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**INSERTION SITE COMPLICATIONS DURING
THE FIRST YEAR OF NORPLANT® USE***Susan L. Klavon and Gary S. Grubb**

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ABSTRACT

Although review articles have provided much information on the NORPLANT® system, information on insertion site complications based on multi-country trials has been limited to infection rates. This paper examines 2,674 NORPLANT® acceptors from seven countries who were enrolled and followed for one year. The one-year incidence rates of infection (0.8%), expulsion (0.4%) and local reaction (4.7%) varied widely among countries and clinics within a country. In contrast to previous reports that insertion site complications occur during the first few weeks of use, these data show that a substantial proportion of insertion site infections (34.6%) and implant expulsions (64.3%) were reported after the first two months of use, while 35.7% of local reactions were reported after 4.5 months of use. Of the 16 women with infections who did not have the implants immediately removed, 8 eventually required or requested removal, indicating that the ICCR recommendation for immediate removal in case of infection appears appropriate. An awareness of the frequency of insertion site complications, distribution of the time of onset post-insertion and potential sequelae of complications will aid clinicians in better client counseling and complication management.

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INTRODUCTION

Much has been written about side effects related to the use of NORPLANT® contraceptive subdermal implants. However, information on insertion site complications based on multi-country trials has been limited to infection rates (1-3); several single-country trials have reported local complication rates (4-6). Review articles have noted that local complications at the insertion site are uncommon (1,2) and that placement-related problems tend to occur "early in use" (7).

Some of women's major concerns regarding implant use include factors related to the insertion site, such as visibility of the implants, scarring, and discomfort (1). Therefore, further knowledge concerning insertion site complications could aid client counseling before acceptance of the method and during implant use. Data about the time of onset post-insertion, frequency, and sequelae of complications could also aid clinicians in complication management. This paper reports on the one-year experience of NORPLANT® acceptors from seven countries enrolled in pre-introductory Phase III clinical trials with regard to complications occurring at the implant site.

METHODOLOGY

The same study protocol, prepared by Family Health International (FHI) and approved by FHI's Protection of Human Subjects Committee, was used in each of the pre-introductory trials. Local Institutional Review Board approval was obtained by the research committees of each participating institution prior to initiation of the trials.

Subject Enrollment and Follow-up

Recruitment intervals for the clinical trials varied among clinics and countries. The first clients were enrolled in February 1985; recruitment was completed in March 1987. Women with any contraindication to hormonal contraceptive use were excluded from the trials. Additional selection criteria have been previously described (8). Prior to insertion of the implants, a physical and pelvic examination was performed on each woman. All study subjects were fully informed about the purpose of the study and their rights and obligations during their participation in the clinical trial by the clinic staff. Written informed consent was obtained prior to insertion of the implants.

A total of 2,674 women from 19 sites in 7 countries (Bangladesh, Haiti, Nepal, Nigeria, Philippines, Singapore and Sri Lanka) who completed at least 15 months of implant use by June 1988 in the FHI NORPLANT® studies are included in this pooled analysis. Follow-up of all acceptors was scheduled at 1, 3, 6 and 12 months after admission to the study. Follow-up is continuing at six-month intervals until removal of the implants. This paper is based on clinic visits through April 1988 and on data processed through 22 June 1988.

Analysis of Insertion Site Complications

During the pre-admission counseling session, each client was told to return to the clinic if there were any symptoms of infection at the insertion area or if any one of the six NORPLANT® implants

came out. Acceptors could report less serious insertion site complications (such as pruritus) at their next scheduled follow-up visit. A local reaction was defined as any insertion site complication not involving infection or expulsion. Although more than one insertion site complication could be reported at any visit, only the most serious complication ever reported was included in calculating incidence rates, while occurrence rates were based on the most serious complication reported at each follow-up visit. Insertion site infection and implant expulsion were treated as distinct events.

