Outcomes of etonogestrel subdermal contraceptive implants

A single center cross-sectional study

Taghreed M. Shams, *MBBS, FRCSC,* ***Hashem H. Alhashemi,*** *MBBS, FRCPC,* ***Albaraa A. Fallatah,*** *Medical student,* ***Asma M. Alkhalid,*** *Medical student,* ***Fai M. Alhazmi,*** *Medical student,* ***Mohammed K. Bin Yunus,*** *Medical student,* ***Rani N. Radey,*** *Medical student,* ***Asalah F. Hamad,*** *MBBS,* ***Hatoon T. Beyari,*** *MBBS, SBOG,* ***Shahad S. Alharazi,*** *MBBS, SBOG.*

ABSTRACT

الأهداف: دراسة مدى انتشار اضطرابات الدورة الشهرية، والآثار الجانبية، ومعدلات التوقف عن غرسات الإيتونوجيستريل تحت الجلد (ESI) لدى النساء المترددات على مدينة الملك عبد العزيز الطبية، جدة، المملكة العربية السعودية.

المنهجية: أجريت هذه الدراسة العرضي بناءً على السجلات الطبية الإلكترونية واستبيان عبر الهاتف تم إجراؤه على النساء اللاتي خضعن لإدخال ESI في مستشفى واحد للرعاية الثالثية في جدة، المملكة العربية السعودية، بين عامي 2019م و 2022م. كان الهدف الأساسي هو انتشار اضطرابات الدورة الشهرية. شمل هدف الدراسة الثانوية معدل التوقف، وأسباب التوقف، والآثار الجانبية لـ ESI.

النتائج: بشكل عام، اشتملت الدراسة على 345 امرأة مع ESI في هذه الدراسة. وكان معدل انتشار أي نوع من تشوهات الدورة الشهرية 88%. وشملت الآثار الجانبية الأخرى تغيرات في الجلد والمزاج وألم في الذراع وتنميل. وكانت نسبة التوقف 11% في السنة الأولى و22% قبل إتمام 36 شهراً.

الخلاصة: على الرغم من أن اضطرابات الدورة الشهرية هي أحد الآثار الجانبية الشائعة لـ ESI، إلا أن 22% فقط من المستخدمات توقفن عن استخدام هذه الطريقة لمنع الحمل.

Objectives: To examine the prevalence of menstrual irregularities, side effects, and discontinuation rates of etonogestrel subdermal implants (ESI) in women attending King Abdulaziz Medical City, Jeddah, Saudi Arabia.

Methods: This cross-sectional was carried out based on electronic medical records and a phone-based questionnaire administered to women who underwent ESI insertion in a single tertiary care hospital in Jeddah, Saudi Arabia, between 2019 and 2022. The primary objective was the prevalence of menstrual abnormalities. The secondary study objective included the discontinuation rate, reasons for discontinuation, and ESI side effects.

Results: In total, 345 women with ESI were included in this study. The prevalence of any type of menstrual abnormalities was 88%. Other side effects included skin and mood changes, arm pain, and numbness. The discontinuation rate was 11% in the first year and 22% before the completion of 36 months.

Conclusion: Although menstrual abnormalities are a common side effect of ESI, only 22% of users discontinued this method of contraception.

Keywords: contraception, etonogestrel, implants, menstrual abnormalities

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From the Department of Obstetrics and Gynecology (Shams), College of Medicine, King Saud bin Abdulaziz University For Health Sciences;

from the Department of Obstetrics and Gynecology (Shams, Hamad, Beyari, Alharazi), King Abdulaziz Medical City, Ministry of National Guard Health Affairs, from the Department of Medicine(Alhashemi), King Abdulaziz Medical City, Ministry of National Guard Health Affairs, from the Batterjee Medical College (Alkhalid, Alhazmi), Jeddah, from King Abdullah International Medical Research Center, Riyadh; from the College of Medicine (Fallatah, Bin Yunus), Taibah University, Al-Madinah Al-Munawwarah, and from the College of Medicine (Radey), Umm Al-Qura University, Makkah, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Taghreed M. Shams, Department of Obstetrics and Gynecology, King Saud bin Abdulaziz University for Health Science, Jeddah, Kingdom of Saudi Arabia.
E-mail: shamsta@ngha.med.sa
ORCID ID: https://orcid.org/0000-0002-0454-406X

