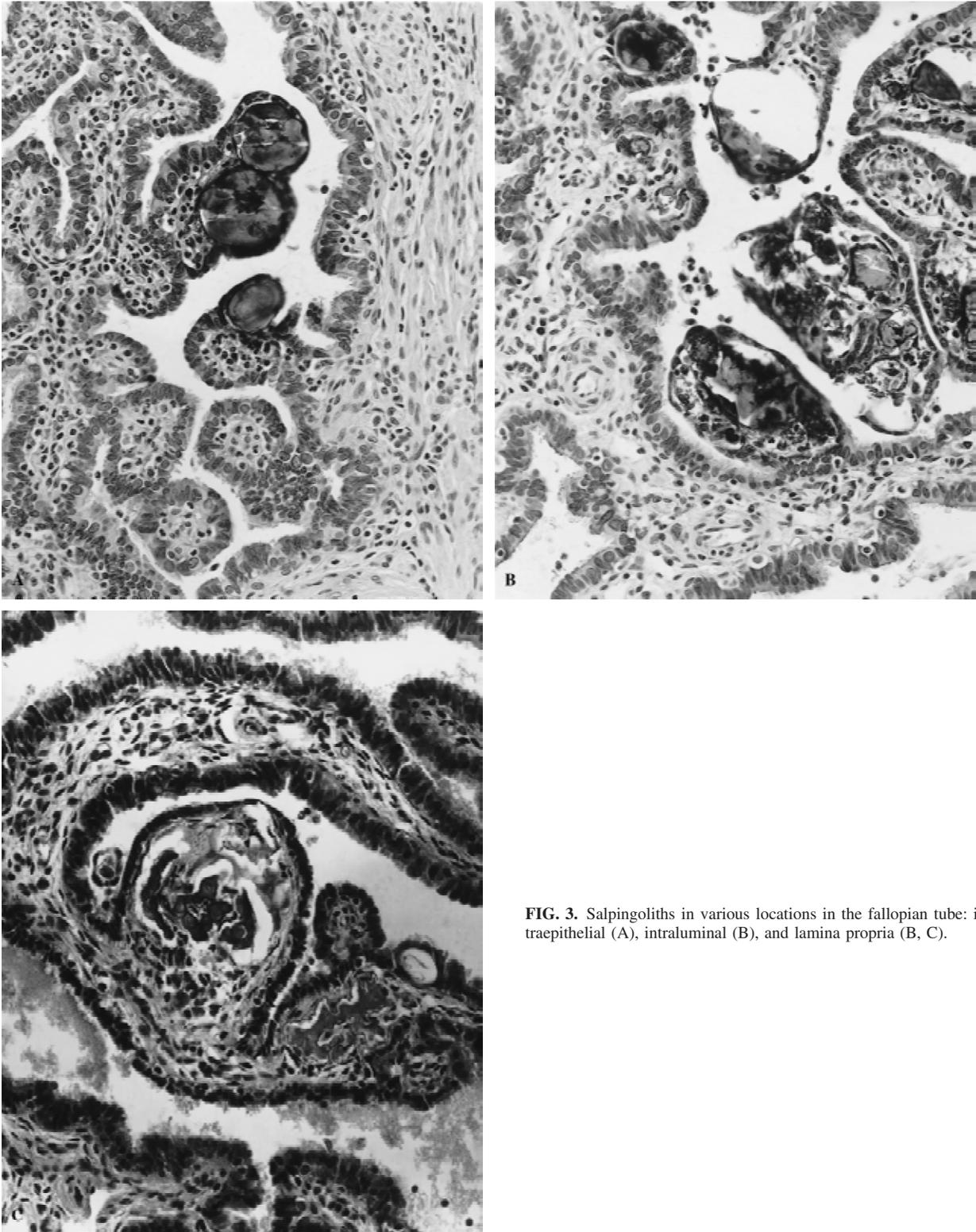


FIG. 3. Salpingoliths in various locations in the fallopian tube: intraepithelial (A), intraluminal (B), and lamina propria (B, C).

ship is significant in comparison to all nonserous epithelial tumors and normal and nonneoplastic ovaries with the exception of those with endometriosis. With regard to the mucosal and luminal calcifications, which we have termed salpingoliths, these lesions are strongly associated with serous tumors, particularly APSTs/MPSCs and carcinomas, and the association with APSTs/MPSCs is stage-dependent, that is, the frequency of salpingoliths increases with increasing stage.

