A multicentred phase III comparative study between single-implant containing 3-ketodesogestrel (Implanon®) and implants containing levonorgestrel (Norplant®) II. Vaginal bleeding patterns

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Abstrak

Uji klinik fase III dilakukan di 8 senter di Indonesia untuk membandingkan Implanon® dengan Norplant®. Efektivitas, penerimaan dan keamanan kedua kontrasepsi implant tersebut telah dilaporkan dalam makalah ini. Sejumlah 899 wanita Indonesia secara acak dipasang Implanon® atau Norplant®. Hanya 883 subyek yang dapat dianalisis pola perdarahannya. Analisis dilakukan berdasarkan "reference period" (RP) yang dikembangkan oleh WHO. Pada kelompok Implanon® analisis di lakukan pada 415 subyek pada RP I dan 271 subyek pada RP XII perlu. Sedangkan pada kelompok Norplant® analisis dilakukan pada 417 subyek dan 318 subyek. Penghentian pemakaian karena perdarahan tidak teratur terjadi pada 1,1% kelompok Implanon® dan 0.9% kelompok Norplant®. Sedangkan alasan amenorea hanya ditemukan pada 1 subyek pemakai Implanon® (0,2%). Rata-rata jumlah hari perdarahan dan bercak pada Implanon® 2,0 - 14,0 hari. Sedangkan pada Norplant® 6,0 - 12,0 hari. Sebagian besar perdarahan berupa bercak. Amenorea lebih banyak terjadi pada pemakai Implanon®. Terutama setelah RP III. Perbedaan ini secara statistik bermakna. Tidak ditemukan perbedaan bermakna dalam hal perdarahan jaring, sering dan lama.

Abstract

A multicentred Phase III clinical trial was conducted in Indonesia to compare two implantable contraceptives i.e. a single implant containing 3-ketodesogestrel (Implanon®) and implants containing levonorgestrel(Norplant®). Efficacy, acceptability and safety of both implants were reported in paper I. This paper reports the comparison of bleeding patterns. A total of 899 women were randomly assigned to each implantable contraceptive. The comparison of the bleeding patterns is made using a 90-day reference period approach according to WHO guidelines. A total of 883 subjects contributed to reference period analysis. In the Implanon® group 415 subjects contributed to the first reference period and 271 to the 12th reference period. In the Norplant® group those figures were 417 and 318 respectively. There were five subjects (1.1%) in the Implanon® group and 4 in the Norplant® group (0.9%) discontinued during the study due to bleeding irregularities. One subject (0.2%) in the Implanon® group and none in the Norplant® group discontinued due to amenorrhea. The median number of bleeding spotting days ranged over the first 12 reference periods from 2.0 to 14.0 for Implanon® and from 6.0 to 12.0 for Norplant®. For both groups, the majority of bleeding-spotting days were spotting days. In both groups the incidence of amenorrhea in reference period 3 was higher than in the previous reference periods. In reference periods 3 to 12 amenorrhea occurred statistically significantly more frequent in the Implanon® group compared to Norplant® group. Although the incindence of infrequent bleeding was initially high (approximately 60% in reference period 1), it decreased during the study to about 30% in reference period 3, while no significant differences (except for RP10)between groups were observed. The incidences of frequent bleeding and prolonged bleeding were low in both groups.

Keywords: *Implanon®, implant contraceptive, Norplant®, vaginal bleeding patterns, comparative study.*

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With the development of synthetic polymers, it has become possible to develop hormonal delivery systems with long duration of action and continuous release of the drug. Advantages of the long-term contraceptive implants are lack of concern for compliance and prompt return of fertility after removal.[1,2] Furthermore, the parenteral route of administration results in a lower metabolic burden on the liver than with oral contraceptives.

Implantable contraceptive method, one of long-acting progestin-only preparations, has been introduced to family planning programs since two decades ago. It is a successful method for long-term prevention of pregnancy.[3-5]

Studies indicated that implantable contraceptive with 3-ketodesogestrel is a promising method for further investigation.[6-9]

NV Organon (Oss, The Netherlands) has developed a single-rod implant containing 3-ketodesogestrel (Implanon®) with a length of 40 mm and a diameter of 2 mm, which is applied subdermally by a disposable sterile inserter. The rod is made of an ethylene vinyl acetate copolymer (EVA) with a core containing approximately 68 mg of etonogestrel (ENG) or 3-ketodesogestrel.

