นิพนธ์ต้นฉบับ • Original Article

ศึกษาการติดเชื้อแอคติโนมัยเสสในหญิงที่ใส่ห่วงอนามัยคุมกำเนิดในโรงพยาบาลศรีนครินทร์

นิภา กาญจนาวิโรจน์กุล[1], ยุทธพงศ์ วีระวัฒนตระกูล[2], ปัทมาวดี พินิจสุนทร[3], บรรจบ ศรีภา[1], เอมอร ปาสาทัง[1], จงรักษ์ ศรีภา[1]

[1]ภาควิชาพยาธิวิทยา [2]ภาควิชาสูติศาสตร์และนรีเวชวิทยา

[3]หน่วยวางแผนครอบครัวในโรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

Study of Actinomyces in IUD Users in Srinagarind Hospital

N. Kanjanavirojkul[1], Y. Werawattakul[2], P. Pinitsoontorn[3], B. Sripa[1], E. Pasatung[1] and C. Sripa[1]

[1]Department of Pathology, [2]Department of Obstetrics and Gynaecology,

[3]Family Planning Unit in Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002 Thailand

Background: The most common temporary contraception is intrauterine device (IUD) in Thai women. *Actinomyces* infection is commonly found in cervical smear from women using an IUD, who have an increased risk of pelvic inflammatory disease.

Objective: to determine the factors associated with the presence of *Actinomyces* infection and compare the prevalence rate of women with and without IUD users.

Subject and Method: Cervical smears from 234 users of IUD attending family planning clinics and from a randomly selected control group of 229 women from out patient clinic in Srinagarind Hospital were stained by Papanicolaou method and were screened for *Actinomyces* infection. Follow up was done after 6 months, one year, one and a half year.

Result: The prevalence rate in IUD users was 17.1%. The rate of *Actinomyces* infection was significantly higher in IUD users for more than two years (p=0.013). No significant association of *Actinomyces* infection with the type of IUD and age were found. The percentage of women reporting gynecologic symptoms also did not differ significantly between IUD users with and without *Actinomyces* infection on Papanicolaou smear.

หลักการและเหตุผล: การคุมกำเนิดชนิดขั้วคราวที่นิยมใช้กันมากในหญิงไทยคือ การใส่ห่วงอนามัย หญิงที่คุมกำเนิดด้วยวิธีนี้มักพบการติดเชื้อแอคติโนมัยเสสซึ่งสามารถวินิจฉัยได้จากการทำแป้บสเมียร์ และหญิงเหล่านี้มีโอกาสเพิ่มความเสี่ยงของการเกิด pelvic inflammatory disease ได้

วัตถุประสงค์: เพื่อศึกษาปัจจัยต่าง ๆ ที่เกี่ยวข้องกับความชุกของการติดเชื้อแอคติโนมัยเสส และเปรียบเทียบความชุกของการติดเชื้อระหว่างหญิงที่ใส่ห่วงอนามัย และหญิงที่ไม่ได้ใส่ห่วงอนามัย

กลุ่มตัวอย่างและวิธีการ: เก็บตัวอย่างแป้บสเมียร์จากหญิงที่มารับการตรวจรักษาที่หน่วยวางแผนครอบครัว จำนวน 234 คนที่ใส่ห่วงอนามัย แล้วนัดคนไข้มาตรวจติดตามโดยทำแป้บสเมียร์อีก 3 ครั้งต่อมาคือ 6 เดือน หนึ่งปี และหนึ่งปีครึ่ง หญิงที่เป็นกลุ่มควบคุมไม่ได้ใส่ห่วงอนามัยเก็บแป้บสเมียร์จากหญิงที่มารับการตรวจรักษาที่ห้องผู้ป่วยนอกแผนกนรีเวชวิทยา โรงพยาบาลศรีนครินทร์ จำนวน 229 คน แป้บสเมียร์ทั้งหมดนำไปย้อมด้วยวิธี Papanicolaou เพื่อวินิจฉัยหาการติดเชื้อแอคติโนมัยเสส

ผลการศึกษา: อัตราความชุกของการติดเชื้อในหญิงที่ใส่ห่วงอนามัยคือ 17.1% การติดเชื้อแอคติโนมัยเสสในหญิงที่ใส่ห่วงอนามัยมากกว่า 2 ปี พบอัตราการเพิ่มขึ้นอย่างมีนัยสำคัญ ชนิดของห่วงอนามัยและอายุไม่มีความแตกต่างกันอย่างมีนัยสำคัญต่อการติดเชื้อแอคติโนมัยเสส จำนวนหญิงที่มีอาการทางสูติ-นรีเวชไม่มีความแตกต่างอย่างมีนัยสำคัญระหว่างกลุ่มที่ใส่ห่วงอนามัยและกลุ่มที่ไม่ใส่ห่วงอนามัย

Conclusion: The result has shown that the duration of using IUD but not types of IUD is associated with *Actinomyces* infection.

