A multicentred phase III comparative study between single-implant containing 3-ketodesogestrel (Implanon®) and implants containing levonorgestrel (Norplant®)
I. Efficacy, acceptability and safety (three-year results)

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Abstrak

Untuk mengetahui efektivitas, penerimaan dan keamanan Implanon®, dilakukan uji klinik acak multisenter. Norplant® dipakai sebagai pembanding. Sebanyak 898 wanita direkrut dalam penelitian ini di delapan senter. "Follow-up" dilakukan selama 3 tahun. Waktu insersi rata-rata Implanon® 0, 8 menit, sedangkan Norplant® 4,4 menit. Waktu pencabutan Implanon® 4,9 menit, sedangkan Norplant® 30,2 menit. Kedua perbedaan tersebut bermakna (p<0,01). Selama tiga tahun memakai implan tidak ada satupun subyek yang hamil, baik yang memakai Implanon® maupun Norplant®. Kelangsungan pemakaian 1 tahun Implanon®: 97,3% sedangkan Norplant ®97,6%. Setelah tiga tahun, Implanon®: 90,6% dan Norplant® 92,0%. Tidak ditemukan perbedaan yang bermakna antara kedua kelompok. Tidak ditemukan efek samping yang serius pada kedua kelompok.

Abstract

With the objective to evaluate the efficacy, acceptability and safety of subdermal-single-rod ethylene vinyl acetate (EVA) implant contraceptive containing 68 mg 3-ketodesogestrel (Implanon®), a multicentred comparative study has been conducted between Implanon® and Norplant® (subdermal implant contraceptive consisting of six silastic capsules, each capsule containing 36 mg levonorgestrel). A total of 898 women were recruited into an eight centre, randomized clinical trial. One subject was excluded from the study because she had been already pregnant when the implant inserted. Follow up scheduled for 3 years. The mean insertion time was 0.8 minute for Implanon® and 4.4 minutes for Norplant®. The mean removal time was 4.9 minutes for Implanon® and 30.2 minutes for Norplant®. These differences are statiscally significant (p<0.01). In three- year follow up, the study showed none of the subjects became pregnant in both groups. One-year continuation rates were 97.3 per hundred women for Implanon® and 97.6 per hundred women for Norplant®. After three years the continuation rates were 90.6 and 92.0 respectively. In Implanon® group there were 42 subjects discontinued the method use. The reasons were: bleeding irregularities (4 subject), amenorrhoea (1 subject), other medical reasons (4 subjects) non-medical reasons (24 subjects) and lost to follow- up (9 subjects). While in Norplant® group there were 36 subjects discontinued the method use. The reasons were bleeding irregularities (4 subjects), other medical reason (5 subjects), non-medical reasons (11 subjects), and lost to-follow up (16 subject). There are no statistically significant differences between the groups. None of the subjects in both groups suffered from serious side-effects.

Keywords: *Implanon®, Norplant®, implant contraceptives, comparative study, phase III.*

Within the past 35 years, steroidal preparations have become available which allow the user contraceptive protection over extended periods of time, either because of their intrinsic long-acting properties such as injectable contraceptive or through the use of various delivery systems, e.g. implants, IUDs or vaginal

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rings. Implantable contraceptives are a successful method for long term prevention of pregnancy.[1,2]

It is estimated that in 1997 in the world some 3 million women opted implantable contraceptives (mainly Norplant®) as their method of contraception. Norplant® -implant contraceptive consists of 6 capsules.

In response to the demand for a single implantable contraceptive with high efficacy, high acceptability and safety NV Organon (Oss, the Netherlands) developed a single-rod implant containing 68 mg 3-ketodesogestrel or etonogestrel (ENG). The rod is made of an ethylene vinyl acetate (EVA) copolymer. The initial rate of the implant is approximately 67 µg/day which slowly decreases over time. The constant release profile results in sufficiently high plasma ENG contraceptions (90 pg/ml) to inhibit ovulation for at least three years.[3]

Etonogestrel (ENG) is a progestin, structurally derived from 16-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 characteristic 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.[4-6]

With the objective to find out the efficacy, acceptability and safety of Implanon® a randomized- multicentred comparative study between Implanon® and Norplant® has been conducted in Indonesia. The study was approved by the Ethics Committee of all study centres.

