ELSEVIER

Contraception 80 (2009) 457–462

Contraception

Original research article

Insertion and 3-year follow-up experience of 372 etonogestrel subdermal contraceptive implants by family physicians in Granada, Spain☆,☆☆

Lorenzo Arribas-Mir[a,b,e,*], Dolores Rueda-Lozano[a,e], María Agrela-Cardona[a,e], Tania Cedeño-Benavides[a,e], Carmen Olvera-Porcel[d], Aurora Bueno-Cavanillas[b,c,d]

[a]*University Health Centre of La Chana, Health District of Granada, Andalusian Health Service, Granada 18015, Spain*
[b]*Department of Preventive Medicine and Public Health, University of Granada, Granada 18014, Spain*
[c]*Preventive Medicine Service, University Hospital San Cecilio, Andalusian Health Service, Granada 18014, Spain*
[d]*CIBER Epidemiology and Public Health (CIBERESP), Granada 18014, Spain*
[e]*Teaching Unit of Family and Community Medicine of Granada, Andalusian Health Service, Granada 18001, Spain*

Received 2 February 2009; revised 6 April 2009; accepted 8 April 2009

Abstract

Background: User profile, continuation rate, reasons for discontinuation, problems during insertion and removal, and effectiveness of an etonogestrel subdermal contraceptive implant (ESCI) were assessed.
Study Design: A follow-up of 372 women 3 years after insertion of an ESCI performed by family physicians in Granada, Spain, by means of consultations, examination of medical records and telephone interviews.
Results: Data were available for 356 (95.7%) women. The average age was 27.2 years, and 159 (42.7%) were nulliparous. Continuation rates were 91.0% at 1 year, 74.7% at 2 years and 65.1% at 2 years and 9 months. The main reasons for discontinuation were excessive bleeding (44, 12.4%), wish to become pregnant (44, 12.4%) and side effects not related to menstruation (21, 5.9%). However, 141 (39.6%) received a second implant when the first one expired. No pregnancy occurred in 893.4 women-years.
Conclusions: Family physicians can achieve excellent results with the ESCI. It should be included in the range of contraceptives offered by primary care physicians.

Keywords: Contraception; Family physician; Primary care; Subdermal implants; Implanon; Etonogestrel

1. Introduction

Unplanned pregnancy is a problem in Granada, where in 2003 the rate of induced abortions was 14.4 per 1000 women aged between 10 and 49 years, and 37.6 per 1000 among 20- to 24-year-olds [1].

The contraceptive methods that have proven to be most effective in the prevention of unplanned pregnancy are those that are not dependent on compliance and are long-acting, reversible and have high continuation rates. Intrauterine devices (IUD) and subdermal contraceptive implants (SCI) fit this profile. An etonogestrel subdermal contraceptive implant (ESCI) called Implanon®, the first SCI in our country, became available in 2002, and so could be added to our choice of contraceptives. Currently, the SCI is among the most effective methods (Pearl index 0.05 [2]) and has an excellent safety profile [3,4]. The ESCI Implanon® is a flexible, nonbiodegradable single rod of ethylene vinyl acetate, measuring 2×40 mm and containing 68 mg of etonogestrel. It provides 3 years of effective contraception.

Like all gestagen-only methods, use of the ESCI may result in irregular and unpredictable menstrual bleeding, and acceptability depends greatly on sociocultural factors and counseling. Initial studies have been carried out in other countries and many of them took place in specialized

☆ This study has been funded by Health District of Granada, Andalusian Health Service.
☆☆ Conflicts of interest: The undersigned authors certify that they have no conflicts of interest related to the submitted article.
* Corresponding author. University Health Centre of La Chana, Health District of Granada, Andalusian Health Service, Avenida Vírgen de la Consolación s/n, Granada 18015, Spain. Tel.: +34 958295906; fax: +34 958285478.
E-mail address: l.arribas@terra.es (L. Arribas-Mir).

0010-7824/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2009.04.003

contraception centers [5]. Currently, little is known about ESCI acceptability in our country [6]. Use levels of any contraceptive among the population depend greatly on accessibility and on the quality of counseling [7]. Given its accessibility, primary care facilities could prove to be the ideal environment for delivery of the ESCI, once the obstacles related to the insertion and removal techniques have been overcome.