สรุป: ผลการศึกษาแสดงว่าการติดเชื้อแอคติโนมัยเสสขึ้นกับระยะเวลาที่ใส่ห่วงอนามัย แต่ไม่ขึ้นกับชนิดของห่วงอนามัย

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Introduction

The most common temporary contraception in Thai women is intrauterine device (IUD) because of its high efficacy and low incidence of side effects[1]. The association of *Actinomyces* infection with the use of an IUD has been well documented by Gupta.[2-3] He first report *Actinomyces* in Papanicolaou-stained vaginal smears.[2] His description of these organisms were seen as basophilic, filamentous, branching structure running in parallel fashion and usually occurring in isolated islands or as sulfur granules surrounded by dense acute inflammatory and histiocytic response. *Actinomyces* is a gram positive, non-acid fast anaerobic bacteria which is not usually found in the female genital tract. Morphologically similar structures that resemble *Actinomyces*, as observed in Pap smear, include both filamentous and nonfilamentous substances[3]. Filamentous structures resembling *Actinomyces* were *Candida, Aspergillus, Nocardia, Penicillium, Trichophytous, Leptothrix,* fibrin threads, mucus strands, sulfa crystals, cotton and synthetic fibers. Nonfilamentous structures resembling *Actinomyces* were contraceptive cream, *Cornybacterium vaginalis, Lactobacilli,* hematoxylin pigment, spermatozoa, hematoidin crystals and foreign material. When viewed under low-power magnification filamentous and non-filamentous structures can look like *Actinomyces*. A careful higher-magnification examination is generally sufficient for correct interpretation of *Actinomyces* from Pap smear. *Actinomyces* organisms can classify to 3 species; *Actinomyces israelii, Actinomyces bovis, Actinomyces naeslundii.* The species isolated in most of the studies has been *Actinomyces israelii* [2,4]. Special stains, immunofluorescence and anaerobic cultures had confirmed these *Actinomyces* to be *Actinomyces israelii.* Gupta furthers showed that anaerobic culture is difficult and disappointing results but Pap smear gives 95% accuracy in detection these organisms.[5] The reported incidence of *Actinomyces* in cervical Pap smear is as high as 44%[6]. Many studies confirmed that prolonged IUD use increases the chance of *Actinomyces* infection.[6-8] Mali et al[9] showed that long-term use of IUDs can promote the overgrowth of *Actinomyces* in the vagina. This can lead to pelvic actinomycosis[10] with severe complications. In Thailand, There is the first reported case of ovarian and myometrial actinomycosis[11] associated with IUD in 1986 and the first case report of uterine perforation due to Lippes loop IUD-associated actinomycotic infection in 2000.[12]

This study was carried out to determine the prevalence of *Actinomyces* in women with and without IUD and its association with duration, age, type of IUD, presence of clinical symptoms and inflammatory response to IUD.

Patients and Method

Cervical smears from 234 users of IUD attending at family planning clinic and from a randomly selected control group of 229 women from out patient clinic in Srinagarind Hospital were stained by Papanicolaou method and were screened for evidence of inflammation and *Actinomyces* infection on the first Pap smear and three time follow up Pap smear. Follow up (FU) was done after 6 months (FU1), one year (FU2), one and a half year (FU3). The clinicians fill out questionares concerning the data included; patientís age, type of IUD, duration of IUD use and patients pelvic symptoms. Statistical analysis of above datas in IUD users with and without *Actinomyces* were performed by Chi-square. A p-value of less than 0.05 was accepted as being significant.

Cytomorphology of *Actinomyces* infection.

The background of smears containing *Actinomyces* is variable. Inflammatory response are evidenced by neutrophils, histiocytes and multinucleated giant cells. The *Actinomyces* aggregates reveal difinite, delicate, filamentous organisms that branch at acute angles.

