The rate and predictors of amenorrhea at 1-year follow-up in women using etonogestrel implant

Running title: Amenorrhea at 1-year follow-up with etonogestrel implant

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Abstract

Objective: To identify the rate and the predictors of amenorrhea related to 1-year use of etonogestrel implant (ESI).

Material and methods: It was a single-center; longitudinal study conducted at The Dairut Central Hospital, Assiut, Egypt from 1st of October 2021 to August 2023 included women who requested ESI for pregnancy prevention for at least 1 year. The rate of amenorrhea associated with 1-year use of ESI was reported. The changes of body mass index (BMI), the uterine and ovarian volume as well as the uterine blood flow during ESI use were also documented. Finally; the predictors associated with amenorrhea were also explored. The data were analyzed by Independent sample t-test, means of non-parametric tests and Chi-square test. Multivariate logistic regression was conducted to test for the predictors.

Results: Three hundred women were included in the study. The rate of amenorrhea at 1-year use of ESI was 38.6%. The predictive model found that fewer bleeding days, the shorter cycle, smaller uterine and ovarian volume, and higher uterine artery pulsatility index were significant predictors for amenorrhea at 1-year of ESI use.

Conclusion: The ENG implant users have a significant rate of amenorrhea at 1-yer use. A significant increase in the BMI, decreases in the uterine and ovarian volume and the uterine blood flow were also observed. The woman should be counseled for the revealed predictors to increase the continuation and satisfaction rate.

Key words: Amenorrhea; Etonogestrel Implant; Implanon; Progesterone only methods.

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Introduction

The use of progestin-only contraceptive methods (POCs) has been increased evidently and progressively over the world in the last few years [1]. POCs are an option for breastfeeding women or for whom an estrogen-containing contraceptive is either contraindicated or causes significant health problems [2, 3]. POCs include progestin-only pills, depot-medroxyprogesterone acetate, ESI, and levonorgestrel intrauterine devices (LNG-IUS) [4].

Unscheduled vaginal bleeding among women using POCs is high and it is responsible for dissatisfaction and discontinuation in the majority of the users [5]. Bleeding patterns associated with POCs have different forms such as amenorrhea, vaginal spotting, pronged heavy bleeding, and sometimes normal monthly menses [6].

The ESI has been available worldwide for more than 15 years [7]. The action of ESI is principally via suppression of ovulation, but it also has effects on cervical mucus and in some women induces a suppression of endometrial proliferation [8]. ESI discontinuation is common in many countries and the majority of those discontinuers is in the childbearing period and is still in need of contraception [9]. ESI discontinue is up to 43% of women prior to completion of the 3 years and a considerable number of those women request early removal because of amenorrhea [10, 11].

Despite the presence of many studies reported the prevalence of ESI associated bleeding [12, 13, 14], a little is known about the rate of amenorrhea and the predictive factors causing amenorrhea after ESI insertion. These predictive factors should be provided to the clients prior to the ESI insertion which may improve acceptance and continuation of ESI. So the aim of this study was to explore the rate and the predictors of amenorrhea related to 1-year use of ESI.

Material and methods

It was a single-center; longitudinal study. It was prospectively registered at Clinicaltrial.gov (NCT05040282). The study was conducted at Dairut Central Hospital, Assiut, Egypt from 1st of October 2021 to August 2023. The protocol of the study was approved by The Assiut University Medical Ethical Review Board (IRB17101567).

Eligible participants

We included women aged between 18-40 years who were not lactating) more than 12 month postpartum). Those women had regular menstrual cycles (21–35 days length with less than 7 bleeding days) and wanted to use ESI only for pregnancy prevention for at least 1-year. The women had any contraindications for progesterone only contraception in accordance with WHO eligibility criteria [15] or refused the participation in the study were excluded.

Enrollment

Written consent was obtained from all eligible participants. Then; women were subjected to detailed demographic, menstrual, obstetrics and contraceptive history. BMI was calculated. Transvaginal ultrasound (TVS) examination by the DP-10 ultrasound device (Mindray - China) using 4- to 7-MHz was used to assess the uterine and ovarian volume (Length x Width x antero-posterior diameter). Uterine artery was demonstrated by the color Doppler immediately after the crossing of the external iliac artery. The pulsatility index (PI) of both uterine arteries was measured and the average value was calculated [16].