Time interval analysis of complication rates was based on the periods inclusive of the follow-up visit schedule: 1-month (days 1-60 post-insertion), 3-month (days 61-136), 6-month (days 137-273) and 12-month (days 274-456). Infection/expulsion and local reaction rates beyond the 1-month follow-up interval are not directly comparable given the reporting differences discussed above.

RESULTS

Sociodemographic and Follow-up Characteristics

Women with insertion site complications had similar characteristics to the pooled population of women in the trials with respect to age (28.3 and 28.6 years) and parity (3.0 and 3.2 live births). The educational level for women with insertion site complications was slightly lower than for the pooled group (4.6 and 5.3 years, respectively).

The one-year follow-up rates for the insertion site complication group and the pooled group were 100.0% and 94.9%, respectively, corresponding to 1,682 and 30,328 woman-months of implant use. Overall one-year continuation rates were 88.1% for the insertion site complication group and 93.1% for the pooled group.

Infection and Expulsion

Each case of insertion site infection or implant expulsion was examined for the time of onset post-insertion (in weeks), signs/symptoms, number of implant capsules expelled (partially or totally) and treatment, including implant removal and removal complications (Table I). During the first year of NORPLANT® use, infection occurred in 22 cases (0.8%). Of these 22, nine (40.9%) were accompanied or followed by implant expulsion. Implant expulsion without the report of any accompanying infection occurred in only three cases (0.1%).

Expulsion of multiple NORPLANT® capsules was reported in four cases. The first case, at the Bangladesh/C clinic, was an infection at 15 weeks post-insertion which did not respond to antibiotics; complete expulsion of one capsule and partial expulsion of another occurred two weeks later. The infection continued despite therapy and all of the implants were removed.

In the second case, at the Philippines/A clinic, a serous discharge from the incision site and fever occurred at 4 weeks post-insertion. After antibiotic treatment and apparent cure, two capsules were partially expelled at 13 weeks post-insertion. All of the implants were subsequently removed.

Table I
Insertion Site Infection and Implant Expulsion Case Histories

Center/Case #	Onset (post-insertion)	Signs/Symptoms	Number expelled/extent	Treatment
Bangladesh/B 1	6 weeks	infection; itching; expulsion	1, partial	ampicillin; implant removal
Bangladesh/C 1	1 week	inflammation; slight fever		antibiotics
Bangladesh/C 2	1 week 24 weeks	inflammation recurrent swelling, itching, redness		antibiotics antibiotics and antihistamines provided temporary relief; implant removal
Bangladesh/C 3	2 weeks	purulent discharge; site inflamed, tender; slight fever		daily dressing, antibiotics, analgesics
Bangladesh/C 4	15 weeks 17 weeks	infection; site red, hot, swollen expulsion; insertion point more infected, ulcerated; gap at site	2; 1 total, 1 partial	ampicillin, dressing; infection not controlled clonacillin, dressings; implant removal
Bangladesh/C 5	33 weeks	purulent discharge (<i>Staph aureus</i>); redness, swelling		clonacillin; removal 2 weeks later after infection controlled
Haiti/B 1	5 weeks	infection	1, partial	implant removal
Nepal/A 1	5 weeks	expulsion		none specified; reinserted 1 capsule
Nepal/A 2	6 weeks 11 weeks	infection pus; open wound; expulsion	1, 1mm	dressing/Neosporin implant removal
Nepal/A 3	14 weeks	slight pus discharge; small hole 6 days earlier		implant removal
Nepal/B 1	6 weeks	pus discharge; swelling; low grade fever		implant removal; 1 capsule not removed due to induration; removed 4 days later
Nepal/B 2	7 weeks	infection		antibiotics given prior to visit; infection not controlled; implant removal; 1 capsule not removed due to induration; acceptor never returned for removal
Nepal/B 3	7 weeks	infection; expulsion	1, total	implant removal
Nepal/B 4	14 weeks	expulsion	1, partial	none specified; reinserted 1 capsule
Nepal/B 5	31 weeks	expulsion	1, total	none specified; reinserted 1 capsule