Etonogestrel subdermal implant (ESI) is a long-acting reversible contraceptive containing 68 mg of etonogestrel. It is flexible, measures 4 cm in length and 2 mm in width, and is inserted under the skin of the inner upper arm by a trained healthcare provider. It can be left in place for 3 years and removed via a small surgical incision. Etonogestrel is an artificially active metabolite of the synthetic progestin desogestrel.[1] Progesterone prevents pregnancy by suppressing ovulation, thickening the cervical mucus, and modifying the endometrium to inhibit fertilized ovum implantation.[2] Studies have reported a clinical effectiveness rate of 100%, and the overall Pearl index ranged from 0-1.4.[3]

Abnormal menstruation was the most commonly reported adverse effect of ESI. Irregular bleeding was the most common type of abnormality, occurring in 86% of users, followed by prolonged bleeding in 56% of users, amenorrhea in 39%, and heavy bleeding in 35%.[4] Other side effects include headaches, with frequency ranging from 5-60%, reduction in libido in 9%, abdominal pain up to 50%, and acne ranging from 11-45%, in addition to ovarian cysts or persistent ovarian follicles in 27%.[5-9] Short-term side effects of ESI, including mastalgia, breast tenderness, emotional lability, mood changes, and dizziness, have also been reported.[3] There was no reported significant difference in bone mineral density at a one-year follow-up, and the continuation rates ranged from 57-97% at one year, 44-95% at 2 years, and 25-78% at 3 years of use.[3]

This study aimed to examine the prevalence of menstrual irregularities, side effects, and discontinuation rates of ESI in women attending King Abdulaziz Medical City, Jeddah, Saudi Arabia. This government hospital provides free medical care to national-guard employees and their dependents. Most of the population are Muslims and pay attention to menstrual irregularities because it interferes with prayer and fasting.

Methods. This cross-sectional study was carried out at King Abdulaziz Medical City, Jeddah, Saudi Arabia, from June 2019 to 2022. All women who underwent ESI insertion during the study period were included in the study. The ImplanonNXT® 68 mg etonogesterel implant (CM Mediclinic, Thailand) was used. Data were collected via a review of the participants' electronic health information (BestCare) and from the patients via a phone questionnaire carried out by the research team. The primary study objective was the evaluation of menstrual abnormalities during ESI use. The secondary study objectives were early discontinuation of ESI, defined as switching or stopping the method within 12 months of insertion; ESI discontinuation, defined as discontinuation at less than 36 months after ESI insertion; reasons for discontinuation; and side effects of ESI. All women who had ESI insertion during the study period and agreed to participate in the study were included. No women were excluded.

The study was carried out according to principles of Helsinki Declaration and ethical approval was obtained from the institutional review board of King Abdullah International Research Center, Riyadh, Saudi Arabia.

After 2 of the research team independently searched the literature via PubMed looking for previously published similar studies, with permission, the questionnaire was adopted from a study examined the early discontinuation rate of ESI among women in Ethiopia.[10] Two research group members translated the questionnaire from English into Arabic. An independent bilingual expert then carried out a backward translation. The questionnaire was validated through preliminary pilot testing of the questionnaire items in a small sample (23 women). Validity testing was carried out by analyzing whether the questionnaire measured the desired variables and whether the questions were straightforward. The questionnaire items were revised after reviewing the results of the preliminary pilot test, and a final draft of the questionnaire was prepared.

The final questionnaire included equations regarding reasons for choosing ESI, counseling provided, duration of use, ESI side effects, past medical history, and use of other medication. The questionnaire was incorporated in data abstraction sheet with the information gathered from The BestCare. The data sheet also included information regarding women's demographic data, unplanned pregnancy, and management of side effects.

As the ESI discontinuation proportion varied in the literature (3-43%), sample size estimation was carried out using MedCalc software assuming that the discontinuation proportion in the study population was 25% with a confidence interval (CI) ranging from 15-35%. The estimated sample size to have 80% power and 95% CI, accounting for a non-response rate of 15%, was 330 patients. The study population consisted of all women attending obstetrics and gynecology clinics for contraception counseling during the study period (3000 patients). A non-probability consecutive sampling technique was used.

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Statistical analysis. Descriptive statistics were summarized as numbers and percentages (%) for categorical variables and means and medians for numerical variables. The primary outcomes were menstrual abnormalities in patients undergoing ESI and the proportion of patients who discontinued ESI. The risk factors associated with these outcomes were evaluated using the Chi-square test. The multiple logistic regression model included significant factors in the univariate analyses (Chi-square test). Data analysis was carried out using the Statistical Package for the Social Sciences, version 28.0 (IBM Corp., Armonk, NY, USA).