Our objectives were to assess user profile, continuation rates, reasons for discontinuation, adverse events related to insertion and removal, and contraceptive efficacy when used within family medical practice, including 3 years of follow-up after insertion.

2. Material and methods

2.1. Design, scope and period of the study

Analysis was conducted on a series of cases involving women who had an ESCI inserted in the University Health Centre of La Chana (Granada, Spain) run by the Andalusian Health Service (AHS). The majority of insertions were carried out by two of the 12 family physicians (FP) at the center and by family medicine residents under supervision of the former. Insertions carried out between March 14, 2003, and December 13, 2005, were included. They were followed up until December 13, 2008, in order to guarantee a follow-up of every ESCI for 3 years. The trial was approved by the Commission of Investigation of the Health District of Granada (HDG). The ESCI was fully funded by the HDG, and surgery attendance did not involve any additional costs.

2.2. Sample population and trial population

The average number of women, aged between 15 and 45 years, registered at the center during the study period was 5220. The insertion was performed in those women who had no contraindications (WHO Categories 3 and 4) [8], chose ESCI over all other methods after receiving full information including accepting possible changes in bleeding pattern and gave verbal consent.

2.3. Follow-up

All women were followed up from insertion until removal with monitoring visits at the health center 1 week and 3 months after insertion and annually until lifespan of the implant terminated at 3 years after insertion. A contact telephone number and free access to the center were made available to the women in case they had any concerns. To record bleeding, a menstrual calendar was handed out which was to be brought to each consultation. The bleeding patterns were defined in accordance with WHO categories [9]: amenorrhea: no bleeding during the reference period; infrequent bleeding: fewer than three bleeding episodes; frequent bleeding: more than five bleeding; irregular bleeding: between three and five episodes with less than three bleeding-free intervals of length 14 days or more; prolonged bleeding: one or more bleeding episodes lasting 14 days or more; none of the above: a normal bleeding pattern. Prior to the insertion, a normal cycle was defined as having a duration of 24–35 days with an intra-individual variability of ±3 days. When renewal or removal took place after 2 years and 9 months after insertion, it was considered that the implant had been used to its full duration. Removals carried out during the first 33 months of use were therefore defined as premature discontinuations.

2.4. Insertion and removal techniques

The implant was inserted in the nondominant arm in the groove between the biceps and triceps 6–8 cm above the elbow fold, under local anesthesia; approximately 2 mL of 2% mepivacaine was injected under the skin where the implant was to be inserted. For removal, a 2-mm incision was made towards which the distal end of the implant was pushed in order to dissect the fibrous capsule and remove it. Compressive bandaging was kept in place for 3 days. The preferred timeframe for insertion was within the first 5 days of a cycle; other options were accepted in agreement with WHO recommendations [10].

2.5. Information gathered

The personal characteristics of the women were collected (age, nationality, smoking, preexisting pathologies, gynecological history and previous use of contraception). Also, dates of insertion and removal, adverse events during insertion and removal, discontinuation, reasons for discontinuation, where removal took place, pregnancy rates, bleeding patterns and any medical treatment required to control excessive bleeding were collected.

2.6. Information sources and methodology of information gathering

Clinical records were reviewed. If more than one reason for removal was noted, the most severe was included, and if they were of equal severity, the one closest to the time of removal was recorded. At insertion, a contact telephone number was requested as well as permission to make follow-up calls or calls to complete information, which proved to be necessary in 89 cases.

2.7. Data analysis

Excel 2008 for Mac version 12.1.1 (Microsoft Corporation, Redmond WA, USA) was used as well as SPSS version 15.0 (SPSS, Inc., Chicago, IL, USA). For quantitative variables, a comparative test of averages was carried out and a chi-squared test was performed for the qualitative variables. The Kaplan–Meier method was used to describe duration of use.

3. Results

ESCI insertions were performed on 372 women. The implant was used by 5.09% of our population of women of childbearing age. The 12 FP contributed a total number of 281 women from their patient lists, an average of 8.5 implants/FP per year. Another 91 women were registered with a FP in a different medical center.