(continued)

Table I (continued)
Insertion Site Infection and Implant Expulsion Case Histories

Center/Case #	Onset (post-insertion)	Signs/Symptoms	Number expelled/extent	Treatment
Nigeria/E 1	4 weeks	sepsis		none specified
Philippines/A 1	4 weeks	serous discharge; small hole at site; redness, tenderness; fever of 1 day		antibiotics, antiinflammatory analgesic, antipyretic
	13 weeks	incision gaping; expulsion	2, partial	implant removal
Philippines/B 1	46 weeks	pus; swelling, redness; expulsion	1, partial	ampicillin, cloxacillin, mefenamic acid, magnesium sulfate compresses
	51 weeks	pus; swelling, redness		ampicillin, cloxacillin; advised removal
Sri Lanka/A 1	1 week	mild infection; swelling		none specified
Sri Lanka/A 2	2 weeks	superficial infection; slight swelling		none specified
Sri Lanka/A 3	2 weeks	mild infection; slight swelling, warmth, slight tenderness		none specified
Sri Lanka/A 4	2 weeks	superficial infection; erythema; mild swelling		none specified
	4 weeks	mild superficial infection		none specified
	6 weeks	mild infection; severe pain; expulsion	1, total	normal saline cleansing; 1 capsule reinserted 11 days later
Sri Lanka/A 5	15 weeks	infection		none specified
	32 weeks	expulsion	1, 2 mm	none specified; 1 capsule reinserted 3 days later
	63 weeks	expulsion; high fever, slight discharge 2 weeks before expulsion	1, partial	none specified; implant removal
Sri Lanka/B 1	2 weeks	moderately severe infection (pus)		implant removal; 1 capsule not removed due to cellulitis; removed 3 weeks later
Sri Lanka/C 1	4 weeks	small abscess		none specified
	6 weeks	expulsion; non-infected ulcer	1, total	dressing
	9 weeks	expulsion; large ulcer	2, extent unspecified	none specified; 3 capsules reinserted 2 weeks later

CONTRACEPTION

The third case occurred at the Sri Lanka/A clinic. An insertion site infection was noted at 15 weeks post-insertion and resolved. However, one capsule began to protrude out of the incision site at 32 weeks post-insertion. The protruding capsule was removed and another one was inserted through a new incision site three days later. At 61 weeks post-insertion, the woman had a high fever and slight discharge from the original incision site. Two weeks later she returned to the clinic when one capsule was protruding out of the original incision site without signs of infection. This protruding capsule was located immediately adjacent to the previously expelled implant and was promptly removed. At 66 weeks post-insertion, the woman came back with her husband, who insisted that the implants be removed because he did not want his wife to be inconvenienced by more expulsions.

Expulsion of three capsules was reported in the fourth case at the Sri Lanka/C clinic. At 4 weeks post-insertion a small abscess had formed at the incision site and two weeks later one capsule had been expelled. At 9 weeks two more capsules had been expelled. Three new capsules were reinserted at 11 weeks; no further insertion site complications were reported through one year of implant use.