After that; the principle investigator inserted ESI (etonogestrel 68 mg-Implanon NXT; Organon, USA Inc.) in all participants during their menses. The bleeding pattern was followed up by the menstrual diary which included bleeding and spotting days.

Follow-up plan

All women were instructed to come for follow-up at 6 and 12 months. The menstrual pattern was assessed by the menstrual diary. Amenorrhea was considered if the cycle stopped for three consecutive cycles. Most of the women brought their diaries during the follow-up visit which were reviewed by the principal investigator. Any women, who did not bring a diary, were asked to phone the principal investigator to complete the diary and they had to bring the missed diary at their next scheduled visit. BMI, the uterine and ovarian volume and uterine artery Doppler indices were also assessed. The side effects of ESI were also documented.

Termination visit

At study termination (12 month), the final status of the participants was classified as “completed study", "lost from follow up" or "discontinued the ESI”. Additional 4 weeks were needed for the participants who were lost from follow-up. Participants would continue the ESI and the follow-up visits if they wish so.

The study outcomes

The primary outcome was the rate of amenorrhea at the 1-year of ESI use. The secondary outcomes included the potential predictors of the amenorrhea at 1st year of ESI use and the changes in BMI, uterine volume, ovarian volume and uterine artery Doppler among ESI users.

Sample size

A previous study reported that the rate of amenorrhea with ESI at one year of use is 22% [17]. Using population size 1000000 and hypothesized % frequency of outcome factor in the population equal to 22% with confidence limits 5%, a total sample size of at least 300 women were needed in the study assuming the rate of lost from follow-up 10% (Epi-info™, CDC, USA).

Statistical analysis

The data was collected and analyzed by the Statistical Package for Social Science (SPSS Inc., Chicago, version 25). Shapiro-walik test was used first, to test for the distribution of the variables. Normally distributed variables were expressed in means ± standard deviation and compared either by Independent sample t-test. While abnormally distributed variables were presented by medians and compared using means of non-parametric tests. Chi-square was used to compare proportions. Multivariate logistic regression was conducted to test for predictors of amenorrhea among ESI users. The results of the logistic regression were expressed in Odds ratio, confidence interval (C.I.), and p-values. We constructed receiver operating characteristic (ROC) curves to evaluate the sensitivity, specificity, positive predictive value, negative predictive value, the accuracy of the potential predictors revealed by logistic regression. The p-value <0.05 was considered statistically significant.

Results

Three hundred twenty-three women were counseled for participation. Twenty-three women were excluded during the screening phase. However; 35 women were lost from follow up and 11 women requested ESI removal. So, 254 women finally analyzed **(Figure 1)**.

The mean age of the women was 28.45. About 50% had bleeding days of 2-3 days and a cycle length of 21-28 days. The median of parity was 3. About 44.7% of women delivered before by CS only. The most frequent contraceptive method used before was COCs (24.4%) **(Table 1)**. At 6 months, 27.5 % of women used ESI had amenorrhea, while at 1-year, 38.6% of women used ESI had amenorrhea **(Table 2)**.

There was a statistically significant difference

between the women regards the BMI and uterine artery PI during the first year follow up visits. However; there was a statistically significant difference between the uterine and ovarian volumes from baseline and 12 month and also from 6 month to 12 month. While no a statistical significant difference was noted between baseline and 6 month (p=0.372, p=0.247; respectively) **(Table 3)**. At 6 month; the breast tenderness (12.6%) was the common side effect. While at 12 month; the most common side effect was nausea (15.4) **(Table 4)**.

The multiple logistic regression model confirmed that fewer bleeding days (p=0.020), the shorter cycle (p=0.002), smaller uterine (p=0.000) and ovarian volume (p=0.002), and higher uterine artery PI (p=0.000) were significant predictors for amenorrhea at 12 month of ESI use **(Table 5)**.

