

PN-ABH-337
70768

AGENCY FOR INTERNATIONAL DEVELOPMENT PPC/CDIE/DI REPORT PROCESSING FORM

ENTER INFORMATION ONLY IF NOT INCLUDED ON COVER OR TITLE PAGE OF DOCUMENT

1. Project/Subproject Number

2. Contract/Grant Number

3. Publication Date

DPE-3041-A-00-0043

1990

4. Document Title/Translated Title

A Three-Year Clinical Evaluation of NORPLANT in Singaporean Acceptors

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6. Contributing Organization(s)

FAMILY HEALTH INTERNATIONAL

7. Pagination

8. Report Number

9. Sponsoring A.I.D. Office

9 pages

90-30

POPULATION

10. Abstract (optional - 250 word limit)

Empty box for abstract text.

11. Subject Keywords (optional)

- 1. NORPLANT
- 2. continuation
- 3. long-term study
- 4. clinical trial
- 4. method acceptability
- 5. evaluation
- 6. fertility

12. Supplementary Notes

Empty box for supplementary notes.

13. Submitting Official

14. Telephone Number

15. Today's Date

Debbie Wade

919/544-7040, ext 247

March 7, 1991

16. DOCID

17. Document Disposition

DOCRD [] INV [] DUPLICATE []

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A three-year clinical evaluation of Norplant in Singaporean acceptors

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Abstract

A three-year clinical evaluation of Norplant implants in Singaporean acceptors shows that no pregnancy occurred during the first three years of use. The continuation rate at the end of three years was 69%. Desire for planned pregnancy and disruption of menstrual rhythm were the two main reasons for implant removal during the three years. The post-removal conception rate in women desiring pregnancy was 94.1% at the end of one year. It thus appears that Norplant offers a highly effective, safe, acceptable and reversible method of contraception.

Introduction

Norplant^R subdermal implants are Silastic implants containing levonorgestrel. Norplant implants are currently undergoing clinical trials in several countries, including Singapore. The primary objective of this clinical study is to evaluate the efficacy, safety, acceptability and reversibility of Norplant implants among Singaporean women.

Methodology

Enrollment of the cases began in May 1985, and 100 women were recruited by November 1985. This report is based on data from clinic visits through November 1988.

In recruiting acceptors, the principal selection criteria used by the Population Council's International Committee for Contraceptive Research were followed. Acceptors in the study had to be between 18 and 40 years of age, sexually active, of demonstrable fertility (at least one birth), neither pregnant nor breastfeeding at the time of insertion, having not used any long-acting steroidal contraception in the six months prior to insertion, and having none of the standard contraindications to the use of steroids. They should be easily followed-up on a regular basis and also be

agreeable to using no other contraceptives during the study period.

Women who met all the criteria for inclusion were fully informed about the purpose of the study and the risks and benefits associated with the use of this contraceptive method. Each woman who volunteered to participate in the study was requested to give informed consent by signing a Volunteer Agreement. Each acceptor was also given a complete medical examination before insertion and on subsequent follow-up visits.

Acceptors were asked to maintain diaries of menstrual events throughout their participation in the study. Each woman participating in the study was asked to keep a daily record of the menstrual bleeding events coding '0' for no bleeding; '1' for spotting or light bleeding but no sanitary protection needed; and '2' for heavy bleeding with sanitary protection needed. Data analysis of the daily bleeding calendar is based upon completed 90 day intervals or reference periods [1-3].

Women were told that they could terminate use of implants at any time by returning to the clinic to have them removed. Follow-up of all acceptors was scheduled at 1, 3, 6 and 12 months after admission and, thereafter, twice yearly. However, the women were encouraged to return to the clinic for any problems at any time, regardless of the next scheduled follow-up visit. Follow-up of all acceptors at each scheduled visit in the first three years was 100%.

Results

(i) Demographic characteristics of acceptors

The mean age of the entire group was 29.5 years, with an average education of 7.8 years and average parity of 2.1 live births. Sixty-nine percent of the women said they did not want any more children.

(ii) Contraceptive effectiveness

No accidental pregnancies occurred during the three years of use.