MATERIALS AND METHODS

Implantable contraceptives

Implanon® is a single-rod EVA implant with a length of 40 mm and a diameter of 2 mm, containing 68 mg ETN, was manufactured by NV Organon, Oss, Netherlands.

Implanon® is delivered in the needle of a sterile, disposable specially designed inserted which was packed individually in a aluminium sachet.

Norplant® is a six-capsule silastic implant with a length of 34 mm and a diameter of 2.4 mm, each capsule contains 36 mg levonorgestrel (LNG), was manufactured by Leiras, Turku, Finland.

Both implants were inserted in the inner part of upper arm. The insertion procedure had been published elsewhere.

Design of the study

All subjects were normal, healthy, women between 18 and 40 years of age. They were not pregnant or lactating but were sexually active and childbearing potential, had regular menstrual cycles. The women consented voluntarily to participate in the trial and were free to have the implant(s) removed at any time during the study.

Contra-indicators to recruitment were significant gynecological disorder of uterus and or ovaries, which include tumors, trophoblastic disease, undiagnosed vaginal bleeding, history of ectopic pregnancy, history of pelvic inflammatory disease and Papanicolaou smear of grade III or higher; history of herpes gestations, uncontrolled significant endocrine disorder, history of breast discharge (other than lactation), benign or malignant tumors of liver function, history of hyperlipoproteinaemia, hypertension i.e. systolic >140 mmHg and or diastolic > 90 mmHg, past or present otosclerosis, porphyria, abnormal laboratory values which are clinically relevant, Hb < 10 g%.

Women were also excluded if they used one or more of the following drugs: sex steroids, hydantoins, barbiturates, pirimidone, carbamazepine, rifampicine and griseofulvin. They should not have received injectable-contraceptives in the 6 months prior to admission or any investigational drug in the previous 2 months.

In the cycle prior to admission into the study the women had a screening interview and a physical examination to a certain whether they confirmed to the admission criteria.

Those women who did were asked to return to the clinic during the first 5 days of their next menstrual cycle.

At this time they were admitted into the study, assigned at random to one of the two implant group,

Table 1. Flow chart of the study

	Time in months	Vital signs (weight, BP)	Gynecol. exam	Physical exam	Cervical pap smear	Hb
Screening	-1					
1st year	0	x				
	3	x				
	6	x				
	9	x				
	12	x	x	x		
2nd year	15	x				
	18	x				
	21	x				
	24	x	x	x	x	x
3rd year	27	x				
	30	x				
	33	x				
	36	x	x	x	x	x

and had the implant inserted. The procedures of Implanon® and Norplant® insertions had been published in details elsewhere. They were then scheduled to return to the clinic for follow-up visit every 3 months, until 36 months. In every follow-up visit the women had a complete physical examination and recordings were made of weight, blood pressure and drugs taken during the period. The flow chart of the study is described in Table 1.

Each subject was given a vaginal bleeding record card at every 3-month visit and requested to note the days on which bleeding or spotting occurred. At each follow-up visit, any complaints by the women which were elicited by indirect questioning, recorded. Each subject could also attend the clinic at any time for unscheduled visits, at which time she could also report her complaints. If a subject wished to discontinue method use for any reason or was advised to by the physician responsible for the study, then a record was made of the one or two principal reasons given for her discontinuation together with full physical examination. The implant(s) were removed. The procedures of removal were published elsewhere.

It was assumed from previous studies that Implanon® would be effective in preventing pregnancy for at least 3 years. However, the study would have been terminated at any time if the lower 95% confidence limit of the pregnancy rate exceeds 3 pregnancies per 100- women-years.