The characteristics of the population are shown in Table 1. One hundred sixty-one (43.3%) were under 26 years and 15 (4.0%) under 18 years of age. Nearly a fifth (72, 19.2%) of the women were immigrants, with the majority, 37, from South America and Eastern Europe, 24. Sixty- three (16.9%) smoked more than 15 cigarettes a day. Prior to insertion, 190 (51.1%) were using less effective contraception and 36 (9.7%) were using no method. The timing of insertion is shown in Table 2. Thirty (8.1%) were breastfeeding at the time of insertion. Most (346, 93.0%) implants were inserted in the left arm and 26 (7.0%) in the right arm.

Only 16 subjects (4.3%) were lost to follow-up of whom 14 were immigrants, resulting in a follow-up rate of 95.7%.

Of the 356 implants inserted, 324 (91.0%) were still in situ after 1 year, 266 (74.7%) after 2 years and 232 (65.1%) at 2 years and 9 months (Fig. 1). Just over a third (124, 34.9%) of implants were removed early. Table 3 shows the reasons for discontinuation, among which excessive bleeding and the wish to conceive are the most common. Discontinuation as a result of nonmenstrual side effects (21, 5.9%) had 12 different causes. Four women had two reasons for removal (Table 4). At the end of the study, 141 (39.6%) women renewed the implant, 89 (25.0%) had it removed when it expired and three (0.8%) still have the implant in place. Twenty- five (7.0%) women had the implant still in situ more than 2 months after the expiration date, one of them up to 10 months. Total exposure during the trial amounted to 326,095 days, 11,646 cycles of 28 days of treatment, 32.7 cycles/woman. Not a single pregnancy occurred during a period of 893.4 women-years of exposure.

During insertion, two light vagal episodes occurred as well as one instance of minimal cutaneous perforation. One week after insertion, 351 (93.0%) implants were examined; one was impalpable; the tips of two palpable implants were positioned somewhat deeply, while two others were observed to be somewhat superficial. The majority of the implants examined, 346 (98.6%), were correctly positioned; nine (2.6%) women described slight local itching, one (0.3%) complained of pain at the insertion site, one (0.3%) was found to have injuries due to scratching and one (0.3%) had a small granuloma where the implant had been inserted.

One implant that could not be found has not been removed. It has not been found either by ultrasound scanning nor by magnetic resonance imaging by the radiologist, but

Table 1
Baseline characteristics of the study population (*N*=372)

	n	%		*n*	%
Age			Pregnancy		
Mean±SD	27.17±6.41		0	131	35.2
Range	14–45		1	103	27.7
≤19	49	13.2	2	90	24.2
20–24	92	24.7	3	29	7.8
25–29	96	25.8	>3	19	5.1
30–34	84	22.6	Parity		
≥35	51	13.7	0	159	42.7
Nationality			1	104	28.0
Spanish	300	80.6	2	87	23.4
Immigrants	72	19.4	3	16	4.3
Smoking habits			>3	6	1.6
Smokers	188	50.5	Prior induced abortion	54	14.5
			Menstrual cycle		
Nonsmokers	158	42.5	Regular (24–35 days)	335	91.5
Previous disorders			Irregular	31	8.5
Psychiatric disease	36	9.7	Last contraceptive method		
Bronchial asthma	23	6.2	Male condom	174	46.8
Migraine	22	5.9	Combined pill	102	27.4
Dyspepsia	9	2.4	Copper IUD	14	3.8
Learning disabilities	9	2.4	Others	46	12.3
			None	36	9.7

Table 2
Timing of Implanon® insertion (*N*=372)

	n	%
Days 1 to 5 of the cycle	228	61.3
≥Day 6 of the cycle	75	20.2
Postnatal	33	8.9
After induced abortion	14	3.8
After spontaneous abortion	2	0.5
Amenorrhea	2	0.5
After emergency hormonal pill	2	0.5
Using other effective contraception	7	1.9
Unspecified	9	2.4
Total	372	100.0

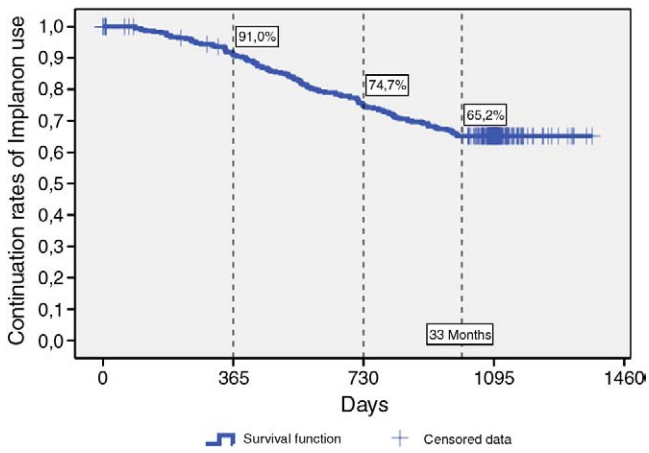

Fig. 1. Continuation rate of Implanon® (*N*=372).