A ROC curve analysis included the revealed predictors of amenorrhea at 12 month of ESI use in the predictive model. The analysis demonstrated that the bleeding days ≤ 3 days, cycle length ≤ 28weeks, uterine volume ≤ 44, ovarian volume ≤ 5ml, and uterine artery PI > 2.62 clearly predicted the amenorrhea with a sensitivity (68.37 %, 71.43%, 86.73%, 69.39%, and 65.31%; respectively) **(Table 6) (Figure 2)**.

Discussion

The present work demonstrated that 38.6% of women who were using ESI had amenorrhea at the end of the first year of use. Moreover; our results revealed that the fewer bleeding days, short menstrual cycle, lower uterine and ovarian volume and high uterine PI were risk factors to develop amenorrhea at 1 year use of ESI.

The number of users of POCs of contraception has been increasing progressively because they are effective, safe and the long-acting properties of some of them [18]. The subdermal implants are attractive because they are simple, long-term action, and with relatively little contraindications, with additionally non-contraceptive benefits [19].

Despite abnormal bleeding patterns with the ENG implant may reach up to 78% in a 3-month period, 50% of women will improve with continuous use and 30% of users will be amenorrheic by one year of use [20]. Most implant users will experience a reduction in the frequency of menstrual bleeding with time [21]. The main cause of unscheduled bleeding with ESI is due to the significant endometrial thinning [22]. With sustained use of method, inhibition of ovulation will occur; this lead to a great improvement in the bleeding pattern [23].

In our study; the rate of amenorrhea at 6 month and 12 month after ESI use was 27.5% and 38.6%. Yildizbas B et al reported that the rate of amenorrhea after 3 month of ESI use was 32.1% [24]. Mansour D et al., in their study found that the rate of amenorrhea was 22% after three years of use [17].

In this study; the rate of discontinuation of ESI was 2.2% and 4.3% at 6 and 12 month of ESI use; respectively. All of them were complaining of abnormal uterine bleeding and none of them requested ESI removal due to amenorrhea. The relation between abnormal uterine bleeding and the early removal of the implant is very strong.

Removal rates for bleeding range from less than 1% in Southeast Asia, 22.6% in England and 13.0% in USA [7]. Harvey C et al. study showed that the continuation at 6 months after insertion was 94% of women and 74% continued at 1 year [25]. Again; Moray K.V et al. concluded that the continuation rates were 89% at 6 months, 75% at 1 year [26]. The main cause of the discontinuation was the frequent and/or unpredictable bleeding. So, we are in the same track with these previous studies.

Our results showed that there was a statistically significant increase in BMI from baseline to 12 month. Weight gain is a common side-effect of hormonal contraceptives and is given as an important reason for method discontinuation [27]. Casey PM et al found no

relation between obese women and implant removal for bleeding [28].

A significant decrease in the ovarian volume had been observed in this study. This can be easily explained. ESI suppress FSH and LH with continued use, hence decreasing the follicular activity and lead to decrease in ovarian volume [29].

The uterine volume and uterine artery blood flow decreased significantly at 1-year of ESI use. Prolonged use of POCs associates with a pseudogestational status and hypoestrogenemia which causes significant decrease in blood flow to and inside the uterus [30].

The most common reported side effects of ESI during the follow-up visits were the breast tenderness and nausea. Hidalgo MM et al. found that the ovarian cysts were detected in 7.2%, and 26.7% at 6, and 12 months [31]. We reported a lower figure than he did (5.2% at 6 month and 6.7% at 12 month). The acne developed in 6.3% at 6 month and 5.7 % at 12 month in this study. Funk S et al. reported a figure of 23.8% [32]. While mood changes (17.1%) and acne (26.8%) were the most common side effects of ESI in Yildizbas B et al study [24]. The most commonly reported side effect was headache (15.3%) in Blumenthal PD et al study [33]. In contrast; Olaifa BT et al mentioned that the arm discomfort and weight gain were causes of women dissatisfaction and devise removal [34].

