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A multicentre efficacy and safety study of the single contraceptive implant Implanon®

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An open, multicentre study was performed to assess efficacy, safety and acceptability of the single-rod contraceptive implant Implanon®. The study involved 635 young healthy women, who were sexually active and of childbearing potential. The women were followed up every 3 months over the entire study period. Originally the study was designed for 2 years, but was extended to 3 years in a group of 147 women from two centres. Altogether, 21 centres in nine different countries participated. The average age of the women was 29 years (range 18–42 years), of whom 83.5% had been pregnant in the past. No pregnancy occurred during treatment with Implanon®, resulting in a Pearl Index of 0 (95% confidence interval: 0.0–0.2). In the first 2 years, 31% had discontinued the treatment. Of the 147 women in the study extension, nine discontinued (6%) treatment. Bleeding irregularities was the main reason for discontinuation during the first 2 years of use (17.2%) and adverse experiences in the third year (3.4%). Implant insertion and removal were fast and uncomplicated in the vast majority (97%) of cases. Return of fertility was prompt. In conclusion, Implanon® has excellent contraceptive action during its lifetime of 3 years. The safety profile is acceptable and not essentially different from progestogens in general.

Key words: contraceptive implant/efficacy/Implanon®/safety/vaginal bleeding

Introduction

Implanon® is a single-rod implant (NV Organon, Oss, The Netherlands) made of an ethylene vinyl acetate copolymer (EVA) with a core containing 68 mg of etonogestrel (3-ketodesogestrel). The implant has a length of 40 mm and a diameter of 2 mm and is provided in a sterile disposable inserter for subdermal application. Contraceptive action is mainly by inhibition of ovulation and lasts for 3 years (Makarainen *et al.*, 1998).

The study was designed to determine contraceptive reliability by means of a pregnancy rate, safety by means of regular medical examinations and assessment of adverse experiences, and acceptability by means of vaginal bleeding patterns. Data were collected in 21 centres situated in nine different countries. The number of women required to provide at least 10 000 cycles of 28 days was calculated to be ~600.

Materials and methods

The study was designed to include healthy women, who were sexually active, of childbearing potential and requesting contraception. Their age had to be between 18 and 40 years. The volunteers were included if they had menstrual cycles with a length of 24–35 days with an intra-individual variation of at most ±3 days. Pregnancy and breastfeeding were exclusion criteria and so was weight outside 80–130% of ideal (Metropolitan Height and Weight Tables, 1983). In general, we used the same recommendations as published in 'Labeling guidance text for progestin-only oral contraceptives' (Corfman, 1995). Liver enzyme inducing medication was not allowed during the study. All volunteers gave their consent in writing after receiving full information on Implanon® and the requirements of the study.

The implant was inserted in the inner aspect of the non-dominant upper arm. The woman had to be on or between days 1–5 of a spontaneous menses. The protocol for the study was submitted to National Health Authorities and to Ethics Committees of the respective sites. The study started in November 1991 and was completed in December 1996. Originally the study was designed to last for 2 years, which was later extended to 3 years in two centres. The decision was based upon data obtained in-vitro, ex-vivo and non-human data. Human data, obtained in sterilized women exposed to an extracted implant, revealed that ovulation inhibition was sustained for longer than 2 years (Davies *et al.*, 1993).

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The assessment schedule was as follows: at baseline medical history and gynaecological history were taken and a physical and pelvic examination including a cervical smear according to Papanicolaou (Pap) were done. The Pap smear at baseline was omitted if results Pap I or II were obtained <1 year previously. The medical examinations were repeated once every year or at the time of implant removal. Body height was recorded at baseline and so were weight and blood pressure (BP). The latter two variables were also recorded at months 3, 6, 12, 18, 24, 27, 30, 33 and 36. Status at implant site was checked once every 3 months and so was the bleeding card to see whether a pregnancy test was indicated in case of amenorrhoea. Women were asked to communicate unwanted effects at each visit and were instructed in further proceedings of the study.