(iii) Termination/removal rates

A total of 31 removals were reported in the first three years of Norplant use. Seventeen implants were removed from women planning for a pregnancy and another twelve for menstrual disturbances. There were only two removals for non-menstrual medical problems (Table 1). The mean time to perform removals was 11.5 minutes (range 5-30 minutes). There were no complications with removal.

Unlike other international studies in which menstrual problems are the most important reason for discontinuation, the most important reason for discontinuation in this study was planning for another pregnancy (Table 1). Of the 17 removals for

planned pregnancy, 11 were in women who had expected a desire for more children in the future at the time of insertion. Only six of these removals were in women who before insertion had expressed no desire for more children. However, this difference was not statistically significant.

Of the 12 removals due to menstrual disturbances, nine were in women who complained of prolonged bleeding or spotting lasting more than 10 days. Of these nine, 44.4% had bleeding or spotting lasting more than 31 days. Another two women had the implants removed for increased frequency of menstruation. Only one woman had the implants removed for prolonged amenorrhea (Table 2).

Table 1 Three-year net cumulative termination and continuation rates per 100 Norplant acceptors

<i>Reason/rate</i>	<i>Year</i>		
	<i>1</i>	<i>2</i>	<i>3</i>
Accidental pregnancy	0.0	0.0	0.0
Menstrual problems	2.0	10.0	12.0
Planning pregnancy	1.0	10.0	17.0
Other medical	0.0	1.0	2.0
Total termination	3.0	21.0	31.0
Continuation	97.0	79.0	69.0
Number of woman-months	1180.0	2209.0	3070.0

Table 2 Reasons for removing Norplant implants in women with menstrual problems

<i>Menstrual problems (No.)</i>	<i>Year</i>			<i>Grand total</i>
	<i>1</i>	<i>2</i>	<i>3</i>	
Prolonged bleeding/spotting	2	5	2	9
Frequent bleeding	0	2	0	2
Amenorrhea	0	1	0	1
Total	2	8	2	12

Of the two removals for non-menstrual medical problems, one was in a woman who had a weight loss of 7 kg over a period of 18 months. The other removal was in a woman who complained of hair loss in the third year of Norplant use.

On subsequent follow-up, the menstrual pattern had returned to normal in all the 12 women who had the implants removed for menstrual disturbances. Similarly at one year post-removal, the hair loss subsided in the woman who had the implants removed for hair loss. However, at one year post-removal, the weight had still not increased in the woman who had the implants removed for weight loss.

(iii) Continuation rates

The net termination rate was 31 per 100 women and the continuation rate was 69% at the end of three years of Norplant use.

(iv) Menstrual pattern changes

Frequent bleeding (5+ bleeding runs) increased slightly over the first three reference periods to reach 5.3% in the third reference period. Analysis of the subsequent reference periods show a further decline to 1.2% in the eighth period. In the first two years of Norplant use, only two women had the implant removed for frequent bleeding. None reported any increased frequency of bleeding in the third year of use.

The percentage of women reporting prolonged bleeding (8+ days) in a run continued to decrease over the three years of use to reach 10.4% in the twelfth reference period. Similarly the percentage of women with numerous bleeding days (21+ days) and numerous bleeding and/or spotting days (31+ days) decreased to reach 2.9% and 1.4% in the twelfth reference period (Figure 1). All in all, there were nine removals in the first three years for prolonged bleeding or spotting of more than 10 days.