The interesting issue in our study was the trial to explore the potential clinical and ultrasonographic predictors associated with amenorrhea at 1 year use of ESI. Mansour D et al. found in their predictive model that implant users with favorable bleeding in the first few months are likely to continue with favorable bleeding over the next 2 years [11]. Darney PD et al. evaluated the predictors of amenorrhea during the first year after levonorgestrel 52 mg intrauterine system (IUS) placement [35]. They found that the amenorrhea at 12 months is most common among women with shorter baseline duration of menstrual flow. So; we are on the same track with their results.

The small uterine volume was a significant predictor for the development of amenorrhea at 12 month of ESI use. The uterine shrinkage had been observed before after using of progestogens for long time [30]. This effect was secondary to changes in uterine artery blood flow from before to after progestogens use. Also; our predictive model proved that the uterine artery PI was a risk factor for amenorrhea at 12 month of ESI use.

There is only one study pointed to the predictors associated the amenorrhea at 12 month of ESI use. Tsevat D et al. in a retrospective study found that patients with amenorrhea at 12 months had higher baseline BMI and were more likely to be amenorrheic prior to insertion [36]. We did not find these factors in our study.

This study has both strengths and weaknesses. To our knowledge; this is the first study which addressed the clinical, ultrasound and Doppler parameters as predictors for development of the amenorrhea at 1-year of ESI use. Furthermore, the ultrasound assessment was performed by a single investigator to decrease the bias. We were able to recruit our calculated sample size for achieving sufficient power to detect a clinically significant difference according to our primary outcome.

However, the present work had some limitations. Subjective rather than objective evaluation for the bleeding pattern by the menstrual diary was a limitation. We tested only the clinical effect of ESI methods but we did not test any markers like estradiol. Long term follow up (more than 12 month) is essential needed. The studying of predictors associated with other uterine bleeding pattern was not addressed in our study. Moreover, the small sample size that was available for the final analysis at 12 month is 254 patients.

Conclusion

Momentous number of women will have amenorrhea at the end of first year of ESI use. The ESI users are associated with significant increase in the BMI, decreases in the uterine and ovarian volume and the uterine blood flow. The fewer bleeding days, short menstrual cycle, lower uterine and ovarian volume and high uterine PI were significant predictors for development of amenorrhea at 1-year use of ESI.

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Authors' contributions

Conception and design of the study: AMK and MHS. Data collection: AMA and AMA. Data analysis and interpretation: MHS. Statistical analysis: AMK. Manuscript preparation: AMK and AMA. Recruitment of patients: AMA. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are attached as a Supplementary file.

Declarations

Ethics approval and consent to participate

Ethical approval is attached as a Supplementary material document. The institutional review board approved the study protocol (code: IRB17101567) in November 2021, and the authors obtained written informed consent from all patients before inclusion in the study.

Consent for publication

All patients provided written informed consent that the study results would be published.

Competing interests

The authors declare that they have no competing interests.

