AFRICAN JOURNAL OF MEDICINE and medical sciences

VOLUME 32, NO 1 MARCH 2003

EDITOR
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ASSISTANT EDITOR
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ISSN 1116—4077

Afr J Med med Sci (2003) 32, 27-31

Nonmenstrual adverse events associated with subdermal contraceptive implants containing normegestrel and levonorgestrel

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Summary
To improve counselling information to Nigerian family planning clients, we compared non-menstrual events reported by 248 Norplant™(R) users and 214 Uniplant(R) users. Women using Norplant were significantly older and of higher parity and greater contraceptive experience than Uniplant users. Other admission characteristics of the two groups were similar. The total women - months of use of Norplant was 2,946 (mean 11.9 ± 0.6 SE) months while that for Uniplant was 2,315 (mean 10.8 ± 0.2 SE) months. About 36% of Norplant users and 15% of Uniplant users reported non-menstrual adverse events, the commonest ones being pain/itching at the insertion site, unexplained low abdominal pains and clinically diagnosed pelvic inflammatory disease (PID). The numbers of women reporting drug-related adverse events were 61 (24.6%) and 23 (10.8%), respectively, among Norplant and Uniplant users. Drug-related serious adverse events were reported by 3 (1.2%) Norplant users and 5 (2%) Uniplant users. The adverse events leading to Uniplant removal were severe urticaria, breast lumps, pruritus vulvae, headache with raised blood pressure, adnexal pains and ovarian cysts, and static weight while those leading to Norplant removal were breast lump and headache with raised blood pressure. Weight gain was reported by only 7 (3%) of Norplant users. Although of no serious clinical consequences, drug-related adverse events should be added to the counselling information to prospective users.

Keyword: *Non-menstrual, menstrual, adverse events, Nigerians, normegestrel, levonorgestrel, contraceptives, sub-dermal implants.*

Résumé
Pour amèliorer les conseils aux clients du planing familial, nous comparions l' èvenèment de la non-mentrue reportè a 2248 utilisatrices du Norplant R et 214 utilisatrices du Uniplant. Les femmes utilisnt Norplant etaient significativement vieille d haute paritè et d'esperience a l'emploi des contraceptives que les utilisatrices du Uniplant. Autres characteristiques d'admission dans las 2 groupes etaient semblable. La quantite totale du Norplant par mois etait 2.496(moyenne 11.9± 0.6 S E) par mois et 2.315 Uniplants (moyenne 10.8 ± 0.2 SE) par mois Environ 36% d utilisatrices du Norplant et 15% du Unipant ne rapportaient aucun effect adverse au non-menstrues. La douleur et les demangesions au lieu de l insertion n'explaiquaient pas les douleurs abdominales et l'inflammation du pelvis diagnostique en clinique (PID). Les nombres des femmes ayant les effects adverses des medicaments etaient de 61(24.6%) et 23 (10.8%) aux Norplant et Uniplant respectivement. Les effects adverse compliques etaient rapporte a 3 (1.2%) des utilisateurs du Norplant et 5(2%) des utilisateurs de l Uniplant. Et conduisait a l enlevement de l uniplant du a l'urticarie severe, l ' elargissement des seins, augmentation de la temperature du vulve , les maux de tete avec l augmentation de la tension artèrielle ,douleur , cyste ovarien et poids corporel contant. Cependant ceux du Norplant inclus : l'enlevèment ,l'elargissement des seins, maux de tete avec l'augmentation de la tension artèrielle. L'augementation du poids ètait observe seulement a 7(3%) des utilisatrices du Norplant . Bien que sans consequences clinique serieux, les effects adverses liès aux medicaments pourraient etre ajoutès aux conseils pratiques aux furtur usagères

Introduction

Considerable variations in the reported adverse events are seen among individual users of sub dermal contraceptive implants, and among populations [1,2]. These include menstrual and non-menstrual ones. The prevalence of headache, nausea, dizziness, breast tenderness, acne, hirsutism and weight gain may be slightly increased with the use of these contraceptives and have been associated with their androgenic activities [1]. Some of these events and others such as loss of libido, depression, anxiety and mood changes have resulted in their discontinuation [3]. The percentage of progesterone-only pills users reporting non-menstrual adverse events is estimated between 21% and 45%. However, the discontinuation rate on account of these is less than 10% [4,5].