Table 3
Reasons for removal of Implanon by duration (n=356)

Months	1–12		13–24		25–33		Subtotal 1–33		34		35		36		>36		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Renewal									1	0.3	10	2.8	46	12.9	83	23.3	140	39.3
Expiration									6	1.7	10	2.8	22	6.2	51	14.3	89	25.0
Excessive bleeding	16	4.5	17	4.8	11	3.1	44	12.4									44	12.4
Planning pregnancy	7	2.0	27	7.6	10	2.8	44	12.4									44	12.4
Nonmenstrual side effect	7	2.0	6	1.7	8	2.2	21	5.9									21	5.9
Amenorrhea	1	0.3	3	0.8			4	1.1									4	1.1
No contraception required			2	0.6	2	0.6	4	1.1									4	1.1
At subject's request	1	0.3	1	0.3	2	0.6	4	1.1									4	1.1
Others			1	0.3	1	0.3	2	0.6									2	0.6
No removal															3	0.8	3	0.8
Renewed early in error			1	0.3			1	0.3									1	0.3
Total	32	9.0	58	16.3	34	9.6	124	34.9	7	2.0	20	5.6	68	19.1	137	38.5	356	100.0

etonorgestrel was detected in plasma. Two other implants are still in place despite our phone calls warning the women about the consequences of the expiration of the implant. Out of a total of 353 removals, 312 (88.4%) were carried out in our health center and 41 (11.6%) took place in other centers. In our center, two removals proved to be difficult as the implant was deep, three women reported instances of transient paresthesia in the hand and two developed local reaction presenting as vesicles close to the removal area due to excess pressure at the ends of the adhesive skin closure strips.

Bleeding patterns were recorded for 347 women on removal of ESCI. The mean overall incidence is as follows: normal bleeding, 34.0%; infrequent bleeding, 21.6%; amenorrhea, 17.9%; prolonged bleeding, 17.3%; frequent bleeding, 6.3; irregular bleeding, 2.9% (Table 5); even though in 40 subjects (11.6%) several patterns had succeeded each other. Medication, ethinyl estradiol, 50 mcg once daily 20 days, was prescribed to 46 (13.0%) women to treat excessive bleeding, of whom 29 (63%) finally had the implant removed before the end of the study period and 17 (37%) continued until expiration of the implant.

Table 4
Reasons for discontinuation due to side effects of Implanon not related to menstruation in 21 (5.6%) women (n=356)

	n	%
Weight increase	5	1.4
Acne	4	1.1
Mastalgia	3	0.8
Ovarian cyst	3	0.8
Headache	2	0.6
Mood changes	2	0.6
Hirsutism	1	0.3
Abdominal pain	1	0.3
Edema	1	0.3
Nausea	1	0.3
Vaginal dryness	1	0.3
Greasy hair	1	0.3

Headache was also complained of by one woman with mastalgia and one with weight increase.
Acne was also complained of by one woman with greasy hair and one with hirsutism.

4. Discussion

The principal advantage of this study is that it proves the practicality of ESCI use by FP. It covers a series of three full years of follow-up of 372 insertions, carried out by FP, a number only exceeded by the 417 of Otero et al. [11]. The fact that this study was carried out in real-life conditions increases its external validity. Also, the loss to follow-up rate (4.3%) was lower than in the majority of other series [12-14], which report between 14.5% and 18.9% rates. The key to obtaining these results may lie in elements such as funding of the ESCI, the accessibility of the FP and their holistic care, as well as the AHS's unique electronic database of patients' medical records.