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References

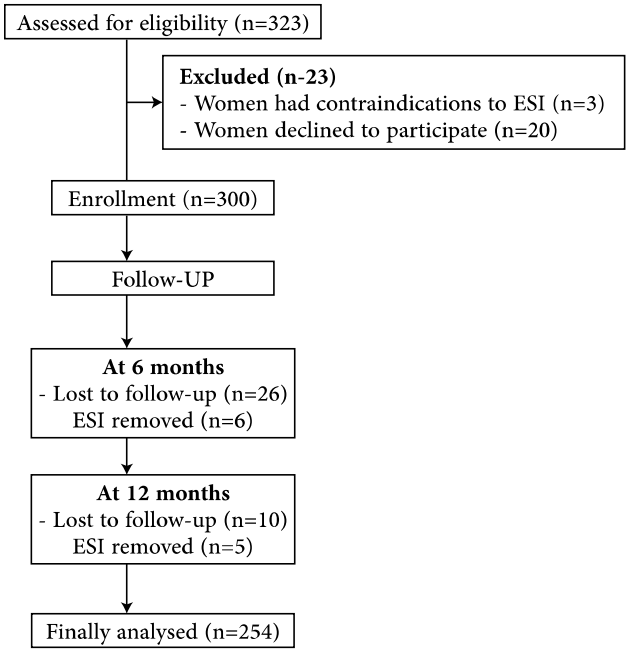
1. Zevidah Vickery, Tessa Madden, Qiuhong Zhao, Gina M. Secura, Jenifer E, Jeffrey F Peipert. Weight change at 12 months in users of three progestin-only contraceptive methods. Contraception. 2013; 88 (4), 503–508.
2. Heinemann L.A., Dinger J.C., Assmann, A., Minh T.D. Use of oral contraceptives containing gestodene and risk of venous thromboembolism: outlook 10 years after the third-generation "pill scare". Contraception. 2010; 81:401–407.
3. Grimes DA, Lopez LM, O'Brien PA, Raymond EG. Progestin-only pills for contraception. 2013. Cochrane Database of Systematic Reviews, Issue 11. Art. No.: CD007541.
4. Diedrich JT, Zhao Q, Madden T, Secura GM, Peipert JF. Three-year continuation of reversible contraception. Am J Obstet Gynecol. 2015; 213(5): 662.e1-8.
5. Moreau C, Cleland K, Trussel J. Contraceptive discontinuation attributed to method dissatisfaction in the United States. Contraception. 2007; 76(4):267-72.
6. Stanczyk FZ. Pharmacokinetics and

potency of progestins used for hormone replacement therapy and contraception. Rev Endocr Metab Disord. 2002; 3(3):211-24.

7. Casey PM, Long ME, Marnach ML, Bury JE. Bleeding related to etonogestrel subdermal implant in a US population. Contraception. 2011; 83(5):426-30.
8. Glasier A. Implantable contraceptives for women: effectiveness, discontinuation rates, return of fertility, and outcome of pregnancies. Contraception. 2002; 65(1):29-37.
9. Bradley S, Schwandt H, Khan S. Levels trends and reasons for contraceptive discontinuation. DHS Analytical Studies No.20. 2008; Calverton, Maryland, USA: ICF Marco.
10. Steyn, P. S. and J. Kluge. "Contraceptives: A guide to product selection." South African Family Practice. 2014; 52: 499-504.
11. Mansour D, Fraser IS, Edelman A, Vieira CS, Kaunitz AM, Korver T et al. Can initial vaginal bleeding patterns in etonogestrel implant users predict subsequent bleeding in the first 2 years of use? Contraception. 2019; 100(4):264-268.
12. Weisberg E, Fraser I. Australian women's experience with Implanon. Aust Fam Physician. 2005; 34:694–6.
13. Weisberg E, Hickey M, Palmer D, et al. A randomized controlled trial of treatment options for troublesome uterine bleeding in Implanon users. Hum Reprod. 2009; 24:1852–61.
14. Agarwal A, Verma A, Agarwal S, Shukla RC, Jain M, Srivastava A. Antral follicle count in normal (fertility-proven) and infertile Indian women. Indian J Radiol Imaging. 2014; 24(3):297-302.
15. Altshuler AL, Gaffield ME, Kiarie JN. The WHO's medical eligibility criteria for contraceptive use: 20 years of global guidance. Curr Opin Obstet Gynecol. 2015; 27(6):451.
16. Ali MK, Amin ME, Amin AF, Abd El Aal DEM. Evaluation of the effectiveness of low-dose aspirin and omega 3 in treatment of asymmetrically intrauterine growth restriction: A randomized clinical trial. European journal of obstetrics, gynecology, and reproductive biology. 2017; 210:231-5.
17. Mansour D, Korver T, Marintcheva-Petrova M, Fraser IS. The effects of Implanon on menstrual bleeding patterns. Eur J Contracept Reprod Health Care. 2008; 13 Suppl 1:13-28.
18. Morotti M, Remorgida V, Venturini PL, Ferrero S. Progestin-only contraception compared with extended combined oral contraceptive in women with migraine without aura: a retrospective pilot study. European journal of obstetrics, gynecology, and reproductive biology. 2014; 183:178-82.
19. Black KI, Trane W, Dorney E, Mola G. A cross-sectional study of factors associated with immediate postpartum uptake of contraceptive implants in Papua New Guinea. Contraception. 2023; 117:25-29.
20. Hohmann H, Creinin MD. The contraceptive implant. Clin Obstet Gynecol. 2007; 50(4):907-17.
21. Weisberg E, Hickey M, Palmer D, O'Connor V, Salamonsen LA, Findlay JK et al. A randomized controlled trial of treatment options for troublesome uterine bleeding in Implanon users. Hum Reprod. 2009; 24:1852–61.
22. Zigler RE, McNicholas C. Unscheduled vaginal bleeding with progestin-only contraceptive use. Am J Obstet Gynecol. 2017; 216(5):443-450.
23. Smith OP, Critchley HO. Progestogen only contraception and endometrial break through bleeding. Angiogenesis. 2005; 8: 117–126.
24. Yildizbas B, Sahin HG, Kolusari A, Zeteroglu S, Kamaci M. Side effects and acceptability of Implanon: a pilot study conducted in eastern Turkey. Eur J Contracept Reprod Health Care. 2007; 12(3):248-52.
25. Harvey C, Seib C, Lucke J. Continuation rates and reasons for removal among Implanon users accessing two family planning clinics in Queensland, Australia.

