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Vaginal bleeding patterns in Nigerian users of nomegestrol acetate subdermal contraceptive implant.

A.O. Arowojolu*, O.A Adekunle, T.O. Ogunnowo, E.O. Otolorin and O.A. Ladipo
Department of Obstetrics and Gynaecology, University College Hospital, Ibadan. Nigeria.

Summary
A 12 months longitudinal study was carried out in 214 consecutive Nigerian women using Nomegestrol acetate subdermal contraceptive implant (Uniplant^{R}) for the first time to establish the rates of different vaginal bleeding patterns according to WHO bleeding/spotting classification, and to assess their relationship with Uniplant$^{(R)}$ discontinuation. The results showed an initial rise in the number of women experiencing altered vaginal bleeding which continued to fall towards the 12th month of use (57.01% vs 26.17%). Similarly, a significant increase in mean menstrual cycle length occurred in the first trimester of use and this disappeared by the third trimester. The mean numbers of bleeding/spotting days and bleeding/spotting free intervals increased significantly from first trimester to the fourth trimester. No change was noted in the mean number of bleeding/spotting episodes throughout the follow up period. The total discontinuation rate was 15.42%. Discontinuation on account of altered vaginal bleeding pattern was 3.27%. One accidental pregnancy occurred during follow up (Pearl index = 0.52). No significant change in haemoglobin levels was noted in the women. It was concluded that changes in menstrual patterns in Uniplant$^{(R)}$users occur mostly in the first six months of use and are unlikely to have any deleterious effects on the general health of the users.

Keywords: *Nomegestrol acetate, uniplant, subdermal implants, vaginal bleeding, contraceptive method, Nigeria.*

Résumé
Une etude longitudinale de 12 mois a ete faite sur 214 femmes Nigeriannes, utilisant l'implantation de la contraception sous - dermode de l'acetate Nomegestrol (uniplante) pour etablir la premiere fois le taux des differents saignement vaginaux suivant la classification de l'Organisation Mondiale de la sante (OMS), et pour evalues la relation discontinue avec l'uniplante (R). Les resultati montrent une hausse initiale chez les femmes ayant un saignement vaginal (altere, qui continue de baisser vers les 12 mois d'usage (57,01% contre 26, 17%). De la meme facon une augementation significative de la longueur moyenne du cycle mentruel a eu lien an cours du premier trimestre de l'utilisation, et ceci a disparu au cours du troisieme trimestre. Le nombre moyen des jours de saignement et des intervalles libres (depourou de saignement) augmenta significativement du premier au quatrieme trimestre. Aucum changement n'a ete note daus le nombre moyen des episodes de saignement font an long de la periode de suivi. Le taux de discontinuite etait de 15,42% L'interruption due an saignement vaginal altere etait de 3,27%. Une grossesse accidentelle a en lien au courant de la periode de suivi (index de Pearl = 0,52). Aucum changement significatif de la quantite d'haemoglobine n'a ete observe chez les femmes. Il a ette conclu que les changements mentruels chez les individus utilsant l'uniplante(R) a lien principalement dous les premiers six mois de l'usuge et ont improbablement des effets nefartes sur la sante generale des utilisateurs.

Correspondence: Dr. AO Arowojolu, Department of Obstetrics and Gynaecology, University College Hospital, Ibadan. Nigeria.

Introduction

Subdermal contraceptive implants, such as Levonogestrol (Norplant^{R}; Population council, USA), Nomegestrol (Uniplant^{R}; South to South, Brazil) and Etonogestrel (Implanon^{R}; Organon, U.K) have the advantages of parenteral administration which evades the hepatic first pass effect in the users. They are highly effective long acting contraceptives which are independent of users compliance, unrelated to coital activity, discrete and useful in breast feeding women requesting hormonal contraceptives. [1-5]. Their major disadvantages include the high cost and the need for a trained personnel to perform the insertion and removal procedures.

The first widely used subdermal implant is the Norplant$^{(R)}$ which contains levonorgestrel in 6 silastic non-biodegradable capsules. These are inserted in the medial aspect of the arm for long term contraception lasting 5 years [2-6]. Uniplant$^{(R)}$, a second generation subdermal contraceptive implant, contains 55mg $\pm$ 10% nomegestrol acetate packed in a single capsule of silastic that provides contraception for a year [3,7]. Its introduction into the contraceptive armamentarium was to reduce the number of units of implants given to a user in order to facilitate insertion. More importantly, the use of nomegestrol acetate was to minimise the side effects encountered with the use of levonogestrel in Norplant$^{(R)}$ [7].