Not recording side effects, which did not lead to removal of the implant and which were transient and of little general relevance, could be considered a limitation of this study. We did not carry out any physical or gynecological tests, or any follow-up of biological parameters, mainly because the ESCI produces no significant changes in the latter [15,16]. In our center, the FP had all types of reversible contraceptives available, including intrauterine devices, a fact that has to be taken into consideration when results are extrapolated. In line with recommendations by the WHO, clinical trials

Table 5
Predominant bleeding pattern on removal of Implanon (n=347)

	n	%
Normal	118	34.0
Infrequent	75	21.6
Amenorrhea	62	17.9
Prolonged	60	17.3
Frequent	22	6.3
Irregular	10	2.9
Total	347	100

describe bleeding patterns for 90-day reference periods [17], a criterion we did not apply in our study, as it is difficult to comply with. With an average of five follow-up visits, we determined bleeding patterns by means of an interview at the time of implant removal and by analyzing the data of the menstrual calendars as well as the clinical registers obtained during previous visits (Table 5).

Of 49 adolescents included in the trial, 15 were minors, under 18, who had the implant inserted in the presence of their parents or legal guardian. Some clinical trials and pilot studies only include women between 18 and 40 years. The percentage of immigrants in our series constituted 19.4%, whereas in Granada they made up 4.6% of the total population in 2005 and 34.4% of the induced abortions [18]. The percentage of nulliparous women, 159 (42.7%), is higher than in other series. The types of contraception used prior to insertion (Table 1) are consistent with methods used nationwide [19]. While most clinical trials and pilot studies only admit women who are mentally and physically healthy, our series include women with other conditions which are not absolute contraindications to the ESCI; two exceptions were made concerning two women who were being treated for a psychiatric condition with topiramate because it was not possible for them to use another effective contraceptive method.

The annual continuation rate (91.0%) is high. In other series, this percentage varies between 68% [13] and 96% [20], whereas Trussell [2] has calculated it to be 84%. The economic evaluation of NICE [21] states that Implanon®, even when only used for 1 year, is more cost-effective than the combined pill, the mini-pill, the patch or the vaginal ring, with an annual continuation rate of 68%, while the condom is 53% [2].

Continuation rates after 33 months were 65.1%, which is lower than the 74.7% reported after 36 months in Thailand by Kiriwat et al. [22], or the 84.4% in Indonesia by Affandi et al. [23], carried out in a different cultural context and within trials and pilot studies projected or extended towards a period of 4 years. Our results are more consistent with those obtained by Croxatto et al. [24] in Chile and Hungary (63%) and by Otero et al. [11] in Mexico (61.4%). Under real-life conditions, which applied in our series, without any sponsorship or funding by the manufacturers, without any rigorous inclusion or exclusion criteria and without a strict follow-up, the continuation rates have to be lower, which is what was found in the United Kingdom, where 53% reached the benchmark of 35 months with the implant still in place [12], 30.2% reached 36 months [13] and 47% continued use for 33 months [14]. From the latter [14], we took the time frame of 33 months as a reference for complete use of the implant, since it is not unusual for some women to request removal or renewal of the ESCI before the "exact" expiration date of 3 years, a trend which should not be referred to as premature discontinuation. In the 3 months before the expiration date, 57 of the 141 women who opted for renewal and 38 of the 89 women who opted for discontinuation due to expiration of its approved duration of use had the original implant removed (Table 3).

With regard to excessive bleeding, 12.4% of women discontinued; other series reported 8.4% [20], 9.9% [25], 17.2% [24] and 22.64% [13]. Some trials in Asia, however, obtain very low rates: 0% [23] and 6% [22]. The same number (12.4%) had an early removal because they wanted to become pregnant, whereas in other series this percentage is 8.1% [11], or 10.46% [13], possibly because our selection criteria were not as strict, or because 42.7% of our participants were nulliparous. The number of dropouts for adverse events not related to menstruation of 21 (5.9%) (Table 4) was small compared to other studies reporting percentages from 6.9% [11] to 11.9% [24]. In the day-to-day running of the study, these adverse events may initially create a negative perception of the ESCI, which disappears when the series is evaluated as a whole.

We found 25 (7.0%) women who were using the implant more than 2 months after the expiration date, which seems to warrant the setting up of a system whereby the patient is contacted when expiration is due. Nevertheless, no pregnancies have been reported in the trials that lasted 4 years [22,23], possibly related to the small number of women included in these trials.