Assuming a cumulative continuation rate at 12 months, 24 months and 36 months were 95%, 90% and 85% for both implant(s) which was observed in previous studies, a sample size of 450 women in each group was determined as large enough to rule out any difference in cumulative continuation rates between the two implantable contraceptives.

The study was undertaken at the Department of Obstetrics and Gynecology, Faculty of Medicine/ Teaching Hospitals in the following cities: Medan, Palembang, Jakarta (2 centres), Semarang, Surabaya, Malang and Ujung Pandang. This paper is reporting three-year results of the study.

RESULTS

Profile of subjects

The study was started in November 1992 and the last assessment was completed in February 1997. In all, a total of 899 women were admitted. Table 2 shows the numbers of eligible subjects recruited at each centre.

Table 2. Number of subjects by centre

Centre	Number of subjects
Medan	100
Palembang	100
Jakarta: Raden Saleh	99
Jakarta: Gatot Subroto	100
Semarang	150
Surabaya	150
Malang	100
Ujung Pandang	100
Total	899

The admission characteristics of the women are summarized in Table 3 by implant type and show that the two groups were very similar with respect to age, weight, height, quetlet index, systolic and diastolic blood pressure and previous contraceptive history.

One subject in Implanon® group (subject 0042) had been pregnant at admission. The pregnancy was diagnosed on day 85 after Implanon® insertion. The diagnosis was based on clinical judgement and a gestational age of 22 weeks was estimated. The pregnancy continued without complications and ended in a spontaneous full term delivery of a girl, 34.5 weeks after Implanon® insertion. The child was examined by a pediatrician at the age of 2.5 years and no abnormalities were found.

Table 3. Characteristics of subjects

		Implanon®	Norplant®	Total
Number of subjects		449	450	899
Age (years)	mean	29.0	29.5	29.2
	SD	5.0	5.3	5.2
Weight (kg)	mean	49.6	50.0	49.8
	SD	8.4	8.3	8.3
Height (m)	mean	152.6	152.4	152.5
	SD	5.4	5.3	5.4
Quetlet index (kg/m²)	mean	21.3	21.5	21.4
	SD	3.4	3.1	3.3
Blood pressure(mmHg)				
systolic	mean	114.1	114.3	114.2
	SD	9.5	9.8	9.6
diastolic	mean	74.6	74.9	74.8
	SD	7.4	7.7	7.5
Previous contraception (%)				
none		30.1	33.1	31.6
pill		29.2	34.0	31.6
implantable		5.3	5.1	5.2
injectable		12.0	9.3	10.7
IUD		18.9	16.2	17.6
condom, spermicide		3.6	2.2	2.9
other		0.9	0.0	0.4

Efficacy

There was no pregnancy occurred in both groups making the one-year cumulative pregnancy rate for both implant groups 0.0%.

The number of subjects who completed the study, discontinued implants use or were lost to follow up is shown in Table 4. A total of 407 subjects completed 3 year study in Implanon® group and 414 subjects in Norplant® group.

Table 4. Cumulative events for terminating study by number of subjects at 3 years

Reasons for terminating study	Cumulative events					
	Implanon® (N=448)			Norplant® (N=450)		
	year-1	year-2	year-3	year-1	year-2	year-3
Pregnancy	0	0	0	0	0	0
Amenorrhea	0	0	1	0	0	0
Bleeding irregularities	1	3	4	0	3	4
Other medical	1	2	4	2	4	5
Non-medical	5	12	23	3	5	11
Lost to follow-up	5	7	9	6	8	16
Total terminating	12	24	41	11	20	36
Total completing study	436	424	407	439	430	414

