Effectiveness and Adverse Effects of the Implanon®

Implanon®'un Etkinlik ve Istenmeyen Etkileri

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ABSTRACT Objective: To evaluate the effectiveness, adverse effects, and discontinuation rate of Implanon during the first year of its insertion. **Material and Methods:** In this prospective cohort study 41 healthy women aged between 18-40 years were included. After insertion the women were followed for a year and at each visit blood pressure, body mass index, side effects, bleeding patterns, discontinuation rates and the reasons were recorded. SPSS package programme and paired samples-T test were used for statistical analysis. **Results:** The mean age of the participants were 29.2 ± 4.80 years, mean gravida was 3.66 ± 2.45. The observation period was 12 months and no unwanted pregnancy occurred during this time. The significantly increased unwanted side effects were dizziness 32.5%, nausea 33.3%, mood changes 14.7% and acne 26.5%. Amenorrhea was seen in 24.4%, infrequent bleeding in 17.1%, frequent bleeding in 7.3%, irregular bleeding in 29.3%, prolonged bleeding in 17.1% of the participants. Dysmenorrhoea decreased from 41.5% to 5.7%. Hirsutismus was seen in 5.7% and mastalgia in 8.6% of the patient. After 12 months of insertion 29.26% of 41 patients applied for the removal of the implant because of bleeding disorder (83.3%), mood changes requiring medical treatment (8.3%) and weight gain (8.3%). **Conclusion:** Although Implanon has high efficacy and safety, the discontinuation rate is high in this region and the most common cause of discontinuation is bleeding disorders.

Key Words: Adverse effects; 3-keto-desogestrel; menstruation disturbances

ÖZET Amaç: Yerleştirilişinin birinci yılında implanonun etkinliğini, istenmeyen etkilerini ve bırakma oranını değerlendirmek. **Gereç ve Yöntemler:** Bu prospektif çalışmaya 18-40 yaşları arasında 41 sağlıklı kadın dahil edildi. Yerleştirildikten sonra takip eden ilk yılın her vizitinde kadınların kan basıncı, beden kitle indeksi, yan etkileri, kanama paternleri bırakma oranları ve nedenleri kaydedildi. İstatistiksel analiz için SPSS paket programı ve paired samples-T kullanıldı. **Bulgular:** Katılımcıların ortalama yaşları 29.2 ± 4.80 yıl, ortalama gravidaları 3.66 ± 2.45 idi. Takip edilen süre 12 aydı ve bu süre zarfında istenmeyen gebelik oluşmadı. Arzu edilmeyen yan etkilerden anlamlı olarak artış %32.5 baş dönmesi, %33.3 bulantı, %14.7 ruhsal durum değişiklikleri ve %26.5 akne idi. Katılımcıların %24.4'ünde amenore, %17.1'inde nadir kanama, %7.3'ünde sık kanama, %29.3'ünde düzensiz kanama %17.1'inde uzamış kanama görüldü. Dismenore %41.5'ten %5.7'ye düştü. Hastaların %5.7'sinde hirsutizm, %8.6'sında mastalji görüldü. Yerleştirildikten 12 ay sonra kanama düzensizlikleri (%83.3), ruhsal durum değişiklikleri (%8.3), kilo alımı (%8.3)'ndan dolayı hastaların %29.26'sı implantı çıkarmak için başvurdular. **Sonuç:** İmplanon yüksek etkinlik ve güvenilirliğine rağmen bölgemizde bırakma oranları yüksektir ve en yaygın bırakma nedeni kanama düzensizlikleridir.

Anahtar Kelimeler: İstenmeyen etkileri; 3-keto-desogestrel; menstruasyon bozuklukları

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Implanon® (Organon, Oss, The Netherlands) is one of the new contraceptive implant system that have become available in many countries. It is a single rod subdermal implant made of ethylene vinyl acetate co-

polymer that contains a core of 68 mg of etheno-gestrel (3-ketodesogestrel).[1] The levonorgestrel releasing six capsule system Norplant® and the two rod system, Jadelle, Nestorone implant system/ Elcometrine, surplant (nomegestol) are some of the other contraceptive implant system that are available in many countries.[2] Implanon being a simple rod system (4 cm long and 2 mm diameter) has a simple insertion and removal procedure and its efficacy lasts for 3 years.[3] The etenogestrel in Implanon is released at an initial rate of 60-70 microgram/day, which gradually decreases to 30 microgram/day.[4,5] Early dose finding studies showed that a release rate of 25-30 microgram/day of etenogestrel is required to suppress ovulation.[4,6-7] The safety and effects of this methods has been widely studied.[2-4,8] Like other progestin-only contraceptives besides being effective and safe these methods also have adverse effects. The acceptability of adverse effects of a contraceptive method and the discontinuation rates vary widely in different populations. The objective of this study was to evaluate the menstrual and non menstrual bleeding patterns, side effects and discontinuation rates of the implant, Implanon, during the first year of its use in a region with high fertility rate. The fertility rate in eastern Turkey is 3.65, higher than the rate in western Turkey which is 1.88.[9]