Results. A total of 548 files were reviewed via an electronic health information system (BestCare). The research team phoned all the women, and a total of 345 women answered and agreed to participate in the study.

Women in this study were young with low parity. Their mean body mass index (BMI) was in the overweight range, 22% of women had a history of chronic medical illnesses including endocrine disease in 29%, central system disease in 16%, cardiovascular and respiratory dieases in 8%, genitourinary and gastrointestinal disease in 5%, and other disease in 3%. All women were Muslim and of Middle Eastern ethnicity. High effectiveness was the most common reason for choosing an ESI. The median duration of use was one year. Almost half of the users chose ESI based on doctors' recommendations (Table 1).

In total, 88% of ESI users had some menstrual irregularities. An irregular interval was the most common abnormality, followed by increased flow then. amenorrhea, and increased duration of menstruation.

Menstrual abnormalities were common regardless of age, BMI, or chronic disease. Menstrual abnormalities occurred in 89% of women above or equal to 40 years of age and in 87% of women younger than 40 years (p<0.7). Menstrual abnormalities occurred in 86% of obese women and in 90% of non-obese women (p<0.3). Furthermore, 87% of women with a history of chronic medical disease had menstrual irregularities compared to 89% of healthy women (p<0.6) (Table 2).

After menstrual abnormalities, skin changes were the second most common side effect. A rash was the most common skin change, followed by acne, and itching. Other side effect were mood changes, arm pain at the site of insertion or numbness, headaches, self-reported weight gain, changes in bowel habits, and bothersome vaginal discharge (Table 3).

One patient showed symptomatic and deep ESI migration; the ESI was not palpable in the subcutaneous tissue. Arm x-ray showed the ESI was located in the biceps muscle approximately 2 cm deeper than the overlying skin. The patient required surgical removal of the ESI under general anesthesia and radiographic guidance 36 months after insertion.

One woman had an unintended pregnancy 21 months after ESI insertion. She presented to the clinic 5 weeks after her last menstrual period, and a pelvic ultrasound confirmed 5 weeks of gestation, and the implant was removed. The patient had an average BMI at the time of insertion. The pregnancy continued without any complications. The patient vaginally delivered a normal baby at 38 weeks of age. Another

Table 1 - Baseline characteristics of women using etonogestrel subdermal implants (N=345).

Variables	n (%)
Mean Age, mean±SD	30.7±6.3
Parity, median (IQR)	2 (3)
BMI, mean±SD (rage)	28.09±5.9
Chronic disease*	77 (22.0)
Have you ever used any contraception?	298 (86.0)
Reason for choosing ESI	
High effectiveness	145 (42.0)
Long duration of use	108 (31.0)
Medical advice	66 (19.0)
Fewer side effects	37 (11.0)
Who influenced your decision to choose ESI?	
Doctor`s recommendation	188 (54.0)
Advised from family or friends	99 (29.0)
Self-reading	68 (17.0)
Received counseling from the doctor before insertion	279 (83.0)
Choosing ESI for the second time	32 (9.0)
Duration of use, median (IQR)	12 (16) months

Values are presented as numbers and percentages (%), mean ± standard deviation (SD), or median and interquartile range (IQR). *Chronic disease: endocrine, central nervous system, cardiovascular and respiratory, genitourinary, gastrointestinal, and others.
ESI: etonogestrel subdermal implants, BMI: body mass index

Table 2 - Menstrual abnormality of women using etonogestrel subdermal implants (N=345).

Menstrual abnormality	n (%)	95% CI
Any menstrual abnormality	303 (88.0)	85-92
Abnormal duration		
Increased	134 (39.0)	34-44
Decreased	46 (13.0)	10-17
Amenorrhea	104 (30.0)	25-35
Abnormal amount		
Increased	66 (19.0)	15-23
Decreased	78 (23.0)	18-27
Irregular interval	284 (84.0)	80-88

Values are presented as numbers and percentages (%) and 95% confidence interval (CI).

Table 3 - Side effect of etonogestrel subdermal implants in users.