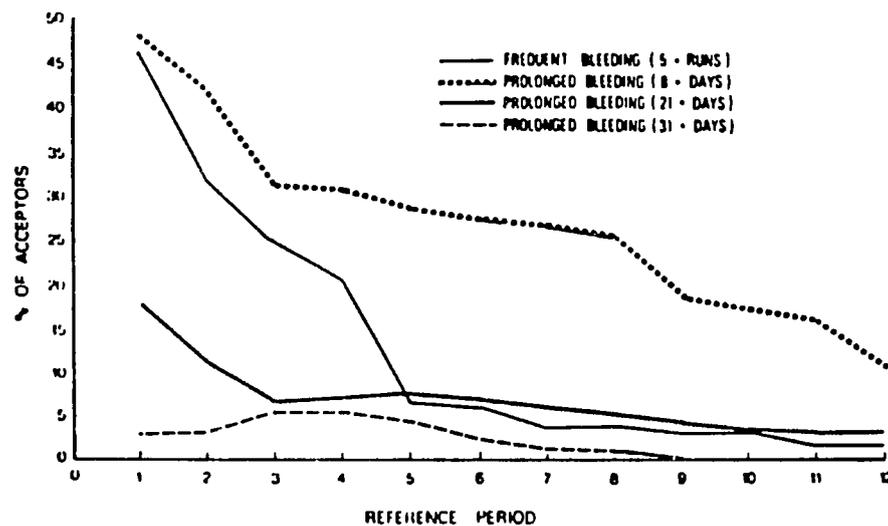


Figure 1 Percentage of Norplant acceptors with increased frequency of menstruation and prolonged bleeding/spotting by reference period

The percentage of women reporting infrequent bleeding (< 2 runs) declined with time and was 4.3% in the twelfth period. Similarly, the percentage of women with amenorrhea (60+ days) decreased during the three years and was below 4.0% at the end of three years. Likewise, the percentage of women reporting few bleeding days

decreased and was below 3.0% at the end of three years of use (Figure 2). Only one woman had the implants removed for prolonged amenorrhea of 400+ days after having scanty menses in the first three months following insertion.

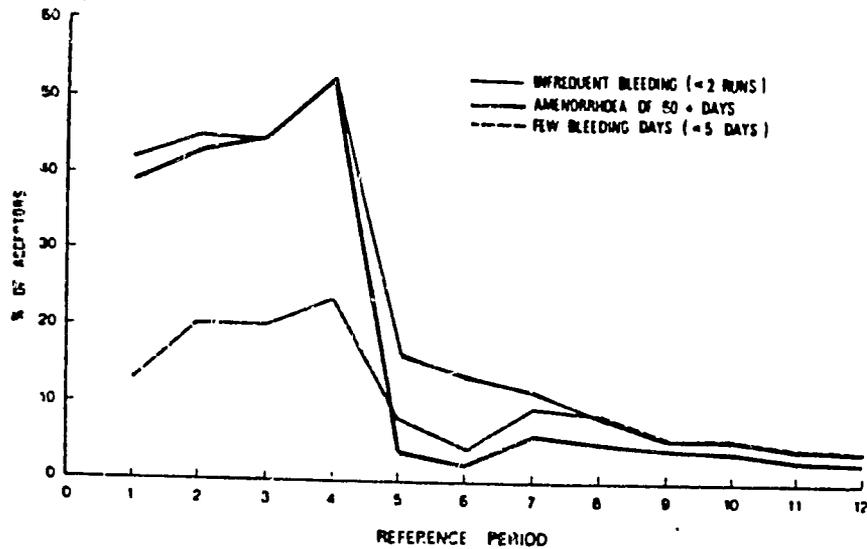


Figure 2 Percentage of Norplant acceptors with decreased frequency of menstruation and amenorrhea by reference period

(v) *Other side-effects*

The number of acceptors reporting other adverse experiences decreased from 37% during the first year of use to only 8% during the third year of use. There was only one scheduled clinical visit in the third year as compared to two and four scheduled clinical visits in the second and first year, respectively. However, patients were encouraged to come for unscheduled clinical visits at any time, should they have any complaints. As such, it would appear that the putative decline in the frequency of adverse experiences from year 1 to year 3 is not related to the less frequent clinical visits in the second and third year. Local reaction at the implant site and dizziness were frequently reported in the first year. The incidence of these experiences decreased in the second and third years of use. In the second and third years, an increase in weight was the most frequently reported non-menstrual adverse experience but there were no removals due to this adverse experience. There was, however, one removal due to a weight loss of 7 kg in the second year of use.

(vi) Post-removal return of fertility

During the first three years of use, 17% of the acceptors discontinued implant use, stating that they wished to have another child. Cumulative pregnancy rates after implant removal is shown in Table 3. About 53% conceived within three months of removal of the implants. The 12 and 24 month pregnancy rate was 94.1% (Table 3). In fact, the only woman who had not conceived at one year post-removal was noted to have decided against planned pregnancy and was now using condoms as a method of contraception.