Two recent studies have examined the fallopian tubes in patients with APSTs. Robey and Silva (5) found a significantly increased frequency of tubal epithelial hyperplasia in these women, but Yanai-Inbar et al. (6) could not confirm this finding. In neither of these studies was any comment made on calcifications or the frequency of salpingitis. We abandoned our early attempts to evaluate tubes for epithelial hyperplasia due to our inability to define reproducible criteria. We also note that it is difficult to control for factors that may influence the appearance of the tubal epithelium, such as hormonal status and location in the tube (i.e., intramural, isthmus, infundibulum, ampulla, or fimbria). In addition, in our opinion, several published photomicrographs purporting to show epithelial hyperplasia of the fallopian tube are unconvincing for that lesion (5–8).

The mechanisms involved in endometriosis-associated infertility are incompletely understood (9–16), and some authors have suggested that the evidence for a causal relationship is weak at best (15). We identified salpingitis in 66% of women with endometriosis. Czernobilsky and Silverstein (10) previously reported that 33% of patients with ovarian endometriosis have salpingitis. Although 34% of our patients with endometriosis had tubal endometriosis, tubes directly involved by endometriosis did not demonstrate salpingitis significantly more frequently than tubes lacking direct involvement by endometriosis. Similarly, Czernobilsky and Silverstein did not favor endometriosis of the fallopian tube as a cause of salpingitis; only 2% of their cases of endometriosis involved the fallopian tube (10). We suspect that endometriosis of any pelvic organ may be related to salpingitis by unknown mechanisms.

The strong association of APSTs/MPSCs with chronic salpingitis and salpingoliths may be important. The finding of a high frequency of salpingitis is of particular interest because epidemiologic data indicate that patients with APSTs/MPSCs share similar risk factors with ovarian carcinoma patients with the sole exception of a significantly higher frequency of infertility in women with APSTs/MPSCs (17). It is possible that the higher frequency of infertility in these patients is related to the high frequency of salpingitis.

Most subgroups in our study had a high frequency of salpingitis, but only patients with serous tumors and endometriosis had significantly higher frequencies of chronic salpingitis than the 27% baseline. Notably, nonserous tumors were associated with a frequency of salpingitis that was not significantly different from baseline (23%), suggesting that an ovarian mass *per se* is not associated with an increased likelihood of salpingitis.

The 27% baseline level of salpingitis (postpartum ligations specimens and normal ovaries from TAH specimens) seems high, but is in a similar range as other reports. For example, in a prospective study of 124 patients who underwent hysterectomy, 24% of patients had salpingitis (18). In 1988, 17% of American women received treatment for pelvic inflammatory disease (PID) (19). Self-reported rates of PID vary from 10–23% depending on the year surveyed and other factors (20). Because we have defined salpingitis morphologically, and PID is a clinical diagnosis, the two conditions are not identical. Salpingitis in the presence of a serous ovarian neoplasm or endometriosis may have no relationship with a microbiologic agent or with the clinical features of PID. Nonetheless, PID is a reasonable clinical correlate of salpingitis, albeit an imperfect one.

The salpingoliths are curious findings and their resemblance to the peritoneal “implants” associated with APSTs/MPSCs may indicate a relationship. Perhaps one is a cause of the other, or perhaps both are related to a third factor such as the ovarian tumor itself. Similar calcifications in the tubal mucosa have been illustrated in rare reports but have not been formally studied (21,22). A possible role of tubal obstruction in the etiology of these lesions is suggested by one study. Stock (21), in a study of histologic changes after tubal ligations, noted calcified material and psammoma bodies in the tubal lumen at the site of prior ligation.

There are several limitations of the current study. First, the study cases came from two different populations: APSTs/MPSCs were drawn nationwide from AFIP referrals, whereas the remaining cases came from WHC. Both groups, but particularly the WHC group, may not accurately represent the general population. For example, the WHC gynecology service serves a population that is 76% black. Second, the APST/MPSCs were identified retrospectively from 1980–1989 cases, whereas the comparison group was identified prospectively and at a later time (1996–1998). Therefore, the latter group does not strictly qualify as a “control” group. Third, we used arbitrary criteria for salpingitis, which have not been rigorously tested. For example, a study correlating the degree of plasma cell infiltration with clinical signs and symptoms of PID might lead to refined diagnostic crite-

ria for a morphologic diagnosis of salpingitis with clinical relevance. Finally, unequal sampling of tubes or implants could have influenced our findings.