The initial release rate of the implant is approximately 67 µg/day which slowly decreases over time. The constant release profile results in sufficiently high plasma ENG concentrations (> 90 pg/ml) to inhibit ovulation for at least three years.[8,9]

ENG is a progestin, structurally derived from 19-nortestosterone; it is the biologically active metabolite of desogestrel (DSG). DSG is the progestin component of a number of widely used oral contraceptives with a well established efficacy and safety profile. The characteristics of the implant's EVA membrane, combined with the high specific progestational activity of ENG, allow the use of a single-rod system with a low and almost zero-order release. As a consequence of these properties, dose-related side effects are minimized. However, a known typical disadvantage of progestin-only methods is disruption of the normal menstrual cycle, including amenorrhea.

With the objective to find out the efficacy, acceptability and safety of Implanon®, a multicentered phase III comparative study between Implanon® and Norplant® conducted in Indonesia. The study showed no significant difference in efficacy, acceptability and side-effects between the two-implantable contraceptives. There was no single pregnancy occurred in 3 years in both groups. The continuation rates at year-3 were 90.9% for Implanon® group and 92.0% for Norplant® group. The difference is not significant ($p<0.01\%$). Discontinuation rates for vaginal bleeding irregularities were 0.9% for each group.

This paper presents a detailed analysis of menstrual diaries recorded by 883 (98%) of the women recruited to the study. The vaginal bleeding patterns induced by both implantable contraceptives are compared. The study was approved by National Ethics Committee and by the Ethics Committees of all study centres.

MATERIALS AND METHODS

Design of the study

The implantable contraceptives used in the study are Implanon® (single implant containing ENG) and Norplant® (six-implants containing LNG=levonorgestrel). Both implants were inserted in the inner-side of the upper arm.

Details of the study design, recruitment of the subject and flow chart of the study have been presented in Paper I. A total of 899 women entered the study in 8 centres in Indonesia. Each of them was provided with a menstrual diary with daily record of the occurrence of bleeding, spotting or neither. Only 883 of them brought the diary records back to the study centres.

Bleeding records from the diaries were collected every three months to assess vaginal bleeding patterns during the study. An additional return of the diary card was scheduled one month after implant insertion to ascertain proper recording. Each subject was required to record, in her diary, the bleeding pattern she experienced each day. She was instructed to record a "0" if she experienced no bleeding or spotting on a given day, an '/' if she experienced spotting (any bloody vaginal discharge for which no protection is used or only one pad on a given day), and a '+' if she experienced bleeding (any bloody vaginal discharge for which protection of two or more pads is used on a given day). If bleeding and spotting occurred on the same day, it was considered a bleeding day.

Statistical procedures

The analysis of the bleeding pattern, as recorded by the subjects on the diary cards, was performed by a reference period analysis according to WHO guidelines.[10-2]

The reference period analysis included all subjects treated (with some data excluded) who had at least one evaluable reference period, based on the following guidelines:

Analysis period

All bleeding data starting at the day of implant insertion and ending at the day of implant removal (or last assessment if subject was lost to follow up or continued with Norplan®) were used for analysis. Bleeding data outside this analysis period were not taken into account.

Length of reference period

The length of a reference period was defined as 90 days. Shorter reference periods were not included in the analysis. A 90-day reference period was used for this study because this duration was determined to be sufficient to allow several bleeding events to occur in a reference period. To be included in the analysis, a subject had to contribute at least one complete reference period of 90 days length.

Interpolation rule for missing values

If diary data with bleeding information were missing for ≤ 2 consecutive days, these missing values were converted to the same B-S response reported on the day immediately preceding the missing values (i.e. bleeding, spotting or bleeding free was imputed). If this missing information occurred on the first one or two days of treatment, then the immediately following day was used for interpolation.

Exclusion of reference periods

If diary data with bleeding information were missing for ≥ 3 consecutive days, then the complete reference period of this subject was excluded from analysis. If these missing values were spread across 2 reference periods, then both reference periods were excluded.