Experiences in the past with progesterone only contraceptives have shown that altered vaginal bleeding and spotting are major reasons for users discontinuation [8-10]. This disruption of regular menstrual bleeding is bothersome for some women but generally, it is not hazardous to health (6,7,9). Ethnicity may influence the bleeding patterns with long acting progesterone only contraceptives. For example among users of Depot medroxy-progesterone acetate (DMPA) more days of bleeding were reported in South East Asian women than women from the Caribbean or North Africa while amenorrhoea was more prominent among North African women than European ones [11]. These reported differences might have been influenced by regional differences in nutritional status or users sensitivity to menstrual changes.

The Word Health Organisation-coordinated multicenter clinical trial in which menstrual diaries were kept by women provided the most reliable information on bleeding patterns among women using hormonal contraceptives [12-14]. These records documented the diversity of bleeding patterns compared with the patterns of noncontracepting women [14,15]. Unfortunately, there are few reports on Uniplant$^{(R)}$ use by women from our environment in literature. The aim of this study is to assess the vaginal bleeding patterns in Nigerian women Uniplant$^{(R)}$ for a year according to the WHO bleeding / spotting classification [13,16].

4). Between 91 - 180 days of use (2nd trimester) 38.78% of the subjects experienced altered bleeding pattern while at the same period 61.22% had acceptable bleeding patterns. Between 181 - 270 days of follow up (3rd trimester) 71.96% and 28.04%of the women experienced acceptable and altered vaginal bleeding patterns respectively. Similarly, between 271-360 days (4th trimester) 73.83% and 26.17% of the subjects respectively had acceptable and altered bleeding pattern. Other bleeding parameters were as shown on Table 4. The numbers of bleeding/spotting days, bleeding/spotting episodes and bleeding/spotting free days for the trimesters were as shown on Table 5. The mean number of bleeding and spotting days and mean number of bleeding/spotting free intervals were both increased significantly from the 1st trimester to the 4th trimester at follow up. No such difference was seen in the bleeding/spotting episodes.

Table 4: Proportion (%) of women experiencing different bleeding patterns with Uniplant (R) by 90 days intervals

Days	No of diaries	Amenorrhoea	Infrequent bleeding	Frequent bleeding	Irregular bleeding	prolonged bleeding	Acceptable pattern	Altered pattern
1-90	631	5.14	21.96	0.94	25.23	4.21	42.99	57.01
91-180	594	7.01	7.01	1.87	21.03	1.87	61.22	38.78
181-270	554	2.80	7.94	0.00	15.89	0.94	71.96	28.04
271-360	536	1.87	2.80	2.80	15.89	1.87	73.83	26.17

Table 5: Mean ± SE number of bleeding/spotting days, bleeding/spotting episodes and bleeding/spotting free days among the 214 women using Uniplant(R).

Interval (Days)	Bleeding/ spotting days	Bleeding spotting episodes	Bleeding/ spotting free intervals.
1-90	12.4 ± 0.64	2.8 ± 0.6	69.7 ± 0.61
91-180	14:4 ± 0.73	2.4 ± 0.08	72.6 ± 0.72
181-270	15.1 ± 0.62	2.5 ± 0.07	71.9 ± 0.92
271-360	14.5 ± 0.53	2.6 ± 0.05	73.3 ± 0.74