Table 5. Cumulative life-table discontinuation and continuation rates at 3 years

Reasons for terminating study	Cumulative rates					
	Implanon® (N=448)			Norplant® (N=450)		
	year-1	year-2	year-3	year-1	year-2	year-3
Pregnancy	0.0	0.0	0.0	0.0	0.0	0.0
Amenorrhea	0.0	0.0	0.2	0.0	0.0	0.0
Bleeding irregularities	0.2	0.7	0.9	0.0	0.7	0.9
Other medical	0.2	0.4	0.9	0.4	0.9	1.1
Non-medical	1.1	2.6	5.1	0.7	1.1	2.4
Lost to follow-up	1.1	1.6	2.0	1.3	1.8	3.6
Discontinuation	2.6	5.3	9.1	2.4	4.5	8.0
Continuation	97.4	94.7	90.9	97.6	95.5	92.0

Acceptability

Table 5 shows that the continuation rates for year-2 and year-3 are 94.7% and 90.9% for Implanon and 95.5% and 92.0% for Norplant. There are no significant differences between the groups.

Reasons for discontinuation

After 3 years some 41 subjects (9.1%) discontinued Implanon® Table 5. Cumulative life-table discontinuation and continuation rates at 3 years use i.e. 9 subjects (2.0%) were lost to follow up and the remaining 32 subjects (7.1%) discontinued Implanon® use because of one the reasons listed in Table 4.

Amenorrhea and bleeding irregularities

Only one subject discontinued for amenorrhea i.e. an Implanon® user in year-3 (0.2%). There was no subject in Norplant® group discontinued for amenorrhea.

A total of 8 subjects discontinued for bleeding irregularities. Of these 4 subjects used Implanon® and another 4 subjects used Norplant®, giving cumulative discontinuation rates at three year of 0.9% each.

Other medical reasons

There were 4 subjects (0.9%) discontinued Implanon® use for other medical reasons; 5 subjects (1.1%) discontinued Norplant® use for the same reasons. There was no subject was hospitalized during the course of the study.

Non medical reasons

A total of 23 subjects (5.1%) discontinued Implanon® use for non medical reasons; 11 subjects (2.4%) discontinued Norplant® use for the same reasons.

Weight gain

The combined weight-gain of all subjects in the study was equivalent to 1.15 kgs per year. No statistically significant differences were observed between implant groups.

Blood pressure change

There was a small mean decrease in systolic blood pressure of 0.3 mmHg per year in Implanon® group and 0.7 mmHg per year in Norplant® group.

The decrease in diastolic blood pressure was 0.1 in Implanon group and 0.5 in Norplant® group.

There were no statistically differences between the groups.

Insertion and removal of the implant

Implant insertion and removal times are summarized in Table 6. Both the time required for insertion, as the time required for removal was considerably lower in Implanon® group compared to the Norplant® group. Insertion times ranged from about 0.03 to 5.0 minutes with a median of 0.5 minutes in the Implanon® group and from 0.8 to 11.0 minutes with a median of 4.0 minutes in the Norplant® group. The difference is statistically significant ($p<0.01$)

Removal times ranged from 1.2 to 15.2 minutes with a median of 2.0 minutes in the Implanon® group and from 5.0 to 50.0 minutes with a median of 32.5 minutes in the Norplant® group.

Table 6. Summary statistics for implant insertion and removal time all-subjects-treated group

Time (minutes)		Implanon® (N= 448)	Norplant® (N=450)
Required for insertion*	n	445	442
	mean	0.8	4.4
	SD	0.7	2.1
	median	0.5	4.0
	min-max	0.03-5.0	0.8-11.0
Required for removal**	n	401	48
	mean	2.6	11.1
	SD	2.0	10.5
	median	2.0	7.4
	min-max	0.17-15.2	1.33-50.0

* *for three subjects in the Implanon® group and eight subjects in the Norplant® group insertion time was missing*
** *for two subjects in the Implanon® group removal time was missing*

The assessments of the condition of the implant site are summarized in Table 7. Almost all of the subjects reported no abnormalities during any of the assessments. In Table 7 group swelling was reported by three subjects of whom one subject had also reported redness. One subject discontinued due to reaction at implant site (infection). In the Norplant® group three subjects reported pain and one subject swelling. An additional subject in the Norplant® group reported expulsion on day 110 and discontinued from the study.