Our finding that the association of APSTs/MPSCs with salpingoliths is stage-dependent would support a relationship between salpingoliths and the associated peritoneal "implants." The nature of this putative relationship is unknown, but our data suggest the hypothesis that the salpingitis, salpingoliths, and noninvasive peritoneal implants are all related to an underlying inflammatory process. There are several possible explanations for the salpingoliths. First, the tubal mucosa could produce salpingoliths and by detachment and implantation be the source of the peritoneal "implants." Second, the tubal mucosa could be a site of "implantation" from the primary ovarian tumor analogous to this alleged role of the peritoneum in women with APSTs/MPSCs. Third, the salpingoliths could arise in the tube independently but perhaps due to similar underlying factors (such as inflammation) affecting the origin of the peritoneal "implants," which may also be independent. Molecular studies could be of value in elucidating this process. For example, similar molecular changes in the epithelium of the salpingoliths and the peritoneal lesions, and distinct from those in the ovarian tumor, would support a relationship between the salpingoliths and peritoneal lesions.

REFERENCES

1. Seidman JD, Kurman RJ. Subclassification of serous borderline tumors of the ovary into benign and malignant types: a clinicopathologic study of 65 advanced stage cases. *Am J Surg Pathol* 1996;20:1331-45.
2. Seidman JD, Norris HJ, Griffin JL, Hitchcock CL. DNA flow cytometric analysis of serous ovarian tumors of low malignant potential. *Cancer* 1993;71:3947-51.
3. Scully RE. Histological typing of ovarian tumors. *World Health Organization International Histological Classification of Tumours*. 2nd ed. New York: Springer, 1999.
4. International Federation of Gynecology and Obstetrics. Classification and staging of malignant tumors in the female pelvis. *Acta Obstet Gynecol Scand* 1971;50:1-7.
5. Robey SS, Silva EG. Epithelial hyperplasia of the fallopian tube: its association with serous borderline tumors of the ovary. *Int J Gynecol Pathol* 1989;8:214-20.
6. Yanai-Inbar I, Siriaunkgul S, Silverberg SG. Mucosal epithelial proliferation of the fallopian tube: a particular association with ovarian serous tumor of low malignant potential? *Int J Gynecol Pathol* 1995;14:107-13.
7. Yanai-Inbar I, Silverberg SG. Mucosal epithelial proliferation of the fallopian tube: prevalence, clinical associations, and optimal strategy for histopathologic assessment. *Int J Gynecol Pathol* 2000;19:139-44.
8. Markman M, Zaino RJ, Fleming PA, Barakat RR. Carcinoma of the fallopian tube. In: Hoskins WJ, Perez CA, Young RC, eds. *Principles and Practice of Gynecologic Oncology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:1099-116.
9. Young RH, Scully RE. Ovarian pathology of infertility. In: Kraus FT, Damjanov I, Kaufman N, eds. *Pathology of Reproductive Failure*. Baltimore: Williams & Wilkins, 1991:104-39.
10. Czernobilsky B, Silverstein A. Salpingitis in ovarian endometriosis. *Fertil Steril* 1978;30:45-9.
11. Surrey ES, Halme J. Endometriosis as a cause of infertility. *Obstet Gynecol Clin NA* 1989;16:79-91.
12. Zreik TG, Olive DL. Endometriosis: pathophysiology: the biologic principles of disease. *Obstet Gynecol Clin NA* 1997;24:259-68.
13. Guzick DS. Clinical epidemiology of endometriosis and infertility. *Obstet Gynecol Clin NA* 1989;16:43-59.
14. Metzger DA, Haney AF. Endometriosis: etiology and pathophysiology of infertility. *Clin Obstet Gynecol* 1988;31:801-12.
15. Wheeler JM. Epidemiology of endometriosis-associated infertility. *J Reprod Med* 1989;34:41-6.
16. Thomas EJ. Endometriosis and infertility: a continuing debate. In: Shaw RW, ed. *Endometriosis*. In: *Advances in Reproductive Endocrinology*. Vol 1. Park Ridge, NJ: The Parthenon Publishing Group, 1990:107-16.
17. Harris R, Whittemore AS, Itnyre J and the Collaborative Ovarian Cancer Group. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies: III. Epithelial tumors of low malignant potential in white women. *Am J Epidemiol* 1992;136:1204-11.
18. Moore SW, Enterline HT. Significance of proliferative epithelial lesions of the uterine tube. *Obstet Gynecol* 1975;45:385-90.
19. Damjanov I. *Pathology of Infertility*. St. Louis: Mosby, 1993.
20. Cates W, Rolfs RT, Aral SO. Sexually transmitted diseases, pelvic inflammatory disease, and infertility: an epidemiologic update. *Epidemiol Rev* 1990;12:199-220.
21. Stock RJ. Histopathologic changes in fallopian tubes subsequent to sterilization procedures. *Int J Gynecol Pathol* 1983;2:13-27.
22. McCaughey WTE. Papillary peritoneal neoplasms in females. *Pathol Ann* 1985;20:387-404.