Table 3 Post-removal pregnancy rates per 100 Norplant acceptors in Singapore

<i>Months after removal</i>	<i>Cumulative pregnancy rates (%)</i>
3	52.9
6	76.5
12	94.1
24	94.1

17 women had Norplant implants removed for planned pregnancy

Of the 16 women who conceived, one had an induced abortion at 8 weeks of amenorrhoea due to some marital discord. She subsequently started using the three monthly injectables as a method of contraception. The remaining 15 women have all had full term normal vaginal deliveries. There has been no untoward incidence of ectopic pregnancy, spontaneous abortion, stillbirth or congenital malformation in this small sample of subjects.

Discussion

The findings presented in this three-year clinical study suggests that the Norplant system is a highly effective, safe and acceptable method among Singaporean women. No accidental pregnancies occurred during the period of study and this agrees well with results of other studies which have shown annual pregnancy rates of 0.2 to 1.3 per 100 woman-years during the first years of use [4-6]. A continuation rate of 69% at the end of three years in this study is comparable to the continuation rates mentioned in other international studies [7-9].

Disruption of menstrual rhythm, particularly increased bleeding, appears to be the method's main drawback during the first one to two years of use [10-12]. The net cumulative termination rate for menstrual irregularities in this study is 12.0% at the end of three years of use. This is similar to the rate of 14.1% reported by Sivin *et al.* in 1983 [12]. Holma in 1985 [6] reported a cumulative discontinuation rate of 18.8 per 100 women for menstrual problems at five years of Norplant use. The variation in

discontinuation rates for menstrual problems probably indicates that cultural variables influence a woman's perception and attitude about alteration in her bleeding patterns and her willingness to tolerate and accept such changes. The data presented clinically show a decreased incidence of menstrual irregularities with time [13].

Side-effects other than menstrual disturbances are infrequent and accounted for only 2% of the removals in this study. The two removals in this study were due to weight loss and hair loss. Discontinuation rates for non-menstrual side-effects accounted for 3.0 per 100 women in other international studies [14]. Weight gain, headache, anxiety and nervousness are the few steroid-related side-effects that have been associated with a discontinuation in use.

Besides having problems with a Norplant method, women may have other reasons for discontinuing use of the method. They may be passing from one phase to another in their reproductive lives. They may thus want to change to a permanent method like tubal sterilization or they may wish for a pregnancy. In the Singapore study, unlike other studies, desire for future pregnancy and not menstrual problems is the leading cause for discontinuing Norplant implant use. This difference in trend may be related to the change in the Singapore government's family planning policy in 1986-1987. There is now a more liberal attitude towards three or more children in families who can afford to have more children.

A number of studies now attest to the rapidity of conception among former Norplant implant users seeking pregnancy. Of women having Norplant removed for planned pregnancy 40% became pregnant by three months, 76% by one year and 90% by two years [4]. The postremoval conception rate of 94.1% at one year in this study is excellent and is similar to normal rates of fecundity and the rates for former users of IUD and Depo-Provera [16,17].

Conclusion

It can be seen from this three-year study that Norplant implants are acceptable to Singaporean women. Demonstration of their effectiveness, acceptability, safety and reversibility have convinced many that this delivery system has a potential for wide use in the future.

Acknowledgements

We are grateful to the medical and nursing staff of the Fertility Control Clinic, National University Hospital, for their invaluable help. The study was supported by a grant from Family Health International. We are also indebted to Miss Prema for her secretarial assistance.