Statistical methods

In the calculation of the percentages of discontinuation, the denominator excluded women who were lost to follow-up. The analysis of the bleeding pattern was done using 90-day reference periods (Rodriguez *et al.*, 1976; Belsey *et al.*, 1986; Belsey and Farley, 1988). The first reference period of 90 days started on the day of implant placement. For the analysis of the bleeding pattern, the following definitions were used: amenorrhoea was defined as no bleeding or spotting throughout the reference period. Infrequent bleeding was defined as fewer than three bleeding-spotting episodes (B-S) starting within a reference period, excluding amenorrhoea. Frequent bleeding was defined as more than five B-S episodes starting within a reference period and prolonged bleeding was defined by at least one B-S episode starting within a reference period and lasting >14 days. A B-S episode was defined as any set of ⩾1 consecutive bleeding or spotting days bounded at each end by at least 1 bleeding-free day. Coding of adverse experiences was done using the WHO adverse reactions terminology (WHO Adverse Reaction Dictionary, 1994).

Results

In 635 volunteers, the implant was inserted. Not all women fulfilled the inclusion/exclusion criteria. Most importantly, four women were pregnant at the start of the study. They received an implant as the nidation bleeding was mistaken for a menses. One of these pregnancies was ectopic and a salpingectomy was indicated. Two women had an induced abortion and one gave birth to a healthy baby girl. In the latter woman, the implant was removed 30 days after it was placed. The other three women continued with their implants. Other protocol violations were: age >40 years, weight >130% of ideal and irregular menstrual cycles. Once a woman was included in the study, her data were included in the results.

Centres varied in size between six and 114 volunteers. The centres in Budapest (n = 114) and Santiago (n = 107) contributed substantially more volunteers than the other centres. A total of 147 volunteers from these two centres entered the third year of study. Safety and bleeding data from Chile (n = 107), Hungary with three centres (n = 195) and the remaining centres (n = 333) were compared to detect possible centre effects. Regarding bleeding data, no major differences were observed. Safety reporting, however, showed a difference which is the reason for presenting the adverse experiences by centre (region).

Relevant characteristics of the study population are presented in Table I. The average age at baseline of the total study population was 29 years and 41% of the women were smokers. Baseline characteristics of those who continued for a third year are also presented. Although those who continued were slightly younger at baseline, they were also of slightly higher parity. Of the total study population, 9% were >75 kg in weight at the start of the study, with one woman weighing as much as 110 kg. Those who continued with the implant for a third year were, in 3.4% of cases, >75 kg in weight at the start of the study.

The total exposure to Implanon® was 1200 woman-years or 15 653 28-day cycles. No pregnancies occurred during treatment, resulting in a Pearl Index of 0 (95% confidence interval 0.0–0.2). Altogether, 436 women completed 2 years of treatment (out of 635). In all, 162 women were given the option to participate for a third treatment year. From these, 147 decided to continue, of whom 137 completed. Cycles provided by those who discontinued treatment are included in the total of 15 653.

Discontinuation was as follows: 10% (n = 64) after 6 months. At 12 months, another 62 women had discontinued treatment, resulting in a total of 126 (20%). After 24 months the total number of women who discontinued was 196 (31%). In the third year, 6% (n = 9) discontinued. For calculation of the percentage of discontinuation at 36 months, a different denominator (n = 147) is required due to extension of the study in a sub-group of women only. The reasons for discontinuation are presented in Table II, together with numbers and percentages.

The majority of women who discontinued the method, 17.2% in the first 2 years and 0.7% in the third year, did so because of an unacceptable bleeding pattern. Women who dropped out for 'other reasons' (3.5 and 2.0% in 2 years and the third year respectively) included those who wanted to become pregnant, those who were no longer in need of a contraceptive method, or those moving away from the study centre.