Filaments radiate outwards from a central core of dense, dark-bule wooly masses.

Criteria to diagnose degree of inflammation

Mild inflammation - Smear background consists of little neutrophils and histiocytes

Moderate inflammation - Smear background consists of moderate amount of neutrophils and histiocytes. Multinucleated giant cells may be present

Severe inflammation - Smear background was loaded with neutrophils, histiocytes and a few or many multinucleated giant cells.

Results

On microscopic examination shows variable inflammation and the *Actinomyces* in the form of dark-blue wooly masses with radiating filaments at their periphery in 40, 29, 17, 15 cases on first, FU1, FU2, FU3 Pap smears, respectively (Figure 1A, B, C)

The prevalence of *Actinomyces* in IUD users on first Pap smear, FU1, FU2, FU3 were 17.1%, 18.1%, 13.3% and 9.2%, respectively (Table1). *Actinomyces* were not found in any Pap smears of control women. New cases of *Actinomyces* in FU1, FU2, FU3 were 72.4%, 47.1% and 40% from the total cases of 160, 128 and 164 cases, respectively. Loss follow up cases were 31.6%, 45.3% and 29.9% in FU1, FU2, FU3, respectively.

Table 2 shows the total cases and percentage distribution in IUD users by age, type of IUD, and duration of IUD use for IUD users with and without *Actinomyces* on first Pap smear. Age and type of IUD were not significantly associated with *Actinomyces* on Pap smear. The presence of *Actinomyces* on Pap smear was significantly associated with duration of continuous IUD using for more than two years ($p = 0.013$)

Table 3 shows the percentage of IUD users with and without *Actinomyces* who had various gynecologic symptoms at the time of first Pap smears, FU1, FU2 and FU3. The percentage of women reporting gynecologic symptoms did not differ significantly between IUD users with and without *Actinomyces* on first Pap smear, FU1 and FU2. There were significant difference of various gynecologic symptoms in IUD users with and without *Actinomyces* on FU3. ($p<0.05$).

Table 4 shows the inflammatory response to IUD from cytological findings in control and IUD users whose smear were presence and absence for *Actinomyces* on first Pap smears, FU1, FU2 and FU3. The percentage of women with various degree of inflammation were significant differences between IUD users with and without *Actinomyces* on first Pap smear ($p<0.01$), FU1 ($p<0.01$), and FU3 ($p<0.05$). The inflammation did not differ significantly between the two groups on FU2.