References

1. Rodriguez, G., Faunder-Lathan, A. and Atkinson, L. (1976). An approach to the analysis of menstrual patterns in the clinical evaluation of contraceptives. *Saud. Fam. Plann.*, 7, 42-51
2. Snowden, R. (1977). The statistical analysis of menstrual bleeding patterns. *J. Biosoc. Sci.*, 9, 107-120
3. World Health Organisation (1987). Vaginal bleeding patterns - the problem and an example data set. *Appl. Stoch. Mod. Data Anal.*, 3, 11-20
4. Diaz, S., Pavez, M., Miranda, P., Robertson, D.N., Sivin, I. and Croxatto, H.B. (1982). Five-year clinical trial of levonorgestrel Silastic implants (Norplant). *Contraception*, 25, 447-456
5. Lubis, F., Prihartono, J., Agoestina, T., Affandi, B. and Sutedi, H. (1983). One-year experience with Norplant implants in Indonesia. *Saud. Fam. Plann.*, 14, 181-183
6. Holma, P. and Robertson, D.N. (1985). Cholesterol and HDL-cholesterol values in women during use of subdermal implants releasing levonorgestrel. *Contraception*, 32 (20), 163-171
7. Gu, S.J., Yuan, D.Y., Zhong, L.D. *et al.* (1987). Evaluation of the Norplant subdermal contraceptive system - China. In: *Proceedings of the Pre-Congress Seminar of the XI AFOG Congress*, Bangkok, Thailand
8. Basnayake, S., Thapa, S. and Balogh, S.A. (1988). Evaluation of safety, efficacy and acceptability of Norplant implants in Sri Lanka. *Saud. Fam. Plann.*, 19 (1), 39-48
9. Sivin, I. (1988). International experience with Norplant and Norplant-2 contraceptives. *Saud. Fam. Plann.*, 19 (2), 81-94
10. Population Crisis Committee (1985). Female fertility control - the future. *Singapore J. Obstet. Gynaecol.*, 5 (1), 5-20
11. Diaz, S., Pavez, M., Robertson, D.N. and Croxatto, H.B. (1979). A three-year clinical trial with levonorgestrel Silastic implants progesterone. *Contraception*, 19, 557-573
12. Sivin, I., Diaz, S., Holma, P., Alvarez-Sanchez, F. and Robertson, D.N. (1983). A four year clinical study of Norplant implants. *Saud. Fam. Plann.*, 14, 184-191
13. Singh, K., Viegas, D., Singh, P. and Ratnam, S.S. (1989). Norplant contraceptive sub-dermal implants - two year experience in Singapore. *Adv. Contracept.*, 5 (2), 91-100
14. World Health Organisation Special Programme of Research, Development and Research Training in Human Reproduction (1985). Facts about an implantable contraceptive. *Bull. WHO*, 63, 485-484
15. Singh, K., Viegas, O. and Ratnam, S.S. (1988a). Norplant contraceptive subdermal implants - one year experience in Singapore. *J. Biosoc. Sci.*, 20, 401-409
16. Affandi, B., Santiso, S.S.I., Djajadilaga, D., Hdisaputra, W., Moelock, F.A., Prihartono, J., Lubis, F., Samil, R.S. and Saleh, K.R. (1987). Pregnancy after removal of Norplant implants contraceptives. *Contraception*, 36 (20), 203-209
17. Diaz, S., Pavez, M., Cardenas, H. and Croxatto, H.B. (1987). Recovery of fertility and outcome of planned pregnancies after the removal of Norplant subdermal implants contraceptives. *Contraception*, 36 (2), 203-209

MS received 15 Nov. 89.

Accepted for publication 2 Apr. 90.

Resumé

Une évaluation clinique de trois ans portant sur des femmes de Singapour ayant utilisé les implants Norplant a révélé qu'aucune grossesse ne s'était produite pendant les trois premières années d'utilisation. Au terme de ces trois années, le taux de poursuite atteignait 69%. Le retrait de l'implant au cours de cette période avait été décidé pour deux raisons principales: le désir d'une grossesse planifiée et la perturbation du rythme menstruel. Le taux de conception après le retrait chez les femmes ayant planifié une grossesse s'élevait à 94, 1% au bout d'un an. Il semble donc que Norplant offre une méthode de contraception hautement efficace, sûre, acceptable et réversible.

Resumen

Una evaluación clínica de tres años en mujeres de Singapur que habían utilizado implantes Norplant indicó que no se produjo ningún embarazo durante los tres primeros años de uso. Al cabo de los tres años, la tasa de continuación era del 69%. Los dos principales motivos que llevaron a retirar el implante en el curso de tal período fueron el deseo de un embarazo planificado y la perturbación del ritmo menstrual. La tasa de concepción después de retirarse el implante en las mujeres que deseaban un embarazo planificado fue del 94.1% al cabo de un año. Por consiguiente, parece que Norplant ofrece un método anticonceptivo muy eficaz, seguro, aceptable y reversible.