The analysis of vaginal bleeding patterns was based on the following standard WHO definitions used for summarisation of diary data with a modification used for infrequent bleeding.[10-1,13-6]

1. a 'bleeding-spotting episode' was defined as any set of one or more consecutive bleeding or spotting days bounded at each day by at least one bleeding-free day;
2. a 'bleeding-free interval' was defined as any set of one or more consecutive bleeding-free and spotting-free days bounded at each end by at least one bleeding or spotting day;
3. 'amenorrhea' was defined as no bleeding or no spotting throughout the reference period;
4. 'infrequent bleeding' was defined as less than three B-S episodes starting within a reference period excluding amenorrhea;
5. 'frequent bleeding' was defined as more than five B-S episodes starting within a reference period; and
6. 'prolonged bleeding' was defined by at least one B-S episode starting within a reference period and lasting more than 14 days.
7. 'irregular bleeding' was defined as 3 to 5 B-S episodes and less than 3 B-S free intervals of 14 days or more.

The following within-woman statistics, calculated for each subject for each reference period, are listed individually:

- number of bleeding days, spotting days, B-S days;
- number and mean length of B-S episodes;
- incidence of amenorrhea, infrequent bleeding, frequent bleeding, and prolonged bleeding.

Bleeding patterns were classified as normal pattern amenorrhea, infrequent bleeding, frequent bleeding and prolonged bleeding.

RESULTS

Reference period analysis

Table 1 compares the summary statistics for each reference period following the insertion by implant method. The number of diaries available for analysis in successive reference periods is also indicated.

The data emphasize differences in bleeding patterns between the first reference period and the following ones. The mean numbers of bleeding/spotting days, bleeding/spotting episodes, spotting days and bleeding days are becoming less and less in the following reference periods.

In the first reference period, there appears to be no substantial differences between the two implantable

Table 1. Reference period analysis comparison between Implanon® (I) and Norplant® (N)

	Implant Method	Reference Period (Mean ± SD) I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
Number of B/S days	I	15.5±12.9	9.1±12.1	8.1±11.7	7.3±10.5	6.5±9.9	7.3±11.1	7.2±9.5	7.5±9.6	7.5±9.2	7.8±9.7	8.1±10.0	6.9±9.1
	N	14.0±11.0	10.4±11.6	10.5±11.8	10.2±11.8	9.9±11.5	10.6±11.3	9.2±9.5	10.1±10.5	9.1±9.0	9.0±8.8	9.5±9.9	9.2±10.2
Number of B/S episodes	I	2.3±18	1.8±1.7	1.6±1.8	1.5±1.8	1.3±1.7	1.9±1.7	1.4±1.6	1.4±1.5	1.4±1.6	1.5±1.5	1.5±1.6	1.3±1.5
	N	2.2±1.5	2.0±1.6	2.0±1.8	1.9±1.8	1.8±1.8	2.0±1.9	1.8±1.7	1.8±1.5	1.7±1.6	1.7±1.4	1.8±1.5	1.7±1.5
Number of S days	I	10.0±10.7	5.9±9.3	4.6±7.7	3.8±7.0	3.6±6.4	4.2±7.2	4.1±7.0	4.1±7.5	4.2±6.7	4.4±7.7	4.7±7.9	4.1±6.5
	N	8.4±8.1	6.3±7.9	5.7±7.1	5.6±8.9	5.4±7.9	6.0±7.8	4.9±6.6	5.6±8.1	4.8±6.4	4.4±6.1	4.7±7.7	4.6±7.3
Number of B days	I	5.5±6.4	3.2±5.7	3.5±6.9	3.5±6.3	2.9±6.4	3.2±6.7	3.1±6.1	3.2±5.5	3.3±5.4	3.4±5.4	3.4±5.5	2.8±4.8
	N	5.6±6.9	4.1±7.4	4.8±8.3	4.6±6.8	4.4±6.8	4.6±7.2	4.3±6.4	4.5±6.3	4.3±5.8	4.6±5.8	4.8±6.1	4.6±6.1
Number of diaries for analysis	I	415	422	411	398	387	401	392	380	346	337	315	271
	N	417	418	420	399	401	397	412	393	360	342	322	318

contraceptive methods with respect to any of the summary statistics. However, in the following reference periods the mean numbers of bleeding episodes and bleeding days in Implanon® group are less compared to Norplant® group. There are no differences between the groups.