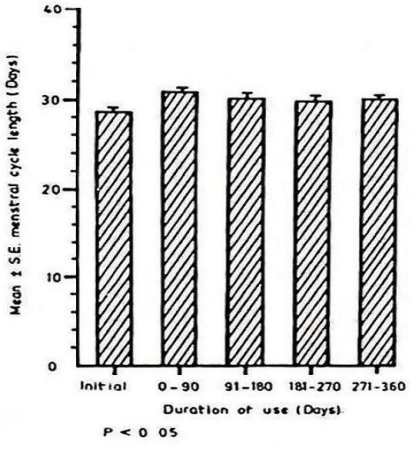


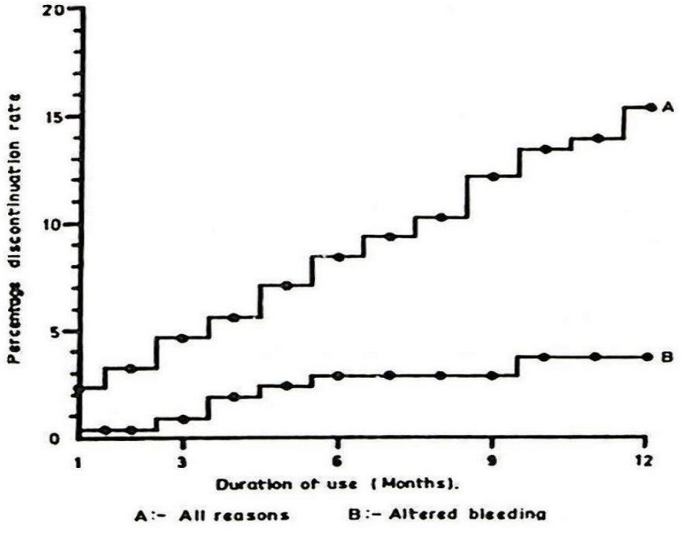
Fig. 1: Changes in mean menstrual cycle length at 90 days interval in 12 months of Uniplant(R) use in the 214 Nigerian acceptors.

The mean menstrual cycle length in the 2,315 cycles studied was 30.84 ± 0.35(SE) days. In the 1st trimester of use, the mean menstrual cycle length was 31.88 ± 0.75(SE) days while in the 2nd trimester of use it was 31.06 ± 0.75(SE) days. In the 3rd trimester of use, the mean menstrual cycle length was 29.98 ± 0.54(SE) days and in the 4th trimester of use it was 30.16 ± 0.58(SE) days (Fig 1). These figures were statistically different using the ANOVA test ($f = 7.42$, $df = 4$, $P < 0.05$). Using Bonferroni t test, the differences were identified between the mean pre-insertion cycle length and the mean cycle lengths of the 1st trimester ($t = 4.19$, $P < 0.05$) and 2nd trimester of use respectively ($t = 3.10$, $P < 0.05$).

The haemoglobin level at insertion did not vary significantly during the one year of Uniplant(R) use (11.81 ± 0.67g/dl vs 12.11 ± 0.92g/dl; $P > 0.05$).

Reasons for discontinuation and efficacy of Uniplant(R)

Thirty three women discontinued the use of Uniplant(R) before the end of one year following insertion, giving a total discontinuation rate of 15.42% for all reasons at 12 months of use(Fig.2). The cumulative life table analysis at 12 months showed that the majority (3.74%) of the subjects discontinued because they preferred other contraceptive methods while 4.67% did so either on the wishes of their husbands or for personal reasons (Table 6). Among those switching to other contraceptive methods only 2 women had experienced altered vaginal bleeding before withdrawing from the study. The discontinuation rate for all medical reasons was 6.54%. Menstrual problems (amenorrhoea and unacceptable vaginal bleeding) which occurred in 3.27% of the subjects were the commonest medical reasons for discontinuation(Table 6). Other medical reasons included headache (0.94%), dizziness (0.94%), urticaria rashes (0.47%) and raised blood pressure (0.47%).



ig 2: Cumulative discountinuation rate for unacceptable aginal bleeding and all reasons.

Accidental pregnancy occurred in only one subject through out the study period. The pregnancy occurred on the 12th month of continued use (Pearl index = 0.52). The cumulative pregnancy rate was 0.47%.

Subjects and method

Between 1st February 1991 and 31st December 1994, 214 consecutive healthy noncontracepting women requesting reversible contraceptives for over a year were recruited into the study at the family planning clinic, University College Hospital Ibadan. The women were recruited if they had regular menstrual cycles during the previous 3 months, able to complete menstrual diaries and had no contraindications to the use of Uniplant(R). Those with endocrine disorders, thromboembolic diseases, obesity, mental disease and unwilling to use hormonal contraceptives or complete menstrual diaries were not selected. They all gave informed consent to participate in the study which was approved by the local ethical committee.