A complication during implantation (Table 8) was reported for one subject in the Implanon® group, where some bleeding (about 1 ml) was reported. None of the subjects in the Implanon® group had complications during removal, while in the Norplant® group in one subject one capsule was broken, which was removed at a later occasion when the incision area had healed.

Table 8. Complications with Implant insertion or removal all-subjects-treated group

		Implanon®	Norplant®
Insertion complications	N	448	450
	n (%)	1(0.2)	0(0.0)
Removal complications	N	8*	6
	n (%)	0(0.0)	1(16.7)

* *excluding missing value for one subject*

Scar formation was assessed during the month-1 assessment after implant insertion. The result are summarized in Table 8. A scar was visible in 40.6 % of the subjects in the Implanon® group. For those subjects where a scar was visible, the size was smaller in the Implanon® group (mean 1.5 mm) compared to the Norplant® group (mean 2.8 mm).

Table 9. Scar formation after insertion all-subjects-treated group

	Implanon® (N=448)	Norplant® (N=450)
Scar visible* n (%)		
No	265 (59.4)	65 (14.6)
Yes	181 (40.6)	381 (85.4)
Scar size (mm)		
mean (SD)	1.5 (0.7)	2.8 (1.2)
median	1.0	2.0

* *for three subjects in the Implanon® group and four in the Norplant® group no data for visible scar were available.*

Table 7. Condition of Implant Site All-subjects-treated-group

Condition	Implanon® (N=448)*				Norplant® (N=450)*			
	Any time		Last measurement		Any time		Last measurement	
	n	%	n	%	n	%	n	%
No Abnormalities	445	99.3	446	99.6	441	98.4	443	99.3
Swelling	3	0.7	2	0.4	2	0.4	1	0.2
Redness	1	0.2	1	0.2	0	0.0	0	0.0
Pain	0	0.0	0	0.0	4	0.9	1	0.2
Hematoma	0	0.0	0	0.0	0	0.0	0	0.0
Expulsion	0	0.0	0	0.0	1	0.2	1	0.2

* *two subjects in the Implanon® group and four subjects in the Norplant® group did not show up for any assessment of status of implant site.*

Vaginal bleeding analysis

Completed bleeding record cards were obtained from the women throughout the study. Paper II will describe bleeding patterns as determined by analysis of these records.

DISCUSSION

This randomized, controlled clinical trial provided 1243.7 woman-years of method use with Implanon® and 1338.4 woman-years of method use with Norplant®.

With regard to contraceptive efficacy, no pregnancy due to method failure was reported in those subjects in Implanon® group nor in Norplant® group.

Implanon® is therefore highly effective and compare favorably with the efficacy of Norplant®.

There was no difference between the two implantable contraceptives, in term of overall discontinuation rates. Nor, as can be seen in Table 4, were there any differences in any of the specific reasons given for discontinuation between the two implants.

There was a slight mean weight gain over the year of study (1.15 kg), however there was no subject discontinued the method use for this reason. With regard to blood pressure, there was a small mean decrease both in systolic and diastolic blood pressure, in both groups, over the period of three year. There was no subject discontinued the method use for this particular reason. Overall, neither implant gave rise to the unexpected side effects.

Similarly, no non medical reasons could be related to either implant group although as stated below, non medical reasons are sometimes given by subjects who wish to discontinue the method even though they may not be the real reasons for discontinuation. Hence, caution must be applied in interpretation of discontinuation for non medical reasons. It should be stressed that this is an analysis of reasons for discontinuation as given by the subject and interpreted by the clinic physician to be recorded on data collection form. Hence it relates to the perceptions of the woman about the method. The reason for discontinuation, however, can be unrelated to any physiological or perceived event but could be a reason which the subject felt would be considered appropriate by the investigator.

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 for statistical analysis and to Dr. Tan Shot Yen for secretarial assistance.

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