The gestagen-only ESCI can cause unpredictable bleeding patterns [26], which affects its acceptability. In a systematic review by Darney et al. [27], infrequent bleeding is diagnosed in 33%, amenorrhea in 21.4%, prolonged bleeding in 16.9% and frequent bleeding in 6.1%, results similar to our own (Table 5). Of the women who had amenorrhea as the main pattern, only four dropped out, representing a good level of acceptability for contraception without menstruation [28]. Excessive bleeding in at least 92 cases, either prolonged, frequent or irregular, caused 44 discontinuations in our study. In spite of this, 48 women continued to use the ESCI until expiration and 14 renewed the implant. These low discontinuation rates could be related to the good quality of counseling prior to insertion whereby information was given about possible menstrual changes, as well as to high acceptability of these changes by our population.

Total exposure, 893.4 women-years, has been extensive and no pregnancy occurred. Although some failures of the method have been reported in more extensive series, they remain rare [29]. We included 49 women who recently gave birth or had an abortion, 30 who were breastfeeding, some who were using hormonal contraception prior to or until the day of insertion and others with a gynecological or systemic pathology, which could apparently improve the efficacy of the ESCI. On the other hand, the 75 insertions carried out after the first 5 days of the cycle might have apparently decreased efficacy.

Despite the fact that our series consisted of first-ever insertions and in spite of the initially limited experience of the participating FP, the number of complications occurring during insertion or removal was low, an encouraging result with respect to the practicality of ESCI use in primary care

facilities. Three women reported instances of transient paresthesia in the hand. The local anesthetic could permeate through to the nerves lying close by [30]. To minimize risk of injury, as described previously [31], the manufacturer recommended a change of position in 2008, to between 8 and 10 cm above the medial epicondyle of the humerus.

In conclusion, the data presented seem to confirm that good results can be obtained when the ESCI is handled by FP, and it should therefore be included in the range of contraceptives offered by primary care physicians.

Acknowledgments

The authors are grateful to the Health District of Granada and to the Andalusian Health Service for the confidence placed in the family physicians for contraception, and to all the professionals at the University Health Centre of La Chana, in particular to Nieves Casarrubios.

References

[1] Voluntary interruption of pregnancy. Andalusía 2002–2003. Evolution of V.I.P. incidence. Years 1991–2003. Spa. Consejería de Salud. Junta de Andalucía. Sevilla 2005. Available at: http://www.juntadeandalucia.es/salud/principal/documentos.asp?pagina=estadisticas_ive_accede.

[2] Trussell J. Contraceptive efficacy. In: Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D, editors. Contraceptive Technology: Nineteenth Revised Edition. New York, NY: Ardent Media; 2007. p. 747–826.

[3] Le J, Tsourounis C. Implanon: a critical review. Ann Pharmacother 2001;35:329–36.

[4] Jordan A. Toxicology of progestogens of implantable contraceptives for women. Contraception 2002;65:3–8.

[5] Edwards JE, Moore A. Implanon. A review of clinical studies. Br J Fam Plann 1999;24(4 Suppl):3–16.

[6] Mattos I, Martinez C, Ripolles M, et al. Satisfaction, efficacy, side effects of the subdermal implant Implanon® In two advice centers for women of the Community of Madrid. Rev Iberoam Fertil 2004;21:93–9 [In Spanish].

[7] Davie JE, Walling MR, Mansour DJ, Bromham D, Kishen M, Fowler P. Impact of patient counselling on acceptance of the levonorgestrel implant contraceptive in the United Kingdom. Clin Ther 1996;18:150–9.

[8] World Health Organization. Reproductive health and research. Improving access to quality care in family planning. Medical eligibility criteria for contraceptive use3rd ed. . Geneva: WHO; 2004. Available at: http://www.who.int/reproductive-health/.

[9] Belsey EM, Machin D, d'Arcangues C. The analysis of vaginal bleeding patterns induced by fertility regulating methods. World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction. Contraception 1986;34:253–60.

[10] World Health Organization. Selected practice recommendations for contraceptive use. 2nd ed. Geneva: WHO; 2005. Available at: http://www.who.int/reproductive-health/.

[11] Otero JB, Balderas ML, Bonilla MC, Vazquez-Estrada L. Clinical experience and acceptability of the etonogestrel subdermal contraceptive implant. Int J Gynaecol Obstet 2005;90:228–33.

[12] Rai K, Gupta S, Cotter S. Experience with Implanon in a northeast London family planning clinic. Eur J Contracept Reprod Health Care 2004;9:39–46.