Of the total study population, 603 women contributed at least one reference period for analysis. If a woman had taken sex steroids or liver enzyme inducing drugs during the study, which was not allowed according to protocol, her data were (partly) excluded from the bleeding analysis. The reasons for discontinuation due to an unacceptable bleeding pattern are categorized and presented in Table III. The clinically most important bleeding indices, together with the numbers of women contributing, are presented in Table IV. It must be borne in mind that the high percentages reported for 'infrequent bleeding' do not include those women having amenorrhoea. The bleeding categories mentioned in Table IV are distinctly different from each other, except for 'prolonged bleeding' which may occur together with 'infrequent bleeding' as well as with 'frequent bleeding'. From reference period 9 onwards the study population is different. Only Budapest and Santiago contributed to reference periods 9–12. The declining incidences of amenorrhoea over the first eight reference periods subsequently show an increase at reference period 9 due to the different population involved.

Safety was monitored by recording of adverse experiences other than bleeding problems, including serious adverse experiences. Serious adverse experiences were those fulfilling the

Table I. Characteristics of the Implanon® study population at baseline

	Two years		Three years			Two years		Three years	
	n = 635	%	*n* = 147	%		*n*	%	*n*	%
Age (years)					Pregnancy				
Mean	29.1		28.2		0	105	16.5	18	12.2
SD	5.6		5.7		1	115	18.1	30	20.4
18–20	39	6.1	14	9.5	2	198	31.2	46	31.3
21–25	147	23.1	36	24.5	3	121	19.1	30	20.4
26–30	192	30.2	48	32.7	>3	96	15.1	23	15.6
31–35	167	26.3	30	20.4					
36–40	86	13.5	19	12.9	Parity				
>40	4	0.6	0		0	145	22.8	28	19.0
Height (cm)					1	154	24.3	37	25.2
Mean	164.4		161.3		2	238	37.5	52	35.4
SD	6.8		6.5		3	81	12.8	28	19.0
Body weight (kg)					>3	17	2.7	2	1.4
Mean	61.6		59.1						
SD	8.7		7.2						
Weight >70 kg	120	18.9	15	10.2	Last contraceptive method[a]				
Body mass index (kg/m^2)					None	15	2.4	0	
Mean	22.7		22.7		Oral contraceptive	336	52.9	65	44.2
SD	2.8		2.7		Implant	2	0.3	1	0.7
⩽20	116	18.3	20	13.6	Injectable	2	0.3	0	
>20–22	153	24.1	41	27.9	IUD	115	18.1	32	21.8
>22–24	178	28.0	50	34.0	Condom, diaphragm, spermicide	143	22.5	38	25.9
>24–26	100	15.7	17	11.6	Other	30	4.7	11	7.5
>26	88	13.9	19	12.9					

[a]More than one method was possible.

definition: 'any experience that is either fatal or life-threatening, permanently disabling, requiring in-patient hospitalization or prolongs hospitalization, or is a congenital anomaly, cancer or an overdose'. Adverse experiences were recorded as those symptoms that either newly occurred or increased in frequency and/or severity, when compared to baseline.

The severity of serious adverse experiences as well as of adverse experiences was classified by the investigator as mild, moderate or severe. In Table V, an overall assessment is presented of adverse experiences during 3 years of treatment. Those adverse experiences that were in the investigator's opinion possibly, probably or definitely drug-related are presented as drug-related.

Of the 50 serious adverse experiences, the following six cases were judged by the investigators to be possibly related to treatment with Implanon®: uterine fibroid, ovarian cyst, intraductal papilloma with fibrocystic mastopathy, headache, transient ischaemic attack (TIA) and 'raised heart rate with pressure over chest'. The woman with the TIA had no pathological findings, i.e. no signs of demyelination on magnetic resonance imaging and the computerized tomography scans were normal. The preliminary diagnosis TIA could not be substantiated but remained. The headache, which was mild, was accompanied by fever. It developed after 187 days on treatment and the woman was withdrawn from the study. The woman who developed 'cardiac' symptoms first noticed these half a day after implant insertion. The symptoms worsened over the next 3 days and the implant was therefore removed. Symptoms remained for at least another week. The half-life of elimination of etonogestrel is ~24 h and a drug relationship therefore appears doubtful. Ovarian cysts were diagnosed by gynaecological examination and followed up by ultrasound. All were found to disappear spontaneously.