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In Nigeria, the effects of levonorgestrel (Norplant(R)) and normegestrel (Uniplant(R)) sub-dermal implants on menstrual, metabolic and immunologic parameters among users of these contraceptives have varied [6-9]. Norplant consists of 6 capsules, each 3.4 cm long and 2.4 mm wide, and contains 36 mg levonorgestrel. This is slowly released at the rate of 50 ug/day in the 1st year of use and 30 ug/day subsequently. Uniplant on the other hand, is made up of a single capsule 3.9 cm long and 2.4 mm wide which contains 55 mg ± 10% that is released at average rate of 100 ug/day. The duration of contraceptive activity of Norplant is 5 years while that of Uniplant is slightly more than a year. With increasing number of women using these methods, the non-menstrual adverse events are now becoming an important cause for concern. This report analyses the non-menstrual adverse events reported by users of the two sub-dermal contraceptive implants available in Nigeria with the hope that it will improve the information provided during counselling.

Materials and methods

Subjects

The analysis is based on data from the records of all women who had either Uniplant(R) or Norplant(R) insertion between January 1, 1991 and December 31, 1994 at the Family Planning Clinic, University College Hospital, Ibadan. These women were aged between 18 and 40 years and had sought reversible contraceptives active for more than a year. They were given the devices if they had a regular menstrual cycle and no contraindications to the use of sub-dermal progestin contraceptives. They were also in good mental and physical health and gave informed written consent. Those with a history of endocrine disorders, thromboembolic diseases, obesity and unwilling to use hormonal contraceptives were excluded. Each client made a choice between Norplant and Uniplant after counselling.

Insertion of the devices

At screening visits, medical history was taken and physical examination performed in all subjects that met the criteria for insertion. If the findings were within normal limits, trained personnel inserted either Uniplant or Norplant in the sub-dermal medial aspect of the nondependent arm during the first 5 days of the menstrual cycle of each subject for Uniplant or first 7 days of the menstrual cycle for Norplant. The insertion was performed according to the manufacturer's guide.

Follow-up

The women were followed-up at the family planning clinic at 6 weeks, 3 months, 6 months, 9 months and 12 months of use, and whenever a complication occurred. At the visits physical examinations were performed. Blood pressure and weights were measured. All adverse events were recorded according to WHO terminology [5] using a prepared checklist.

Definition and report of adverse events

Adverse events are defined as any new complaints or symptoms emerging during the period of use of the devices or any pre-existing complaints or symptoms that increased in severity or frequency during the study period [5]. In short, adverse events are events that are untoward deviations from baseline health without necessarily implying a causal relationship to the study treatment. Serious adverse events are those that are fatal, life threatening, permanently disabling or those that require in-patients hospitalisation, or prolonged hospitalisation. They include congenital anomalies or birth defects, cancer and overdose. The investigators judged the various drug-related adverse events and serious adverse events that were thought to be unlikely related were classified as non-related. Blood pressure was considered clinically raised if the systolic level was above 140 mmHg or there was more than 20 mmHg rise in level above admission level. Conversely, a diastolic pressure above 90 mmHg or a rise of more than 10 mmHg above the admission level was considered as clinically raised. The rise in blood pressure is considered if it occurred on at least two occasions after a rest on the same day or at last assessment (single recording). An increase in body weight of more than 10% from baseline at least once during treatment was considered clinically significant. Pelvic inflammatory disease was suspected when there was offensive vaginal discharge, cervical excitation tenderness, or low abdominal pains with or without fever. Such women were referred to the gynaecological clinics for management.

Statistical analysis

The data was analysed using Epi-info version 6, statistical software (CDC, Atlanta Georgia, USA). Chi squared test was used to compare frequencies of adverse events with Uniplant and Norplant. Changes from baseline readings/measurements were assessed using Mantel–Haenszel chi squared test or Student's t test. For comparative purposes, our analysis was based on events occurring within the first year of use of the implants, in keeping with the period of Uniplant's contraceptive activity. Women who had used either of the implants before the study period were removed from analysis. The numbers and percentages of women with adverse events, serious adverse events, discontinuing due to adverse events, adverse events of intense severity, and drug-related adverse events are presented in frequency tables.

Results

Four hundred and sixty-two women who used the implants during the study period were eligible for evaluation. They included 214 Uniplant users and 248 Norplant users (Table I).

Table 1: Admission characteristics of the women.