Before insertion of Uniplant(R), a complete history and physical examination were performed in all subjects. Uniplant(R) was inserted subdermally in the medial aspect of the arm by trained personnel during the first 5 days of the menstrual cycle in each acceptor who was then given a menstrual diary card. All the women were instructed to record all bleeding events monthly before attending the follow up clinic. Haematological and biochemical parameters were checked. Assessment of bleeding/spotting was carried out every 3 months according to the current WHO criteria [12-14]. Analysis began at the time of last menstrual period prior to insertion of Uniplant(R)

Statistical analysis

Bleeding patterns were evaluated in the clinic at 90 days interval. All entries were made into a computer using Epi-Info version 6 soft ware (CDC, Atlanta, Georgia and WHO, Geneva, Switzerland). Analysis of variance (ANOVA) was used to determine the differences between continuous variables. Subsequently, Bonferroni t test was used to identify the areas of difference if a significant difference was noted with ANOVA. A significant level of P=0.05 was used to reject the null hypothesis.

The definition of bleeding, spotting, episodes of bleeding and spotting were as follows(16):

Bleeding - bloody vaginal discharge that requires protection.

Spotting - bloody vaginal discharge that does not require protection.

Bleeding/Spotting episode - set of one or more bleeding/ spotting days, bounded at each end by two or more bleeding /spotting free days.

Bleeding/Spotting free day - A day on which neither bleeding nor spotting is recorded.

Bleeding free interval - set of two or more consecutive bleeding free days bounded at each end by bleeding/spotting days.

Variations from normal regular pattern of vaginal bleeding (clinically important "altered bleeding" patterns) were defined as shown on table 1 (14).

Table 1: Variation from a normal regular pattern of vaginal bleeding.

Condition	Definition (for a 90-day reference period)
Amenorrhoea	No bleeding
Infrequent bleeding	Fewer than 2 bleeding/spotting episodes
Frequent bleeding	More than 4 bleeding/spotting episodes
Irregular bleeding	A range of lengths of bleeding free intervals exceeding 17 days
Prolonged bleeding	At least one bleeding/spotting episode lasting 10 days or more.

Source WHO (14)

"Acceptable bleeding" patterns were those without the variations.

Results

Characteristics of the subjects:

The total women months of use was 2,315. The average follow up for each subject including both continuing and discontinuing the use of uniplant(R) was 10.8 ± 0.24(SE) months. The mean age and parity of the subjects were 28.6 ± 0.33(SE) years, and 3.2 ± 0.13(SE) respectively. The mean menstrual cycle length before insertion of uniplant(R) was 28.59 ± 0.15(SE) days. All other characteristics were shown in Table 2.

Table 2: Summary of the demographic characteristics of the 214 Nigerian Uniplant(R) acceptors.

Characteristics	Mean ± SE	Range
Age (years)	28.62 ± 0.33	19 - 39
Parity	3.2 ± 0.13	0 - 8
Weight	52.85 ± 0.65	35 - 69
Menstrual cycle length (days)	28.59 ± 0.15	20 - 34
Systolic blood pressure (mmHg)	102.11 ± 0.80	80 - 140
Diastolic blood pressure (mmHg)	63.62 ± 0.56	50 - 90

Most of the subjects (73.9%) had never used any form of modern contraceptives (Table 3). Among those who had ever used modern contraceptives, oral contraceptive pills (11.7%) was the most popular. This was closely followed by IUCD (11.5%). Injectable contraceptive (eg. Medroxy progesterone acetate, Norethisterone enantate) were used by only 0.4% while 2.5% of the subjects used other forms of contraceptives like Barrier contraceptives and, Spermicidal creams and Jellies.

Table 3: Previous modern contraceptive use by Nigerian Uniplant(R) acceptors.

Contraceptives	Percentage of women (n = 214)
Oral contraceptive pills	11.7
Intra uterine device	11.5
Injectables (eg. DMPA)	0.4
Others (eg. Condom, Jellies)	2.5
None	73.9

The interval between last delivery and the date of insertion of Uniplant(R) ranges from less than a year (50.3%) to over 3 years (11.8%) with a mean of 22.86 ± 1.46(SE) months. Respectively, 29.4% and 8.5% of the subjects were in their 2ndyear and 3rd year following last child birth. Breast feeding mothers constituted 18.5%.

Bleeding and Spotting patterns following insertion of Uniplant(R)

Within the first 90 days of Uniplant(R) insertion (1st trimester) 57.01% of the subjects reported altered vaginal bleeding patterns while 42.99% of them had acceptable pattern (Table

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Table 6: Cumulative discontinuation events rate at 12 months of Uniplant (R) use.