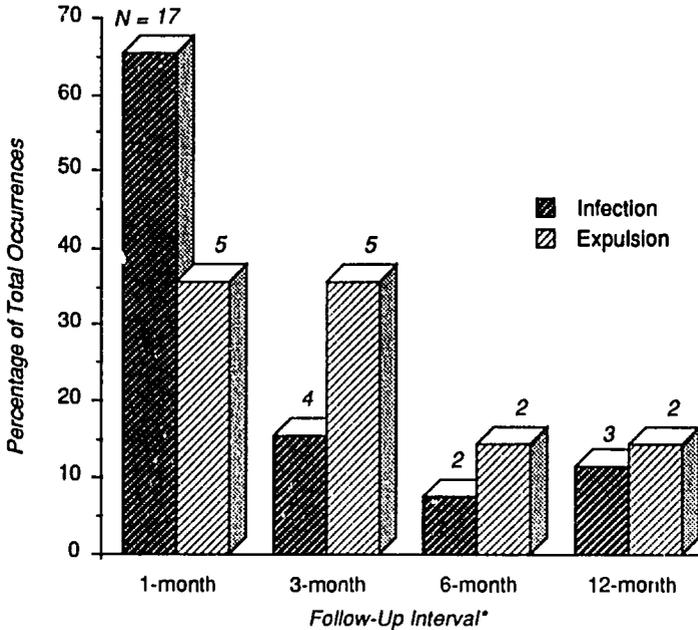


Figure 1. Occurrences of Insertion Site Infection and Implant Expulsion, by Follow-Up Interval.

* Follow-up interval and the inclusive days post-insertion were: 1-month (days 1-60), 3-month (days 61-136), 6-month (days 137-273) and 12-month (days 274-456).

Table 1i
Number of Women with Insertion Site Complications Reported at Follow-Up*

Center	N	Infection	Expulsion	Local Reaction				Total
				Pain ^b	Itching	Rash	Other ^c	
Bangladesh/A	230	0 (0.0) ^d	0 (0.0) ^d	13	22	0	0	35 (15.2) ^d
Bangladesh/B	210	1 (0.5)	1 (0.5)	8	1	0	1	10 (4.8)
Bangladesh/C	226	5 (2.2)	1 (0.4)	11	12	0	1	24 (10.6)
Sri Lanka/A	275	5 (1.8)	2 (0.7)	3	0	0	1	4 (1.5)
Sri Lanka/B	200	1 (0.5)	0 (0.0)	0	0	0	0	0 (0.0)
Sri Lanka/C	200	1 (0.5)	1 (0.5)	0	2	2	1	5 (2.5)
Philippines/A	150	1 (0.7)	1 (0.7)	1	0	0	0	1 (0.7)
Philippines/B	150	1 (0.7)	1 (0.7)	1	2	1	1	5 (3.3)
Nepal/A	307	2 (0.7)	2 (0.7)	9	5	1	0	15 (4.9)
Nepal/B	100	3 (3.0)	3 (3.0)	5	1	0	0	6 (6.0)
Singapore	100	0 (0.0)	0 (0.0)	8	6	2	2	18 (18.0)
Haiti/A	100	0 (0.0)	0 (0.0)	0	0	0	0	0 (0.0)
Haiti/B	100	1 (1.0)	0 (0.0)	0	0	0	0	0 (0.0)
Haiti/C	50	0 (0.0)	0 (0.0)	0	1	0	0	1 (2.0)
Nigeria/A	6E	0 (0.0)	0 (0.0)	0	0	0	0	0 (0.0)
Nigeria/B	51	0 (0.0)	0 (0.0)	0	0	0	0	0 (0.0)
Nigeria/C	53	0 (0.0)	0 (0.0)	1	0	1	1	3 (5.7)
Nigeria/D	54	0 (0.0)	0 (0.0)	0	0	0	0	0 (0.0)
Nigeria/E	50	1 (2.0)	0 (0.0)	0	0	0	0	0 (0.0)
Number of women	2,674	22	12	60	52	7	8	127*
% of insertions		(0.8)	(0.4)	(2.2)	(1.9)	(0.3)	(0.3)	(4.7)

Footnotes

- Only the primary complaint is included in this tabulation. One woman reported local reaction and infection at separate visits, and was counted once in each category total.
- Four women reported pain and itch at two different visits, but were included only in the pain category.
- Includes one case each of bullous edema, tenderness, numbness, skin irritation, excoriation of superficial skin, blister, cheloid formation and hematoma.
- Numbers in parentheses indicate percentages of women.
- Thirteen women reported an additional complaint at a separate visit.

CONTRACEPTION

Of the 22 insertion site infections, 6 resulted in immediate removal. Of the 16 infections where the implants were not immediately removed, 9 were treated with antibiotics, and 7 were not treated (2 of which were later removed). Of the 9 treated with antibiotics, 3 were unresponsive to treatment and led to removal, 3 responded to treatment, but infection recurrence led to eventual removal, and 3 resolved completely.