Contraception. 2009; 80(6):527-32.

26. Moray, K.V., Chaurasia, H., Sachin, O, Joshi B. A systematic review on clinical effectiveness, side-effect profile and meta-analysis on continuation rate of etonogestrel contraceptive implant. Reprod Health. 2021; 18(1): 4.doi: 10.1186/s12978-020-01054-y
27. Beksinska ME, Smit JA, Kleinschmidt I, Milford C, Farley TM. Prospective study of weight change in new adolescent users of DMPA, NET-EN, COCs, nonusers and discontinuers of hormonal contraception. Contraception. 2010; 81(1):30-4.
28. Casey PM, Long ME, Marnach ML, Fleming-Harvey J, Drozdowicz LB, Weaver AL. Association of body mass index with removal of etonogestrel subdermal implant. Contraception. 2013; 87(3):370-4.
29. ESHRE Capri Workshop Group. Ovarian and endometrial function during hormonal contraception. Hum Reprod. 2001; 16(7):1527-35.
30. Shaaban OM, Ali MK, Sabra AM, Abd El Aal DE. Levonorgestrel-releasing intrauterine system versus a low-dose combined oral contraceptive for treatment of adenomyotic uteri: a randomized clinical trial. Contraception. 2015; 92(4):301-7.
31. Hidalgo MM, Lisondo C, Juliato CT, Espejo-Arce X, Monteiro I, Bahamondes L. Ovarian cysts in users of Implanon and Jadelle subdermal contraceptive implants. Contraception. 2006; 73(5):532-6.
32. Funk S, Miller MM, Mishell DR Jr, Archer DF, Poindexter A, Schmidt J et al. Implanon US Study Group. Safety and efficacy of Implanon, a single-rod implantable contraceptive containing etonogestrel. Contraception. 2005; 71(5):319-26.
33. Blumenthal PD, Gemzell-Danielsson K, Marintcheva-Petrova M. Tolerability and clinical safety of Implanon. Eur J Contracept Reprod Health Care. 2008; 13 Suppl 1:29-36.
34. Olaifa BT, Okonta HI, Mpinda JB, Govender I. Reasons given by women for discontinuing the use of progestogen implants at Koster Hospital, North West province. S Afr Fam Pract (2004). 2022; 64(1): e1-e7.
35. Darney PD, Stuart GS, Thomas MA, Cwiak C, Olariu A, Creinin MD. Amenorrhea rates and predictors during 1 year of levonorgestrel 52 mg intrauterine system use. Contraception. 2018; 97(3):210-214.
36. Tsevat, D., R. Mercier, C. Bernheimer, S. Lin and B. Schwartz. "Predictors of Amenorrhea in Adolescents Using the Etonogestrel Contraceptive Implant." Journal of Pediatric and Adolescent Gynecology. 2022; 35(2): 203.