Events	Percentage of women (n=214)
A. Medical reasons:	
(a) Menstrual problems;	
i. Anenorrhoea	0.47
ii Unacceptable bleeding	
1. irregular bleeding	0.94
2. prolonged bleeding	1.87
3. postcoital bleeding	0.47
(b) other medical reasons	2.80
B. Personal reasons	2.80
C. Husbands' wishes	1.87
D. Accidental pregnancy	0.47
E. Prefers other contraceptive method	3.74
All reasons	3.74

Discussion

Unpredictable vaginal bleeding could be embarrassing and a hindrance to a good social life. However, reactions to variations from normal regular pattern of vaginal bleeding in contraceptive users depend on cultural and counselling factors [11]. Menstrual pattern changes are often encountered among progesterone contraceptive users, although the characteristics which predispose a woman to such alterations are unpredictable. In most clinical trials, menstrual alterations were reportedly the most important drawbacks to the use of subdermal implants [8-10]. In a study by Coutinho *et al* [9], approximately 22% of the 1,083 subjects using Uniplant(R) experienced irregular or unpredictable vaginal bleeding. Amenorrhoea and prolonged vaginal bleeding were less frequent. Similar alterations in menstrual pattern without haematological consequences was encountered in our study and irregular vaginal bleeding was the most prominent feature. In both studies, the majority of their subjects had acceptable menstrual patterns. The alterations in the menstrual patterns progressively decrease from the 1st trimester of Uniplant(R) use to the 4th as the body acclimatises with the progesterone in it. This trend was also seen in the menstrual cycle lengths of the users. By the 3rd trimester of use, the significant changes noted in the pre-insertion menstrual cycle had disappeared. Therefore Uniplant(R) users can expect temporary alteration of menstrual pattern in the first 6 months of use. These findings should form the basis for counselling in the family planning clinics.

The reasons that women give for stopping a method may sometimes not be their actual reasons due to the fear that the provider may not accept them [17]. Some may have been troubled by a number of side effects but give only what they think are the most important ones. Others may give reasons they have heard from others who have successfully stopped the same method instead of their personal ones. It is therefore noteworthy that majority(3.74%) of the withdrawals recorded in this study were due to method switch without a major reason. This indicates that these women were not completely satisfied with the Uniplant(R).

However, our overall discontinuation rate within a year of use of Uniplant(R) was as low as in other studies on its efficacy elsewhere [1,9,15]. Majority of cases were due to non-medical reasons. Although menstrual irregularities was common, discontinuation on this account was relatively few. If the single case of post coital bleeding due to cervical erosion is removed, unacceptable bleeding reported in 3.27% of the subjects was the commonest medical reasons for discontinuation. It is notable that discontinuation due to amenorrhoea was very few in keeping with reports elsewhere [9]. Therefore, it is unlikely that menstrual irregularities will be a hindrance to the acceptance of Uniplant(R) by majority of women who chose the method once they are properly counselled.

Overall health concerns, including physical vitalities, social activities, emotional wellbeing and sexual activities are often prominent reasons for acceptance or discontinuation of contraceptive methods by users. In a recent study in Chile, Barnhart *et al*, [18] reported that the changes in menstrual bleeding patterns of users of Uniplant(R) did not influence their sexual frequency, desire or enjoyment. In that study, although, there was a notable increase in menstrual irregularities and spotting, the frequency of sexual intercourse was unchanged. Also, there was no significant change in the users perception of health during the use of Uniplant(R). In another study, Uniplant(R) reportedly had no influence on lactation and infant wellbeing in breast feeding women using it. The mean weight of babies belonging to Uniplant(R) users were not significantly different from that of IUCD users in the same study [19]. The result of a multicenter user satisfaction study carried out in women using Uniplant(R) by Coutinho *et al*, [20] revealed a high level of satisfaction with Uniplant(R when compared with the users' previous contraceptive methods. These users were willing to recommend Uniplant(R) to others and continue with its use in future. However, in keeping with our findings, the changes in menstrual patterns were least liked by a third of their respondents.

In conclusion, changes in menstrual patterns in Uniplant(R) users occur mainly in the 1st and 2nd trimesters following insertion and are unlikely to have any deleterious effects on the general health of the users. Appropriate counselling of patients at insertion will ensure that users continue with the method in order to meet their contraceptive needs.

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