MATERIAL AND METHODS

This longitudinal study was conducted at the Obstetrics and Gynaecology department of Faculty of Medicine of Yüzüncü Yıl University, Van, Turkey, from June 2004 to January 2006. Forty one healthy sexually active female volunteers between the ages of 18-40 years were enrolled in the study. The inclusion criteria for the study were not being pregnant, having regular menstrual cycles, normal physical and pelvic examination no smoking or smoking maximally 10 cigarettes/day, having a body mass index (BMI) between 20 and 30 kg/m^2, blood pressure < 140/90 mm Hg, no history of chronic diseases, no contraindication for Implanon use, no prior use of a oral hormonal contraceptive method within previous 2 months and no prior use of a depot injectable hormonal contraceptive method within 1 year, not using anticoagulant or liver enzyme inducing drugs. Approval of the Institutional Ethical Committee and written informed consent were obtained from all participants. All of the subjects enrolled had their history taken and underwent physical and pelvic examination. Implanon was inserted within the first 5 days of the menstrual cycle, on the inside of the upper none dominant arm within the groove between the triceps and biceps muscle.

Follow up visits were scheduled after each reference period after implant placement. At each visit physical and pelvic examination, weight gain, blood pressure and subjective complaints with the side effects were recorded on questionnaire forms. The bleeding patterns were recorded on menstrual diaries by the participants. The 90 day reference period method was used to analyze the bleeding patterns as defined by World Health Organisation.[10]

According to this:

1. Amenorrhea: no bleeding during the reference period.

2. Infrequent bleeding: fewer than 3 bleeding episodes

3. Frequent bleeding: more than 5 bleeding episodes

4. Irregular bleeding: between 3-5 episodes with less than 3 bleeding-free intervals of length 14 days or more

5. Prolonged bleeding: 1 or more bleeding episodes lasting 14 days more.

6. None of the above: a normal bleeding pattern.

Statistical analyses were performed using SPSS 11.5 software (SPSS Inc. Chicago, USA). Paired samples T test was used far the comparison of changes. $p< 0.05$ was taken as the level of statistical significance.

RESULTS

Mean age of 41 subjects was 29.32 ± 4.80, mean gravida was 3.66 ± 2.45, mean parity was 3.02 ± 1.94 and mean number of living children was 2.95 ±

1.86. The reasons for preference of this contraceptive method were being very effective 80.50%, unsatisfaction of prior contraceptive method (17.10%) and breast feeding (2.40%). The contraceptive methods used prior insertion were; 48.80% was not using any method, 17.10% oral contraceptives,17.10% intrauterine device, 14.60% condom and 2.40% injectable hormonal contraceptives. There were no statistical changes in blood pressure p (systolic blood pressure)= 0.83, p (diastolic blood pressure)= 0.41), BMI (p= 0.06)and headache rate (p= 0.09). At sixth month of insertion, statistically significant increase in the complaints of mastalgia (p= 0.02), dizziness (p= 0.00) nausea (p= 0.00), mood changes (p= 0.01) and acne (p= 0.00) were detected. Hirsutismus was not seen any of the subjects. At 12 months of insertion the rates of these adverse effects did not change significantly compared to rates detected at 6 months of insertion: mastalgia (p= 0.71), dizziness (p= 0.10), nausea (p= 0.10), mood changes (p= 1.0), acne (p= 0.66) and hirsitusmus (p= 0.16). Dysmenorrhoea decreased significantly from 41.50% to 2.40% at the sixth month of application (p= 0.00) and it slightly increased to 5.7% at 12 months of insertion. The increase was not significant (p= 0.57) (Table 1).

All of the subjects had regular menstrual cycle before insertion and at the first and the fourth 90 day reference period this rate decreased to 7.3% and 4.9% respectively. The rate of Amenorrhea was 34.10% at the first and 24.40% at the fourth reference period. Infrequent bleeding increased from 4.90% to 17.1%, the rate of frequent bleeding did not change, irregular bleeding increased from 17.10% to 29.30%, prolonged bleeding decreased from 29.30% to 17.1% (Table 2).