Characteristics Mean (SE)	Uniplant group (n=214)	Norplant group (n=248)
Age yrs	28.6 (0.3)	31.6 (0.4)*
Parity	3.2 (0.1)	3.9 (0.1)*
Weight kg	52.9 (0.7)	53.4 (0.5)
Systolic BP mmHg	102.1 (0.8)	103.0 (0.7)
Diastolic BP mmHg	63.6 (0.6)	62.7 (0.5)

**t test ($P < 0.05$)*

The women using Norplant were significantly older and of higher parity than those using Uniplant. No significant difference was seen in any other admission characteristics. Although majority of the women had never used any form of modern contraceptives before they were recruited, the distribution shows that significantly more Norplant users had used contraceptives in the past (Table 2).

Table 2: Percentage distribution of women who had used modern contraceptives before insertion of implant.

Contraceptives	Uniplant group (n = 214)	Norplant group (n = 248)
Pills	11.7	19.0
IUCD	11.5	19.0
Injectables	0.4	6.4
Others	2.5	7.2
None	72.9	48.0

The sum of the women months of use of Uniplant was 2,315 and the mean follow up for each subject both continuing and discontinuing the use of the implant was 10.8 ± 0.2 (SE) months. In the Norplant group, the total women months of use was 2,946 and the mean follow up for each subject both continuing and discontinuing was 11.8 ± 0.1(SE) months.

About 15.0% women using Uniplant and 36.3% of those using Norplant reported adverse events (Table 3).

Table 3: Frequency distribution of classes of adverse events among the women according to the contraceptive implants.

Classes of adverse events	Number (%) of adverse events Uniplant users (n = 214)	Norplant users (n = 248)
No of women with adverse events	32(15.0)	90(36.3)*
Drug-related adverse events	23(10.8)	61(24.6)*
Serious adverse events	7(3.3)	10(4.0)
Drug-related serious adverse events	5(2.3)	3(1.2)
Adverse events causing discontinuation	6(2.8)	2(0.8)*

**Manthel Haenzell χ^2 test ($P < 0.05$)*

The adverse events were considered serious in, respectively, 3.3% and 4% of Uniplant and Norplant users. Drug-related adverse events occurred in 10.8% of Uniplant users and 24.6% of Norplant users. The percentages of women reporting serious adverse events considered to be possibly or probably drug-related were 2.3% and 1.2%, respectively, for Uniplant and Norplant users. Only one woman using Uniplant with severe urticaria following insertion was considered to be definitely drug-related. No death or prolonged hospitalisation was reported among all the women in the study at follow-up.

The commonest adverse events were pain or itching at the implant site, unexplained low abdominal pains and pelvic inflammatory disease (Table 4).

Table 4: Distribution of various adverse events reported by the women.

Adverse events	Frequency of adverse events seen in Uniplant users n(%)	Norplant users n(%)
Low abdominal pains	4(1.8)	13(5.2)
Pain/itching at the implant site	3(1.4)	13(5.2)
Pelvic inflammatory disease	1(0.5)	13(5.2)
Headache	3(1.4)	14(5.7)
Pruritus vulvae	3(1.4)	7(2.8)
Tiredness/weakness	3(1.4)	5(2.0)
Dizziness	1(0.5)	6(2.4)
Gastrointestinal symptoms	3(1.4)	4(1.6)
Weight loss/stasis	4(1.8)	3(1.2)
Weight gain	0(0)	7(2.8)
Chest pains/palpitation	0(0)	6(2.4)
Generalised body ache	1(0.5)	4(1.6)
Malaria	0(0)	5(2.0)
Back ache	1(0.5)	3(1.2)
Breast tenderness	2(0.9)	2(0.8)
Breast lumps	2(0.9)	1(0.4)
Post coital bleeding	3(1.4)	0(0)
Generalised pruritus	2(0.9)	0(0)

Headache with or without raised blood pressure was considered drug-related only if there were no accompanying symptoms of malaria fever. The 3 women with breast lumps were classified as having serious drug- related events and were referred to the surgeons for management. One of them had fibrocystic disease of the breast while the others had fibro adenomas. Weight-related events were seen in 5 women with weight loss (2 in Uniplant and 3 in Norplant groups), 2 women using Uniplant who complained of static weight and 7 women using Norplant with weight gain. Surprisingly, one woman using Uniplant discontinued on account of static weight. Six women using Norplant presented with chest pains with or without palpitation,

which were classified as drug-related adverse events, had no accompanying ECG changes or clinical signs to suggest cardiac ischaemia or pulmonary embolism. They used their devices till the end of the study. Six (3%) women using Uniplant and 2 (0.8%) women using Norplant with various adverse events were discontinued before the end of the first year of implant use (Table 5).