Figure 1 shows the number of bleeding/spotting days by reference period and implant group. The figure illustrates the extra bleeding/spotting days in the first reference period experienced by the subjects using both implantable contraceptive methods. The median being 14 for Implanon® and 12 days for Norplant® respectively. Thereafter the median numbers of bleeding/spotting days gradually reduces to 2 days for Implanon® and to 6 days for Norplant®. There appears to be no substantial differences between the two implantable contraceptive methods with respect to any of the summary statistics.

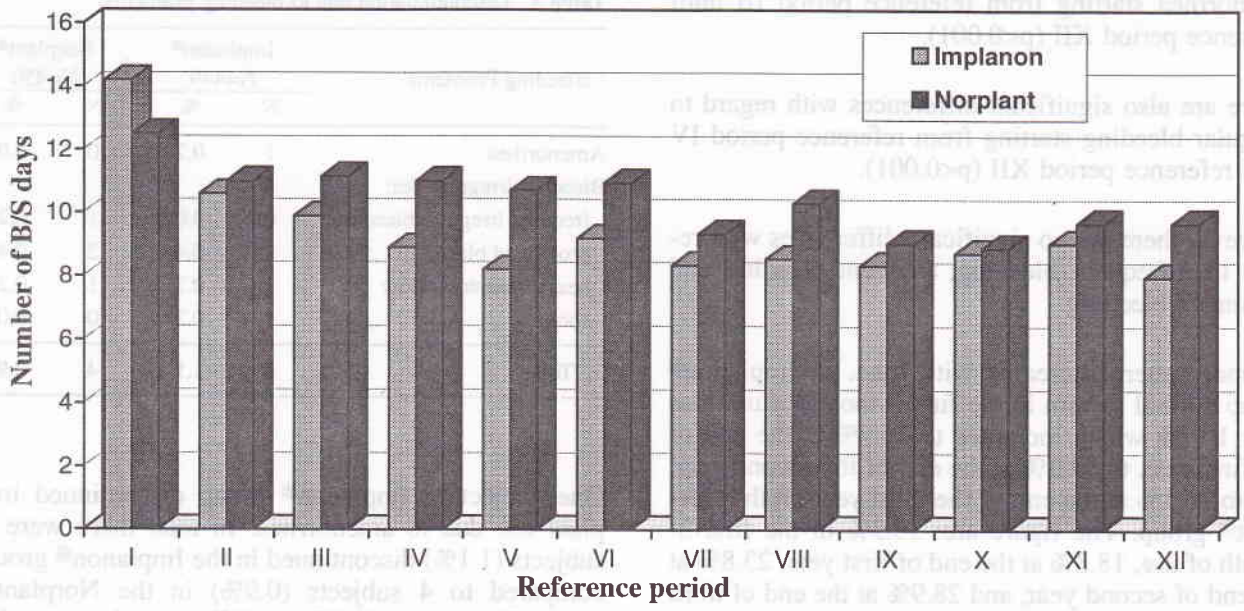

Figure 1. *Comparative trial of Implanon® and Norplant® Menstrual bleeding analysis, Number of bleeding/spotting days per reference period*

Table 2. Bleeding patterns comparison between Implanon® (I) and Norplant® (N)

	Implant Method	Reference Period (%) I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
Amenorrhea	I	3.9	26.8	42.3*	43.5*	45.2*	47.6*	42.6*	44.5*	43.1*	41.2*	43.5*	46.5*
	N	3.8	22.5	29.0	32.6	32.7	30.7	31.6	31.0	32.5	29.2	32.3	33.6
Infrequent bleeding	I	59.5	41.2	29.0	31.4	32.0	26.4	29.6	28.2	28.3	24.6	20.3	24.7
	N	58.8	42.3	31.0	29.6	33.9	29.0	32.8	33.6	30.0	35.1	26.4	29.6
Frequent bleeding	I	4.8	2.4	2.7	3.3	2.3	1.7	1.3	0.8	1.7	1.8	0.6	1.5
	N	2.9	3.1	4.8	4.3	2.5	3.8	2.9	2.3	1.7	0.9	0.9	0.9
Prolonged bleeding	I	8.7	4.0	3.9	3.0	3.1	3.2	2.6	3.2	2.9	2.7	2.5	2.2
	N	7.0	5.5	5.7	5.0	3.5	3.8	1.5	3.6	1.1	1.8	1.6	1.6
Irregular bleeding	I	12.4	10,1	8.9	3.1	1.4	1.3	1.1	1.0	1.2	1.8	0.7	0.0
	N	14.2	10.7	13.7	10.2*	9.3*	9.5*	6.0*	5.7*	7.6*	4.0*	4.5*	5.4*
"Normal" pattern	I	10.7	15.5	13.2	15.7	16.0	19.8	22.8	22.3	22.8	27.9	32.4	25.1
	N	13.3	15.9	15.8	18.3	18.1	23.6	25.2	23.8	27.1	29.0	34.3	28.9
Number of diaries for analysis	I	415	422	411	398	387	401	392	380	346	337	315	271
	N	417	418	420	399	401	397	412	393	360	342	322	318