Table II. Reasons for discontinuation

Primary reason for discontinuation	Implanon®			
	2 years *n* = 635		3rd year extension *n* = 147	
	n	%	*n*	%
Amenorrhoea	11	1.7	0	
Bleeding irregularities	109	17.2	1	0.7
Other adverse experiences	54	8.5	5	3.4
Other reasons	22	3.5	3	2.0
(Lost to follow-up	3	0.5	1	0.7)

Adverse experiences that were reported by >5% of the volunteers are presented in Table VI. Reporting in Santiago (Chile) is substantially higher than in the other centres, due to a different method of recording. Hungary consisted of three centres, one of which was Budapest in which the study extension took place. Adverse experiences reported in the third year are shown separately. These are newly reported, i.e. first occurrences in the third year. There were no remarkable changes in physical and pelvic examination findings.

At baseline the Pap smear had to be class I or II. During treatment and at implant removal changes were recorded. Pap class IV or V was not recorded at any time. In two women a conization was done, indicated by Pap smear findings. In other cases where Pap III was seen, this either resolved spontaneously or upon treatment with antibiotics.

At the start of the study, 36% of the women had a history of dysmenorrhoea. At the end of the study dysmenorrhoea had improved in 87% of the women who had dysmenorrhoea before they received the implant. In 4% this symptom was reported as a new occurrence or as worsening of existing dysmenorrhoea.

Acne, which is one of the most frequently reported adverse experiences, was also recorded at baseline (history). At the end of the study, women were asked about this adverse experience. In 12.8% of the women, acne had improved during treatment with Implanon®, whilst in 12.6% this symptom was new or had worsened.

The BP was measured frequently during the period of study. A systolic BP recording that was >140 mmHg and had increased >20 mmHg from baseline during at least two assessments or at the last assessment (single recording) was considered clinically significant. A clinically significant diastolic BP had to read >90 mmHg and increase >10 mmHg from baseline during at least two assessments or at last assessment. In 10 women clinically significant BP readings occurred; five (0.8%) had a clinically significant systolic reading and seven (1.1%) had a clinically significant diastolic reading during or at the end of the study. The mean systolic as well as diastolic BP showed a small decrease over time.

The body mass index (BMI) showed an increase from baseline >10% once or over several measurements in 20.2% of the women. There was a gradual mean increase in BMI over the full study period. The mean change was 0.80 kg/m^2 (SD 1.59) which also included women who discontinued due to weight gain. The mean percent increase in BMI was 3.5%. In 15 (2.4%) women the weight gain was the reason given for discontinuing treatment.

Swelling, redness, pain and/or haematoma at implant site were rarely reported. A combination of symptoms may have occurred in an individual. In that case each symptom was counted separately and percentages shown indicate not only each woman but also each symptom reported. Incidences are

Table III. Discontinuation in the first 2 years due to bleeding irregularities or amenorrhoea

Reason for discontinuation, categorized	Implanon® (n = 635)	
	n	%
Amenorrhoea	11	1.7
Bleeding irregularities[a]	109	17.2
Frequent irregular bleeding	69	10.9
Heavy menstrual flow	2	0.3
Prolonged menstrual flow	15	2.4
Spotting	21	3.3
Other bleeding problems	2	0.3
Total	120	18.9[b]

[a]In the third year one subject (0.7%) withdrew due to 'prolonged menstrual flow.'
[b]Patients who discontinued as percentage of all those treated with Implanon®.

Table V. Overall assessment of adverse experiences

	Implanon®			
	2 years (n = 635)		3rd year (n = 147)	
	n	%	n[b]	%
Subjects with AE (including SAE)	474	74.6	5	3.4
Deaths	0		0	
Subjects with serious AE[a]	42	6.6	8	5.4
Subjects with AE as primary reason for discontinuation	54	8.5	5	3.4
Subjects with drug-related AE[a]	324	51.0	6	4.1
Subjects with adverse experiences of severe intensity	75	11.8	12	8.2

SAE = serious adverse experience.
[a]See specific definition in text.
[b]Subjects experiencing these various types of adverse experiences for the first time in the 3rd year.