Side effects	n (%)
Skin changes	157 (46.0)
Rash	104/157 (30.0)
Acne	36/157 (10.0)
Generalized itching	7/157 (2.0)
Mood changes	101 (30.0)
Arm pain or numbness	64/345 (19.0)
Headache	59 (17.0)
Self-reported weight gain	42 (12.0)
Changes in bowel habit	28 (8.0)
Bothersome vaginal discharge	7 (2.0)
Migrated implant	1 (0.3)
Unintended pregnancy	2(0.6)
Multiple side effect	7 (2.0)

Values are presented as numbers and percentages (%).

woman underwent ESI insertion 3 months after cesarean delivery. Pelvic ultrasound carried out 20 weeks after insertion for amenorrhea revealed a 22-week fetus. The pregnancy continued with no complications, and incorrect timing of insertion was diagnosed (Table 3).

At the time of insertion, the women were counseled regarding the expected menstrual abnormalities and informed regarding the hospital policy of not removing the ESI before 12 months of use, unless a consultant gynecologist approved the justification for removal.

Considering the discontinuation rate, 13 women who underwent ESI for less than one month were excluded from the analysis of this outcome, and the data from 332 women were analyzed. In total, 73 (22%, 95% CI: [18-26]) underwent removal of the ESI before the competition date at 36 months (discontinuation rate), whereas 38 (11%, 95% CI: [8-15]) underwent removal of the ESI within the first year of use (early discontinuation rate).

In the women who discontinued ESI (n=74), the reasons for discontinuations were as follows: menstrual irregularity in 63 (85%), mood changes in 25 (33%), skin changes in 24 (32%), arm pain or numbness in 24 (32%), headache in 17 (23%), desire to conceive in 7 (9%), and personal or religious reasons in 6 (8%).

Using multiple logistic regression, the factors affecting the women's decision to discontinue ESI were analyzed (Table 4). After counseling, only 20% of users underwent removal of the ESI, as opposed to 35% with no counseling (p<0.02; OR=0.48, 95% CI: [0.25-0.94]). Furthermore, 32% of women with arm pain or numbness after insertion discontinued ESI, whereas only 19% of asymptomatic women discontinued ESI (p<0.002; OR=2.5, 95% CI: [1.35-4.7]).

Table 4 - Risk Factors for discontinuation of etonogestrel subdermal implants in users.

Factors	Discontinuation	*P*-values*	OR (95% CI)**
Age (years)			
<40	9/35 (26.0)	<0.6	
≥40	65/297 (22.0)		
Body mass index (kg/m²)			
<30	46/203 (23.0)	<0.88	
≥30	25/106 (25.0)		
Counseling			
Yes	53/266 (20.0)	<0.02	0.48 (0.25-0.94)
No	19/54 (35.0)		
Arm pain or numbness			
Yes	24/64 (32.0)	<0.002	2.5 (1.35-4.7)
No	50/268 (19.0)		
Mood changes			
Yes	25/101 (25.0)	<0.56	
No	49/229 (21.0)		
Menstrual abnormalities			
Yes	63//294 (21.0)	<0.4	0.694 (0.3-1.59)
No	10/35 (29.0)		
Headache			
Yes	17/59 (29.0)	<0.164	
No	54/267 (20.0)		

Values are presented as numbers and precentages (%) or odds ratio (OR) and 95% confidence interval (CI). *Chi-square test. **Multiple logistic regression analysis.

Discussion. In this study menstrual abnormalities are the most common side effects of ESI, with 88% of women reporting some form of abnormality; irregular intervals were the most commonly reported abnormality. Prospective studies reported that the rate of any menstrual abnormalities was 41%, a 41% rate of amenorrhea, and a 24-56% rate of infrequent menstruation.[5,11] A retrospective clinic-based study with 166 participants reported that 40% had a regular menstrual cycle, and prolonged menstrual bleeding was the most common side-effect reported.[12] In a cross-sectional study of 860 women, irregular bleeding was reported side by 21% of ESI users, but only 7% reported that the bleeding was bothersome.[13] During the 90-day reference period of a pilot study including 41 women, 24 (58.5%) reported at least one type of abnormality regarding menstrual bleeding.[7] In a retrospective multicenter study of 991 women with a median follow-up period of 7.4 months, 28% reported infrequent bleeding, 33% reported amenorrhea, 15% reported prolonged bleeding, and 16% reported menometrorrhagia.[8] Furthermore, in a multi-country randomized control study including 1003 women with ESI, irregular bleeding occurred in 86%, prolonged bleeding in 56%, amenorrhea in 39%, and heavy bleeding in 35% when compared to women with the copper intrauterine device (IUD) and levonorgestrel implants.[4]

Skin changes occurred in 46% of EIS users, mood changes in 30%, arm pain in 28%, and headache in 17%. In a systematic review, the side-effect profile headaches among users of ESI were reported in 4 (19.1%) of the 21 studies, and the frequency ranged from 5-60%.[3] A reduction in libido was reported in one study, which occurred in 9%. Abdominal pain was reported in up to 50%. Acne was reported by 11-45%. Others reported that the short-term side effects included breast pain and tenderness, emotional lability, mood changes, and dizziness.