*) $p<0.001$

Clinically important bleeding patterns

Table 2 shows the percentage of subjects in each implant group experiencing clinically important bleeding patterns in each successive reference period. There are significant differences between the two implantable contraceptive methods with respect to amenorrhea starting from reference period III until reference period XII ($p<0.001$).

There are also significant differences with regard to irregular bleeding starting from reference period IV until reference period XII ($p<0.001$).

However there are no significant differences with regard to infrequent bleeding, frequent bleeding and prolonged bleeding.

Normal pattern increases with time. In Implanon® group normal pattern in the first 3-month of use was only 10.7% which increases to 15.7% at the end of the first year, to 22.3% at the end of the second year, and to 25.1% at the end of the third year on the Norplant® group. The figure are: 13.3% in the first 3-month of use, 18.3% at the end of first year, 23.8% at the end of second year, and 28.9% at the end of third year. There are no significant differences between the groups.

Bleeding problems as a primary reason for discontinuation

A frequency table with all bleeding problems as a primary reason for discontinuation is presented in Table 3.

Table 3. Discontinuation due to bleeding problems

Bleeding Problems	Implanon® N=449		Norplant® N=450	
	N	%	N	%
Amenorrhea	1	0.2	0	0.0
Bleeding irregularities:				
frequent irregular bleeding	0	0.0	1	0.2
prolonged bleeding	2	0.4	2	0.4
heavy menstrual flow	1	0.2	1	0.2
spotting	1	0.2	0	0.0
Total	5	1.1	4	0.9

One subject in Implanon® group discontinued implant use due to amenorrhea. In total there were 5 subjects (1.1%) discontinued in the Implanon® group compared to 4 subjects (0.9%) in the Norplant® group. There is no significant differences between the groups.

DISCUSSION

A comparative clinical trial between Implanon® and Norplant® was conducted in 8 centres in Indonesia, 899 women were randomly assigned to either Implanon® or Norplant®. A total of 883 (98.2%) of them filled a menstrual diary for 3 years thus providing one of the largest menstrual bleeding data sets for a study of this kind.

Their analysis following the reference period method and the classification into vaginal bleeding patterns identified the following results:

1. The mean numbers of B-S days, B-S episodes, S days and B days are becoming less and less with time. There are no significant differences between the groups.
2. Starting from reference period III on, the incidence of amenorrhea among Implanon® users are significantly higher compared to Norplant® users ($p<0.001$).
3. Starting from reference period IV on, the incidence of irregular bleeding among Implanon® users are significantly lower than Norplant® users ($p<0.001$).
4. "Normal" bleeding pattern increases with time. There are no significant differences between the groups.
5. There are no significant differences between the groups with respect to discontinuation due to bleeding problems being 1.1% in the Implanon® group and 0.9% in the Norplant® group.

Acknowledgement

The study was conducted as part of Implanon® Research and Development Program, sponsored and coordinated by NV Organon, Oss, the Netherlands.

Thanks are due to Dr. Stevenson from N.V. Organon Holland for Good Clinical Practice Monitoring, to Drs. Wardojo Gadroen, Bandar Damanik and Susilo from Organon Indonesia for study monitoring, to Dra. Rosminah from Klinik Raden Saleh for patients coordination, to Drs. A.G.M. Theeuwes and R.M.V. Stoleman from SOG NV Organon, Dr. Joedo Prihartono and Sujadi from University of Indonesia for statistical analysis and to Dr. Tan Shot Yen for secretarial assistance.

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