Table IV. Bleeding pattern indices

Reference period[a]	n	Amenorrhoea[b]		Infrequent bleeding[c]		Frequent bleeding[d]		Prolonged bleeding[e]	
		n	%	n	%	n	%	n	%
1	555	5	0.9	283	51.0	64	11.5	223	40.2
2	508	84	16.5	177	34.8	44	8.7	112	22.0
3	487	94	19.3	166	34.1	39	8.0	97	19.9
4	460	91	19.8	139	30.2	38	8.3	84	18.3
5	430	82	19.1	127	29.5	30	7.0	71	16.5
6	407	67	16.5	139	34.2	26	6.4	71	17.4
7	395	66	16.7	123	31.1	29	7.3	67	17.0
8	354	42	11.9	120	33.9	15	4.2	63	17.8
9	140	25	17.9	41	29.3	10	7.1	29	20.7
10	129	18	14.0	44	34.1	7	5.4	26	20.2
11	129	15	11.6	46	35.7	3	2.3	25	19.4
12	122	13	10.7	36	29.5	4	3.3	27	22.1

[a]Reference period: periods of 90 consecutive days starting on the day of implant placement.
[b]Amenorrhoea: no bleeding or spotting throughout a reference period.
[c]Infrequent bleeding: less than three bleeding-spotting episodes starting within a reference period, excluding amenorrhoea.
[d]Frequent bleeding: more than five bleeding-spotting episodes starting within a reference period.
[e]Prolonged bleeding: at least one bleeding-spotting episode starting within a reference period and lasting more than 14 days.

Table VI. Frequently reported (>5% of all volunteers) adverse experiences per region

Adverse experience (WHO preferred term)	Chile %		Hungary %		Other regions
	n = 107 2 years	*n* = 77 3rd year	*n* = 195 2 years	*n* = 70 3rd year[a]	(*n* = 333) 2 years
Acne	11.2	0.0	12.3	8.6	15.6
Headache	69.2	0.0	6.7	1.4	6.3
Libido decreased	15.9	2.6	1.0	0.0	4.8
Nervousness	29.9	2.6	1.0	0.0	1.2
Abdominal pain	34.6	10.4	7.2	1.4	6.0
Weight increase	35.5	6.5	5.6	2.9	5.7
Pharyngitis	25.2	5.2	10.3	14.3	2.7
Upper respiratory tract infection	37.4	5.2	0.0	0.0	1.8
Breast pain female	26.2	5.2	16.4	2.9	10.2
Leucorrhoea	33.6	14.3	7.2	0.0	1.5
Vaginitis	33.6	6.5	9.7	0.0	12.0
Ovarian cyst	9.3	5.2	0.5	0.0	5.1
Influenza-like symptoms	15.9	3.9	7.7	4.3	3.3

[a]Adverse experiences occurring for the first time during the 3rd year.

shown in Table VII. Insertion of the implant took on average 2.2 min (SD 2.1) with a minimum of 0.03 and a maximum of 10 min. In eight cases (1.3%), some complication related to the insertion occurred (e.g. tip of implant visible, some blood loss from injection site etc.). Average time needed for removal was 5.4 min (SD 5.4). The minimum time required was 0.33 and the maximum 45 min. Removal was complicated in 19 cases (3.0%), usually caused by too deep insertion.

After removal of the implant, women were followed-up for 3 months. Of those who chose a non-hormonal method of contraception or no method at all, menses returned to normal in 90.9% within 3 months. This was not influenced by the length of time that the implant was in place. Of the post-treatment pregnancies that were reported, the estimated date of conception was within 90 days in 20 women out of 145 (13.8%) who used 'no contraceptive method'. Some of those pregnant reported to have used condoms or rhythm method. The percentage of women using 'no method', therefore, most probably was lower than stated. It is not known how many actively tried to become pregnant.

Table VII. Incidence of symptoms at implant site

n = 633	Any time during treatment	
	n	%
No abnormalities	609	96.2
Swelling	4	0.6
Redness	3	0.5
Pain	22	3.5
Haematoma	4	0.6

Discussion

This is the first report on a single contraceptive implant with an effective life span of 3 years. The results show that Implanon® provides excellent contraceptive cover for the full period of 3 years, to women of a wide range of ages, weights and cultural backgrounds. There were no pregnancies in a total of more than 15 000 cycles of exposure, 2000 of which were in the third year of use. Total protection in studies of this size is rarely observed, even among the most effective methods, including tubal ligation. This fact allows us to forecast the new implant's high efficacy in the youngest, most fertile women, as well as in those who were overweight, for whom the dose delivered by Norplant® near the end of its effective life has been shown to be insufficient in some cases (Sivin, 1994, 1998).