In this study, one ESI showed deep migration into the biceps muscle. A prospective study of 100 women in whom a fully trained healthcare professional inserted implant rods was carried out.[14] Measurements were obtained from the insertion site to the distal end of the rods at 12 months post-insertion. At the one-year follow-up, 48 (55%) rods had migrated, most of the migration were caudal and less than 2 cm. A few case reports have described implant migration from the left lung to the pulmonary artery and the axilla.[15-17]

In this study, of 345 ESI users, 2 (0.6%) had unintended pregnancies. One patient became pregnant at the time of the insertion. A large prospective cohort study including 7486 participants compared the failure rate of long-acting reversible contraception (IUDs and implants) with other commonly prescribed contraceptive methods (oral contraceptive pills, transdermal patches, contraceptive vaginal rings, and depot medroxyprogesterone acetate injections).[18] The contraceptive failure rate among participants using pills, patches, or rings was 4.55 per 100 participant-years compared with 0.27 among participants using long-acting reversible contraception.

In a systematic review on the ESI clinical effectiveness, 8 studies reported 100% effectiveness, and the overall Pearl index ranged from 0-1.4.[3] Over 200 reported unintended pregnancies associated with ESI occurred during the first 3 years post-marketing in Australia.[19] Of the 218 cases, 84 were attributed to non-insertion (documented evidence that the ESI had not been inserted, as it could not be located by palpation or ultrasound, or serum etonogestrel levels were negative); 19 unintended pregnancies occurred because of incorrect timing; drug interactions accounted for 8 cases, such as hepatic enzyme-inducing antiepileptic drugs, which lower serum etonogestrel levels; the ESI was expelled in 3 cases; the product failed in 13 cases, and there was insufficient information in 45 cases. Finally, 46 unintended pregnancies were due to prior conception, that is, the conception dates indicated that the patient was already pregnant at the time of insertion.

In this study, 12% of ESI users reported weight gain. A study carried out in the United States in 2019 showed no significant difference in weight gain between ESI users and non-users.[20] A prospective cohort study of 150 Brazilian women compared weight gain, body fat percentage, and bone mineral density (BMD) between copper IUD and ESI users; the findings showed that ESI did not result in a significant difference in BMD at 12 months of use compared to non-users.[21] The ESI users experienced a gain in body weight (4.1 kg at 12 months, $p<0.001$) compared with a decrease in 0.1 kg body weight among copper IUD users. The ESI users gained 2% higher body fat than copper IUD user. Also, the ESI group's lean mass significantly increased at 12 months ($p<0.020$). The contraceptive choice project considered 427 women for analysis and showed that 30% of users gained an average of 2.1±6.7 kg at the end of one year.[22]

In this study the rate of early discontinuation was less than the 19% rate reported in Ethiopia and 25% removal rate in the United States.[23,24] Most likely our low early discontinuation rate is due to the local policy of required consultant approval before removal. The overall discontinuation rate in this study was 22% and the menstrual abnormalities increased the likelihood of discontinuation. Both findings are consistent with literatures. A systematic review of the continuation rate of ESI reported variable continuation rates 25-78% after 3 years of use.[3] An open parallel-group randomized controlled trial compared ESI and levonorgestrel (LNG) implants with a non-randomized control group of women with the copper IUD.[4] The method continuation rate for ESI at 3 years was 12.1 (95% CI: [5.2-22.0]) and 52.0 (95% CI: [41.8-61.2]) for LNG implants per 100 women a year. Bleeding disturbance was the most frequent reason for method discontinuation, which was significantly more common in the ESI group (OR=16.7, 95% CI: [14.4-19.3]) than in the LNG group (OR=12.5, 95% CI: [10.5-14.9]; $p=0.019$).

Study limitations. This study was based on a single center that included a homogenous group. There is a potential recall bias; however, people tend to remember the side effects, which was the focus of this study. Breast feeding was not excluded as possible cause of menstrual abnormality.

A population based study controlling for common confounders is required to assess the prevalence of ESI side effect with low risk of bias.

In conclusion, although menstrual abnormalities are a common side effect of ESI, only 22% of users discontinued this method.

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