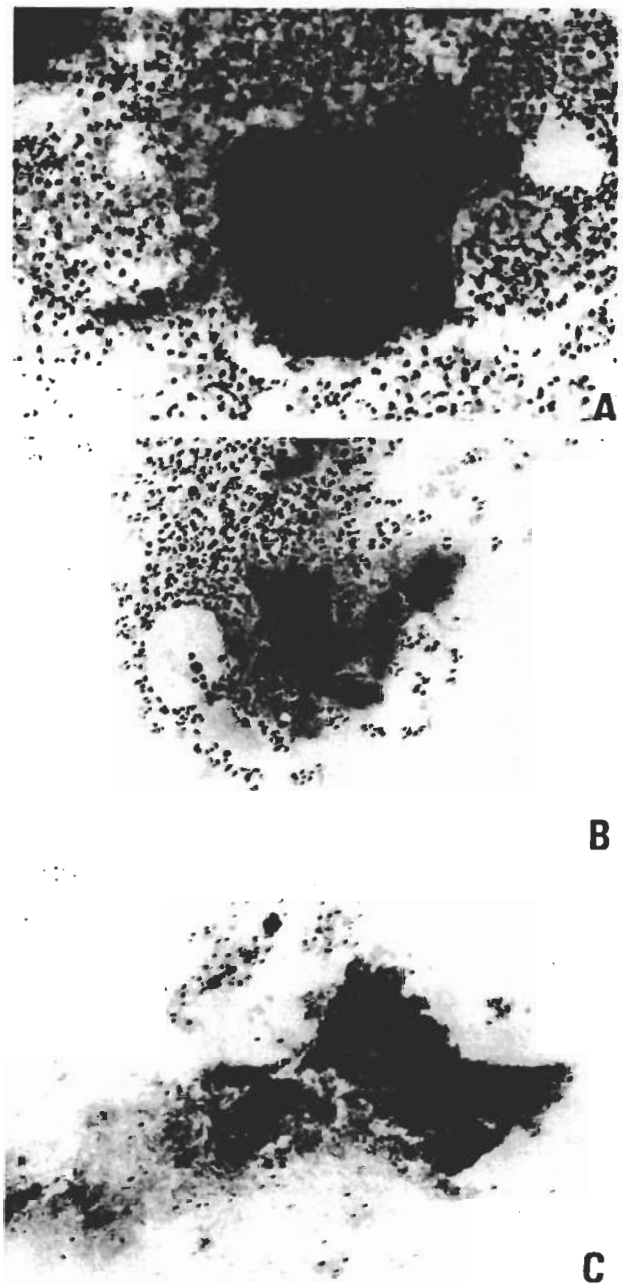

Figure 1 Low-power of cervical smear shows variable inflammation from severe inflammation (A), moderate inflammation (B), mild inflammation (C) surrounding the dense, dark-blue wooly mass with radiating filaments at their periphery should suggest a diagnosis of *Actinomyces* infection (Papanicolaou stain, A, B x 200, C x100)

Table I Prevalence of *Actinomyces* infection in IUD users on first Pap smear and percentage of new *Actinomyces* infection on FU1, FU2, FU3 Pap smear (percentages in Parentheses)

Pap smear	No. Cases	Loss FU Cases	Prevalence Of *Actinomyces*	New cases *Actinomyces*		
				FU1	FU2	FU3
First	234	-	17.1	-	-	-
FU1	160	74(31.6)	18.1	21(72.4)	-	-
FU2	128	106(45.3)	13.3	-	8(47.1)	-
FU3	164	70(29.9)	9.2	-	-	6(40)

Table 2 Cases and percentage distribution by age, type of IUD, and duration of IUD use in IUD users with and without *Actinomyces* infection on first Pap smear (percentage in parentheses)

Factor	Actinomyces presence (N = 40)	Actinomyces absence (N = 194)	
Age (yr) :			
11-20	3(7.5)	25(12.9)	
21-30	26(65)	120(61.9)	
31-40	8(20)	40(20.6)	
41-50	-	3(1.6)	
Unknown	3(7.5)	6(3.1)	P>0.05
Type of IUD :			
ML Cu-250	5(12.5)	11(5.7)	
CuT 380 A	33(82.5)	172(88.7)	
Lippes loop	-	1(0.5)	
Hungarian IUD	-	3(1.6)	
Unknown	2(5)	7(3.60)	P>0.05
Duration of IUD use (yr) :			
<1	10(25)	73(37.7)	
1-2	5(12.5)	44(22.7)	
2-3	12(30)	19(9.8)	
3-4	4(10)	27(13.9)	
4+	8(20)	27(13.9)	
Unknown	1(2.5)	4(2.1)	P<0.01

Discussion

Several publication established the ability to detect *Actinomyces* on cervical smear.[2-5,6,13-16] The prevalence of *Actinomyces* infection noted in the literature varied, ranging from 2.8%[8], 6.9%[9], 14%[16]. The incidence of *Actinomyces* in IUD users has been reported to be between 9.9% and 44%[6,14,15,18-20]. In our study, *Actinomyces* was seen only in IUD users but not in the non-users. The prevalence in IUD users on first Pap smear (17.1%), FU1 (18.1%) were higher than the prevalence rate reported by other authors.[8-9,16]

Prolonged IUD use more than two years from Table 2 was significantly higher in IUD users. The results about duration of IUD use in our data are the same as those of others[8-9,14-18] suggest that infection with *Actinomyces* was associated with long-term IUD use. We found new *Actinomyces* cases on Pap smear on FU1, FU2 and FU3.