While the pooled infection rate was 0.8%, individual centers reported rates ranging from 0.0% to 3.0% (Table II).

Local Reaction

Of the 2,674 women who were admitted into the NORPLANT® trials, 127 acceptors (4.7%) reported a local reaction during the first year of use. The frequency of reported reactions ranged from 0.0% to 18.0% for individual centers (Table II). Thirteen women reported one additional local reaction at a different visit. Pain and itching at the insertion site occurred with similar frequencies (2.2% and 1.9% of all insertions, respectively). Pain at the insertion site with exertion occurred in only four cases. Rash at the implant site was uncommon, occurring in 0.3% of cases.

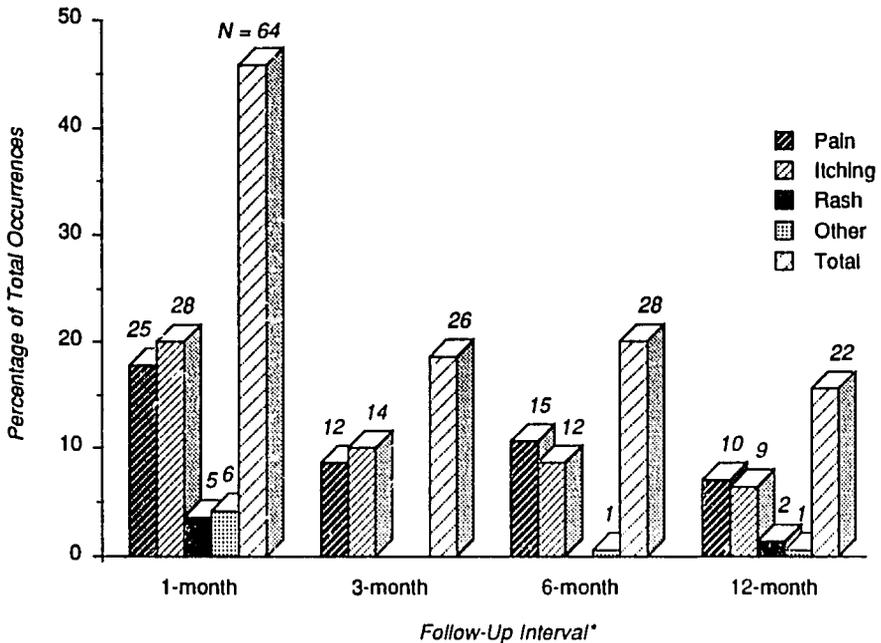


Figure 2. Occurrences of Local Reaction, by Follow-Up Interval.

* Follow-up interval and the inclusive days post-insertion were: 1-month (days 1-60), 3-month (days 61-136), 6-month (days 136-273) and 12-month (days 274-456).

Local reactions categorized as "other" were rare (0.3%), but there were two cases of interest. Cheloid formation at the implant site was reported at the 1-month visit by one Sri Lanka/C clinic acceptor. In the second case, a client at the Singapore clinic presented at her 1-month follow-up visit with a hematoma at the implant site from an unspecified traumatic injury. The resultant swelling and erythema resolved in approximately three weeks.

Occurrence of Complications over Time

Time of complication onset was examined over four follow-up intervals. While the majority of insertion site infections (65.4%) occurred during the 1-month follow-up interval (up to 60 days post-insertion), a substantial proportion (34.6%) occurred after this interval (Figure 1). Of the 9 occurrences of an infection (among 6 subjects) reported after the 1-month follow-up interval, only 2 had been preceded by an infection during the 1-month interval. In contrast, 35.7% of implant expulsions occurred during the 1-month interval with the majority (64.3%) occurring later in use. Of the 9 occurrences of an expulsion (among 8 subjects) found after the 1-month interval, 3 had a prior insertion site infection diagnosed during the 1-month follow-up interval. Three women (12.0%) experienced their first infection/expulsion episode after 7 months of use.