At the sixth month of insertion 8 (19.5%) women asked for removal of the implant. Reasons for discontinuation were abnormal bleeding pattern (75%), depression (12.5%) and weight gain (12.5%). At twelve months 12 (29.26%) women had the implant removed. The reasons for the removal of the implant was bleeding disorders 83.30%, mood changes requiring medical treatment (8.3%) and weight gain (8.3%).

TABLE 1: Adverse effects seen in 12 months of implanon use.

	Prior insertion	After 6 m. of insertion	After 12 m of insertion
	%	%	%
Headache	31.70	39	41.2
Dizziness	22	46.30	34.5
Nausea	4.90	29.30	38.2
Depression	0	17.10	14.7
Acne	0	26.80	26.5
Dysmenorrhea	41.50	2.40	5.7
Mastalgia	0	12.20	8.6
Hirsitusmus	0	0	5.7

TABLE 2: Bleeding patterns of the subjects.

Bleeding Pattern	At the first reference period	At the fourth reference period
	%	%
Normal regular bleeding	7.3	4.9
Amenorrhea	34.1	24.4
Infrequent bleeding	4.9	17.1
Frequent bleeding	7.3	7.3
Irregular bleeding	17.1	29.3
Prolonged bleeding	29.3	17.1

DISCUSSION

The contraceptive efficacy of Implanon is reported to be very good with a pearl index of 0.0 (95% confidence interval 0.00-0.09).[1] The present study also demonstrated that Implanon use was effective as no pregnancy occurred during 12 months of study period. The results show that it is also safe. Similar to reports by Booranabuniyat S, et al the changes in blood pressure, body mass index were not statistically significant.[11] Despite its efficacy and safety like all other contraceptive methods Implanon also has adverse effects. The acceptability of the adverse effects of contraceptive methods is important factors in the continuation rates among the users and this can show wide variations. It is reported that among 1716 Implanon users discontinuation rates were 30.2% over 3 years in Europe and Canada, compared with 0.9% in South East Asia.[12] Edwards and Moore reported that discontinuation rates for Implanon was 5.3% in the first 6 months, 6.4% in the second 6 months, 4.1% during months 13-18, 2.4% during months 19-24 and discontinuation tended to occur more frequently during the first year of use.[13] The discontinuation rate in this study was higher than these reports as at 6 and 12 months and it was 19.5% and 29.26% respectively. Similar to these results the discontinuation rate tended to decrease as 8 patients asked for removal in the first 6 months, 4 patients ask for removal in the second 6 months. Reason for discontinuation was abnormal bleeding pattern at 6 and 12 months with rates of 75% and 83.30%. The study demonstrates that the most common bleeding patterns were amenorrhea, prolonged bleeding and irregular bleeding similar to the reported studies.[14,15] All of the subjects had regular menstrual cycle before the insertion and at the first and the fourth 90 day reference period this rate decreased to 7.3% and 4.9% respectively. The most common bleeding pattern was amenorrhea (34.10%) at the first reference period and irregular bleeding (29.30%) at the fourth reference period.

In the analysis of the non menstrual adverse effects similar to the reports, the rate of dizziness (46.30%, 34.5%) nausea (29.30%, 38.20%), mastalgia (12.20%, 8.6%), mood changes (17.10%, 14.7%), acne (26.80%, 26.50%) at 6 and 12 months of insertion was significantly different than the baseline. But the rates did not change much during the study period as the changes were not significantly different.[16] It is reported that in women with acne at baseline the condition improved in the majority of women, where as it first occurred in 14% or worsened in 10%.[17] Similar to the previous reports mood changes occurred during the study period and 28.6% of these patients required medical treatment for depression.[15] Hirsutismus was not seen any of the subjects at 6 months and it was seen in 1 subject (5.7%) at the 12 months of the study. A small increase was seen in the rates of headache, but the difference was not statistically significant in contrast to some other investigators as they have found headache as the most common non menstrual side effect.[16] Similar to the reports dysmenorrhoea decreased significantly from 41.50% to 2.40% at the sixth month of application and it slightly increased to 5.7% at 12 months of insertion.[3]

In conclusion the present study demonstrates that Implanon is safe and is highly effective, but at 12 months the discontinuation rate was 29.26% and this rate was higher than the reports.[13,16] Similar to these studies most commonly bleeding pattern changes led to premature discontinuation. It also has adverse effects such as nausea, dizziness, acne, mood changes. In order to increase the acceptance counselling should include these adverse effects especially bleeding disorders and their managements in this region.

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