[13] Agrawal A, Robinson C. An assessment of the first 3 years' use of Implanon in Luton. J Fam Plann Reprod Health Care 2005;31:310–2.

[14] Lakha F, Glasier AF. Continuation rates of Implanon in the UK: data from an observational study in a clinical setting. Contraception 2006;74:287–9.

[15] Murat M, Yildirim Y, Ertopcu K, Eftal M, Ozelmas I, Tinar S. Effect of the subdermal contraceptive etonogestrel implant (Implanon) on biochemical and hormonal parameters (three years follow-up). Eur J Contracept Reprod Health Care 2008;13:238–42.

[16] Vieira CS, Ferriani RA, García AA, et al. Use of etonogestrel-releasing implant is associated with hypoactivation of coagulation cascade. Hum Reprod 2007;22:2196–201.

[17] Belsey EM, Farley TMM. The analysis of menstrual bleeding patterns: a review. Contraception 1988;38:129–56.

[18] Ginegranada Clinic. (Internet Page). Granada. (Quantitative and comparative study in relation to abortion and other aspects of reproductive health of immigrant women). Spa. Inc.; c2004–2007 (updated 2008 Dec 14; cited 2009 Jan 25). Available at: http://www.ginegranada.com.

[19] V Questionnaire Bayer Schering Pharma. Contraception in Spain 2007. (Internet Page). Spa. Daphne Group. (Update 2007; cited 2009 Abril 6). Available at: http://www.equipodaphne.es/encuestas.php.

[20] Zheng SR, Zheng HM, Qian SZ, Sang GW, Kaper RF. A randomized multicenter study comparing the efficacy and bleeding pattern of a single-rod (Implanon) and a six-capsule (Norplant) hormonal contraceptive implant. Contraception 1999;60:1–8.

[21] National Institute for Health and Clinical Excellence. (Internet Page). London. Long-acting reversible contraception. Economic evaluation; p 113–136. Inc.; c2007 (updated 2007 Oct 26; cited 2009 24 Jan). Available at: http://www.nice.org.uk/nicemedia/pdf/CG030fullguideline.pdf.

[22] Kiriwat O, Patanayindee A, Koetsawang S, Korver T, Bennink HJ. A 4-year pilot study on the efficacy and safety of Implanon, a single-rod hormonal contraceptive implant, in healthy women in Thailand. Eur J Contracept Reprod Health Care 1998;3:85–91.

[23] Affandi B, Korver T, Geurts TB, Coelingh Bennink HJ. A pilot efficacy study with a single-rod contraceptive implant (Implanon) in 200 Indonesian women treated for ≤4 years. Contraception 1999;59:167–74.

[24] Croxatto HB, Urbancsek J, Massai R, Coelingh Bennink H, van Beek A. A multicentre efficacy and safety study of the single contraceptive implant Implanon. Implanon Study Group. Hum Reprod 1999;14:976–81.

[25] Zheng SR, Zheng HM, Qian SZ, Sang GW, Kaper RF. A long-term study of the efficacy and acceptability of a single-rod hormonal contraceptive implant (Implanon) in healthy women in China. Eur J Contracept Reprod Health Care 1999;4:85–93.

[26] Affandi B. An integrated analysis of vaginal bleeding patterns in clinical trials of Implanon. Contraception 1998;58(6 Suppl):99S-107S.

[27] Darney P, Patel A, Rosen K, Shapiro LS, Kaunitz AM. Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials. Fertil Steril 2008;18, doi:10.1016/j.fertnstert.2008.02.140.

[28] Aubeny E. Will period-free hormonal contraception become the norm of the twenty-first century? Eur J Contracept Reprod Health Care 2006;11:1–5.

[29] Harrison-Woolrycha M, Hill R. Unintended pregnancies with the etonogestrel implant (Implanon): a case series from postmarketing experience in Australia. Contraception 2005;71:306–8.

[30] Webb AM. Why go to Tiger Country? A report of two cases of Implanon removal. J Fam Plann Reprod Health Care 2006;32:193–4.

[31] Wechselberger G, Wolfram D, Pulzl P, Soelder E, Schoeller T. Nerve injury caused by removal of an implantable hormonal contraceptive. Am J Obstet Gynecol 2006;195:323–6.