A substantial proportion of local reactions (35.7%) occurred during the 6- and 12-month follow-up intervals (Figure 2). The incidence of pain and itching decreased sharply from the 1-month to the 3-month interval. Rashes and local reactions categorized as "other" occurred almost exclusively during the 1-month follow-up interval.

DISCUSSION

The infection rate of 0.8% found in this one-year pooled analysis is slightly higher than the 0.3% rate reported in review articles (1,2) and for three of the Population Council's International Committee for Contraception Research (ICCR) Phase III studies. However, this rate falls at the mid-point of a previously reported range of 0.0% to 1.6% among four, single-country studies conducted independently of the ICCR trials (3). Since the ICCR study protocol required that the implants be removed any time an insertion site infection occurred (9), the infection rate and the net cumulative termination rate due to infection were treated as equivalent terms. If infections occurred but did not result in removal, the ICCR infection rate would be an underestimate. This could explain the difference in rates between this analysis and the ICCR trials.

The expulsion rate found in this analysis was 0.4%. This rate is higher than the 0.1% rate reported for a pooled cohort of 816 acceptors enrolled in ICCR trials (9).

The local reaction rate of 4.7% found in these trials is well below the 11% "irritation" rate reported by Indonesian acceptors (5). This rate is not directly comparable to the Chilean results (4), due to differences in reporting and longer duration of use, or the Egyptian findings (6), which were based on complaints reported at the 24-month visit. No comparable data from multi-country reports were available.

Time of onset of insertion site complications reported in the literature has been limited to descriptions such as "early in use" and, in the case of infection, "within a few days or weeks of placement" (7).

CONTRACEPTION

In these trials, however, a substantial percentage of insertion site complications appeared well after early use of the method; 34.6% of insertion site infections and 64.3% of implant expulsions were reported after two months of use. About $\frac{2}{3}$ of the later-appearing infections and expulsions were in subjects without any insertion site complications during the first two months post-insertion. The ICCR infection rate increased to 0.7% at three years before leveling off (3) and complications were still occurring in these trials at the end of one year. Therefore, the one-year infection, expulsion and local reaction rates in this study could increase during the remainder of the five years of NORPLANT® use.

The causes of insertion site infection should be no different from other surgical wound infections, assuming the sterility of the implants. The degree of asepsis maintained during the insertion procedure and the acceptor's care of the insertion site during the healing of the incision are major determinants of infection in the immediate post-insertion period. No data were collected for either of these two determinants. Placement of a NORPLANT® capsule with the proximal end close to the insertion site incision seems to predispose to infection and expulsion (1). This problem should decrease in frequency as the inserter gains skill in the procedure. However, inserter experience does not appear to play an important role in the incidence of infection in this study since the infection rate was not higher among the earlier cases in most centers.

It may be possible that low-grade infections can begin soon after the insertion but remain subclinical for an extended period of weeks, although probably not for several months. For very late-appearing infections, two other etiologies may include the opening of a portal of entry resulting from trauma or a change in the immunologic environment of the implants. The presence of neutrophils and macrophages as part of a mild inflammatory reaction occurring around the implants during the first several months post-insertion should help prevent infections. If this typical inflammatory reaction had prevented a nidus of infection from expanding during the early months of NORPLANT® use, the infection might have an opportunity to grow and become symptomatic as the early inflammatory response decreased in some subjects.

Of the 16 women with infections who did not have the implants immediately removed, 8 eventually required or requested removal, indicating that the ICCR recommendation for immediate removal in case of infection appears appropriate. These findings demonstrate that clinicians must be aware that there can be wide variations in the occurrence of such events between countries and even centers within a country. It remains uncertain whether these variations are due to reporting, or differences in insertion technique, post-insertion hygienic care or physiologic differences. However, these findings add to the information useful in patient counseling and insertion site complication management for NORPLANT® acceptors worldwide.

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