Table 5: Non-menstrual adverse events leading to removal of devices in Norplant and Uniplant users.

Adverse event	Frequency of each type of adverse event in	
	Uniplant users N(%)	Norplant users N(%)
Severe urticaria rash	1(0.5)	0(0)
Breast lumps	1(0.5)	1(0.4)
Pruritus vulvae	1(0.5)	0(0)
Headache + raised blood pressure	1(0.5)	1(0.4)
Lt adnexal pain + ovarian cyst	1(0.5)	0(0)
Static weight	1(0.5)	0(0)
Total	6(3)	2(0.8)

Discussion

Non-menstrual adverse events occurring among most contraceptive implant users are generally considered to be of minor medical importance. However, for individuals, these events may result in discontinuation of the methods in use thereby limiting their contraceptive choices and increasing their unmet contraceptive needs.

The prevalence of non-menstrual adverse events varies with the type of implant. In this study, the prevalences are 36.3% and 15.0% per year, respectively, for Norplant and Uniplant users. In an integrated analysis of reports from Europe, the Americas and Asia, 69% of Norplant users reportedly had non-menstrual adverse events whilst using the device [10]. Comparably less number of women had adverse events in this study than theirs. Similarly, the percentage of women reporting serious non-menstrual adverse events that were considered to be possibly or probably drug related in the Uniplant group (2.3%) and in the Norplant group (1.2%) were less. The reasons for these differences are uncertain and unlikely to be related to the active hormones in the implants because large regional differences in both the severity and types of non-menstrual events have been reported among women using Norplant in various studies [1,5]. Variations in cultural, social and environmental factors seem to play a great role in this regard. The basic rate of symptoms and their interpretation probably contributed to the differences in our study. Moreover, these symptoms are similar to those of other common ailments in our environment and may therefore not be reported by some users without direct questioning in a prospective study. The limitation to this study is a possible bias that can be introduced by the various ways each patient perceived her symptoms and the seriousness attributed to them. Although a checklist of symptoms was used for direct questioning at follow up some implant users might not see the need to mention a symptom that was not bothersome. Another source of possible bias is the significant difference in admission characteristics of the two groups, which might have played a role in the differential number of adverse events reported. A randomised control trial is needed to address these issues. The commonest non-menstrual adverse events reported in this study are pelvic inflammatory disease [PII], low abdominal pains and pain/itching at the site of implant insertion. These are not drug related but are serious enough for concern since they may affect future acceptance of the methods. Pain/itching at the implant site was more frequent among Norplant users and might be related to the number of capsules inserted sub-dermally. The incidence of PID and low abdominal pains in the Norplant group cannot be explained in terms of number of capsules, admission characteristics or otherwise except a possible underreporting in the Uniplant group.

In this study, most of the drug-related events have been previously associated with the use of progestin only contraceptives [1,5]. Most of the non-menstrual adverse events seen were not definitely attributed to the use of the implants studied. The only event that was definitely drug related was the case of severe urticaria reported in a woman following Uniplant insertion, which disappeared immediately it was removed. Acne, breast pain, headache and weight gain were the most frequent drug related non menstrual adverse events reported among Norplant users in studies elsewhere [10 -12]. On the contrary, our study shows that only headache occurred in a significant number of women using either Norplant or Uniplant. While no acne was reported in this series, weight problems included static weight and weight loss in both groups. This suggests that acne and weight gain are less of a problem to our group of implant users than obtains in other areas. The fact that some sectors of our community perceived weight gain as a sign of prosperity may explain why a woman discontinued the use of Uniplant because of static weight. Thus a small steady weight gain over time may be acceptable to users and beneficial in increasing acceptability of the methods. This information should be made available to potential users during counselling. Dizziness, tiredness/weakness and chest pains were other drug-related events encountered in this study. These symptoms have been reported in progestin contraceptive users although they may occur in

other conditions such as malaria or influenza [4,5,11-13]. They do not seem to influence the use of the implants in the majority of our acceptors.

In conclusion, serious drug -related adverse events are few and controllable among users of Norplant and Uniplant. However, providers should add this fact to the counselling information given to contraceptive seekers to enable them make an informed choice.

Acknowledgements

Our gratitude goes to all the family planning nurses especially Mrs Bello and Mrs Ojobe who counselled and recruited the subjects.

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