In the absence of a control group, comparisons between methods have intrinsic limitations due to the multiplicity of factors that affect their performance. In the case of contraceptive implants, the only objective measure of clinical performance is the pregnancy rate, which has been shown to be affected by factors such as age and body weight (Sivin, 1988, 1994). With due consideration to these caveats, at the present time, the performance of Implanon® can only be compared with the performance of other contraceptive implants, using literature reports. This exercise should include Norplant® (six capsule levonorgestrel system), Norplant®-II (two rod levonorgestrel system), Uniplant (nomegestrol acetate) and Nestorone® implants. Literature reports of the latter two implant systems remains very limited, whereas there is a vast literature on Norplant®. Notwithstanding, only recent large studies deal with the present soft tubing formulation. Annual pregnancy rates during 3 years of use ranged from 0.0 to 0.4 per 100 women in a trial that encompassed 1530 users of Norplant® (Sivin, 1994). No pregnancies were reported in another trial encompassing 598 users of the six-capsule system (Norplant®) and 600 users of the two-rod system (Norplant®-II) over 3 years (Sivin *et al.*, 1997). Most recently, results were reported of the six-capsule system in 511 women, in the United States. The annual pregnancy rate ranged from 0.0 to 0.3 per 100 women over 3 years which rose to 1.0 per 100 women over 5 years (Sivin *et al.*, 1998). Therefore, as far as contraceptive efficacy is concerned, Implanon® is as good or better than the only marketed implant.

As for the bleeding pattern, this study confirms the well established concept that the use of continuous progestagen-

only methods is associated with a disturbed pattern in a high proportion of users and that this is the main reason for discontinuation of the method, as is the case with Norplant® (Sivin *et al.*, 1997).

The bleeding pattern reported here, shows a shift towards amenorrhoea and infrequent bleeding. Although the incidence of amenorrhoea was just below 20% during most of the time, it was the reason for discontinuation in only 1.7% of the women. An objective study of the bleeding cards indicated that the acceptance of an irregular bleeding pattern was greatly at variance. Some women accepted very little in the way of an irregular bleeding pattern, while others accepted 'frequent irregular patterns' for long periods of time. Discontinuation rates, therefore, are in the first place a reflection of tolerance, rather than safety.

The percentages of discontinuation due to adverse experiences other than bleeding were 8.5 and 3.4 respectively in the first 2 years and in year 3, whereby weight increase was the most frequently reported reason for discontinuation (2.4%).

Although reporting of adverse experiences was substantially more frequent in Chile, the discontinuation rate was generally lower than in other centres. This most probably was the result of good counselling. The reporting of adverse experiences may be subject to methodological differences, which was also the case in the study reported here. In Chile, women were given ample opportunity to express their complaints freely, which were recorded each time they were expressed. In a study with Norplant® in the same clinic, a symptom was only recorded when it was reported in at least three follow-up visits. Moreover, there had to be an increase from the baseline situation. Using this method of assessment, headache occurred with an incidence of 32.6% (Diaz *et al.*, 1979). In the present study the incidence of headache was 69.2% in Chile, which was in contrast to the average incidence of 6.5% in the other centres.

The low incidence of adverse experiences at the site of implant placement, together with the fast insertion and removal, stand out as practical advantages over multiple unit implants.

Results from this study show that Implanon® has excellent contraceptive action. The bleeding pattern generally was irregular whereby the main tendency was towards amenorrhoea and infrequent bleeding. Weight increase was a side effect that was less well tolerated. There was no untoward effect on BP as reflected in a small mean decrease in systolic as well as in diastolic BP. Implant insertion and removal were fast and uncomplicated in the vast majority (97%) of cases.

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