Table 3 Percentage of IUD users with and without *Actinomyces* infection who had various gynecologic symptoms on first Pap smear, FU1, FU2, FU3 (percentage in parentheses)

Symptoms	*Actinomyces* presence				*Actinomyces* absence			
	first Pap smear	FU1	FU2	FU3	First Pap smear	FU1	FU2	FU3
None	32(80)	25(86.2)	15(88.2)	12(80)	161(83)	117(89.3)	101(91)	141(94.6)
Abnormal bleeding	-	-	-	-	3(1.6)	1(0.8)	1(1)	-
Metrorrhagia	1(2.5)	-	-	-	1(0.5)	4(3.1)	-	1(0.7)
Amenorrhea	1(2.5)	1(3.5)	-	-	5(2.6)	-	-	1(0.7)
Dysmenorrhea	1(2.5)	1(3.5)	1(5.9)	-	10(5.2)	5(3.8)	6(5.4)	3(2)
Leucorrhea	3(7.5)	-	1(5.9)	2(13.4)	4(2.1)	2(1.5)	2(1.8)	2(1.3)
Pelvic pain	1(2.5)	-	-	-	5(2.6)	1(0.8)	-	-
>1 symptom	1(2.5)	1(3.5)	-	1(6.7)	3(1.6)	1(0.8)	1(1)	1(0.7)
Other	-	1(3.5)	-	-	2(1.0)	-	-	-
Total	40	29	17	15	194	131	111	149
P-value	>0.05	>0.05	>0.05	<0.05				

Table 4 Cytological finding in control and IUD users whose smear were presence and absence for *Actinomyces* on first Pap smear, FU1, FU2, FU3 (percentage in parentheses)

Cytological finding	Control	IUD users				Control	IUD users			
		Actinomyces presence					*Actinomyces* absence			
		First smear	FU1	FU2	FU3		First smear	FU1	FU2	FU3
Clean smear	-	2(5)	3(10.4)	3(17.7)	1(6.7)	107(46.7)	55(28.4)	40(30.5)	26(23.4)	29(19.5)
Mild inflammation	-	3(7.5)	3(10.4)	-	1(6.7)	16(4)	11(5.7)	8(6.1)	15(13.5)	9(6)
Moderate inflammation	-	33(82.5)	23(79.3)	13(76.5)	13(86.7)	104(45.4)	128(66)	81(61.8)	68(61.3)	111(74.5)
Severe inflammation	-	2(5)	-	1(5.9)	-	2(0.9)	-	2(1.5)	2(1.8)	-
Total	0	40	29	17	15	229	194	131	111	149
P-value	<0.01	<0.01	>0.05	<0.05						

These data confirm that prolonged IUD use increase the chance of *Actinomyces* infection.

Among the different types of IUD, some researchers found no difference in *Actinomyces* infection.[7,9] Others have found plastic IUDs to be more likely to cause *Actinomyces* than copper-containing IUD.[14,16,18-20] Our results show no significant association of *Actinomyces* with the type of IUD.

In table 3, Seventeen patients from IUD users presented clinically symptomatic findings. The majority of patients were asymptomatic. Six patients had sign of leucorrhea and another patients had sign of metrorrhagia, dysmenorrhea, amenorrhea and pelvic pain. Spence et al[4] found that 80% of *Actinomyces* positive smears were symptomatic and had *Actinomyces* related PID or abscess. Cleghron et al[21] and Westrom[22] reported that IUD users with *Actinomyces* had an increased risk of pelvic inflammatory disease, approximately two to four times the risk of nonusers.

The inflammatory background of smears from table 4

consists of neutrophils, histiocytes and multinucleated giant cells. Most of cases in IUD users with *Actinomyces* infection are moderate inflammation.

Inflammatory response to IUD users with *Actinomyces* infection were the same results as Duguid and gupta. Duguid et al[14] reported correlations between the presence of these organisms and recorded incidences of pain and both clinical and cytological evidence of inflammation were highly significant. Gupta[3] reported that many cases of moderate inflammation have been observed and represented cervicitis and/or vaginitis.

Conclusion

This study has shown that the prolonged duration of using IUD promotes the overgrowth of *Actinomyces* and associated with inflammatory response. *Actinomyces* can be seen in routine smears without inflammatory response in some cases. Cytological findings that can be mistaken for *Actinomyces* include filamentous and nonfilamentous substances. The cytotechnologists experience is an important factor to diagnose *Actinomyces* infection. Therefore in long-term IUD use cervical smears should be examined with special care for the presence of *Actinomyces*. Thus severe complications from actinomycosis may be reduced by simple preventive screened for *Actinomyces* infection from Pap smear.

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References

1. มานี ปิยะอนันต์. ห่วงอนามัย. ใน : กองอนามัยครอบครัว กรมอนามัย กระทรวงสาธารณสุข. คู่มือประกอบการอบรมแพทย์โรงพยาบาลชุมชนให้ความช่วยเหลือผู้รับบริการวางแผนครอบครัวที่มีภาวะแทรกซ้อน, 2539:73-130.
2. Gupta PK, Hollander DH, Frost JK. *Actinomycetes* in cervico-vaginal smear : An association with IUD usage. Acta Cytol 1976;20:295-7.
3. Gupta PK, Intrauterine contraceptive devices : Vaginal cytology, pathologic changes and clinical implications. Acta Cytol 1982;26:571-613.
4. Spence MR, Gupta PK, Frost JK, King TM. Cytologic detection and clinical significance of *Actinomyces israelii* in women using intrauterine contraceptive devices. Am J Obstel Gynecol 1978;131:295-8.
5. Gupta PK, Woodroff JD. *Actinomyces* in vaginal smears. JAMA 1982;247:1175-6.
6. Curtis EM, Pine L. *Actinomyces* in the vaginas of woman with and without intrauterine contraceptive devices. Am J Obstet Gynecol 1981;140:880-5.
7. Valicenti JF Jr, Pappas AA, Graber CD, Williamson HO, Willis NF. Detection and prevalence of IUD-associated *Actinomyces* colonization and related morbidity : A prospective study of 69,925 cervical smears. JAMA 1982;247:1149-52.
8. Nayar M, Chandra M, Chitraratha K, Kermari Das S, Rai Chowdhary G. Indidence of *actinomycetes* infection in women using intrauterine contraceptive devices. Acta Cytol 1985;29:111-6.
9. Mali B, Joshi JV, Wagle U, Hazari K, Shah R, Chadha U, Gokral J, Bhave G. *Actinomyces* in cervical smears of woman using intrauterine contraceptive devices. Acta Cytol 1986;30:367-71.
10. Garland SM, Rawling D. Pelvic actinomycosis in association with an intrauterine device. Aust NZ J Obstet Gynaecol 1993;33:96-8.
11. Suthipintawong C. Ovarian and myometrial actinomycosis associated with intrauterine contraceptive device : A case report. Bulletin of the Department of Medical Sevices 1986;11:541-3.
12. Phupong V, Sueblinvong T, Pruksananonda K, Taneepanichskul S, Triratanachat S. Uterine perforation with Lippes loop intrauterine device-associated actinomycosis : a case report and review of the literature. Contraception 2000;61:347-50.
13. Fiorino AS. Intrauterine contraceptive device-associated actinomycotic abscess and *actinomyces* detection on cervical smear. Obstel Gynecol 1996;87:142-9. Review.
14. Duguid HLD, Parratt D, Traynor R. Actinomyces-like organisms in cervical smears from women using intrauterine contraceptive devices. Br Med J 1980:534-7.
15. Pettiti DB, Yamamoto D, Morgenstern N. Factors associated with actinomyces-like organisms on Papanicolaou smear in users of intrauterine contraceptive deveices. Am J Obstet Gynecol 1983;145:338-41.
16. Chawanpaiboon S, Maythangkul P, Watcharaprapapong O, Kiriwat O. Prevalence of *Actinomyces* in cervico-vaginal smears of intrauterine device users. Siriraj Hosp Gaz 1998,50:410-7.

17. Chatwani A, Amin-Hanjani S. Incidence of actinomycosis associated with intrauterine devices. J Reprod Med 1994,39:585-7.
18. Chawanpaiboon S, Titapant V, Chirdchoothai W. *Actinomyces* colonization in IUD users. Siriraj Hosp Gaz 2001;53:658-64.
19. Keebler C, Chatwani A, Schwartz R. Actinomycosis infection associated with intrauterine contraceptive devices. Am J Obstet Gynecol 1983;145:596-9.
20. Merki-Feld GS, Lebeda E, Hogg B, Keller PJ. The incidence of actinomyces-like organisms in Papnicolaou-stained smears of copper and levonorgestrel releasing intrauterine devices. Contraception 2000;61:365-8.
21. Cleghorn AG, Wilkinson RG. The IUCD-associated incidence of *Actinomyces israelii* in the female genital tract. Aust NZ J Obstet Gynaecol 1989;29:445-9.
22. Westrom L. Incidence, prevalence, and trends of acute pelvic inflammatory disease and its consequences in industrialized countries. Am J Obstet Gynecol 1980;138:880-5.