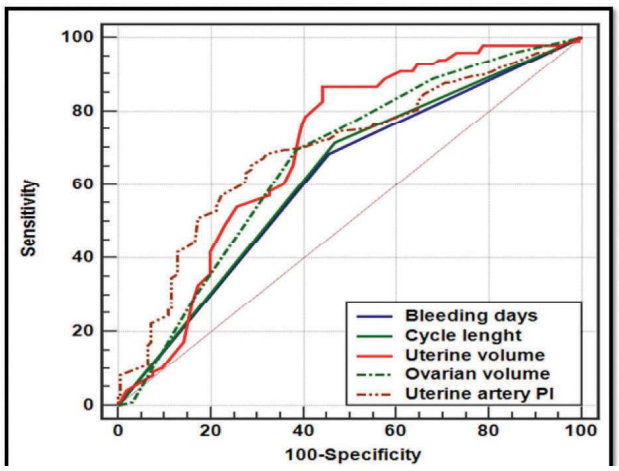


Table 1: Demographic, menstrual, obstetric, contraceptive data of the participants

	No (%) (300)
Demographic data	
Age (years), n (%)	
< 25	106(35.3)
25 - 30	83(27.7)
> 30	111(37.0)
Mean ± SD	28.45 ± 6.83
Residence, n (%)	
Urban	140(46.7)
Rural	160(53.3)
Level of education, n (%)	
Illiterate	54(18.0)
Basic education	133(44.3)
Secondary or more	113(37.7)
Employment, n (%)	151(50.3)
Menstrual data	
Bleeding days, n (%)	
2-3	153(51.0)
> 3	147(49.0)
Cycle length, n (%)	
21-28	160(53.3)
29-35	140(46.7)
Obstetric data	
Parity, Median (Range)	3.0 (1.0-7.0)
Number of living children, Median (Range)	3.0 (1.0-7.0)
Duration from last pregnancy (month), Median (Range)	33.0 (15.0-81.0)
Mode of delivery, n (%)	
VD	124(41.3)
CS	134(44.7)
VD+CS	42(14.0)
History of previous abortion, n (%)	23(7.7)
Contraceptive data, n (%)	
IUD	32(10.7)
ESI	71(23.7)
COCs	73(24.3)
POPs	18(6.0)
DMPA	24(8.0)
CI	15(5.0)
Others	8(2.7)
No	59(19.7)

CI combined injectable, **COCs** combined contraceptive method, **Cs** caesarian section, **DMPA** depot-medroxyprogesterone acetate, **ESI** etonogestrel subdermal implant, **IUD** intrauterine device, **POPs** progesterone only pills, **VD** vaginal delivery

Table 2: The rate and types of uterine bleeding pattern during ESI use at 6 and 12 months

Uterine bleeding pattern	No (%)
At 6 months: (n= 269)	
Amenorrhea	74(27.5)
Spotting	70(26.0)
Hypomenorrhea	66(24.5)
Heavy prolonged bleeding	38(14.2)
Normal menses	21(7.8)
At 1-year: (n= 254)	
Amenorrhea	98(38.6)
Spotting	68(26.8)
Hypomenorrhea	53(20.9)
Heavy prolonged bleeding	29(11.4)
Normal menses	6(2.4)

Table 3: BMI, uterine, ovarian volume and uterine artery PI volume changes during 1st year of ESI use

	Mean ± SD	P-value[1]	P-value[2]	P-value[3]
BMI(kg/m^2)				
Baseline	24.53 ± 2.76			
6 months	26.85 ± 3.12	0.000*	0.000*	0.000*
12 months	29.02 ± 2.83			
Uterine volume (mL)				
Baseline	43.51 ± 13.17	0.372	0.000*	0.000*
6 months	42.33 ± 13.37			
12 months	38.05 ± 13.21			
Ovarian volume(mL)				
Baseline	6.26 ± 1.79	0.247	0.000*	0.000*
6 months	5.97 ± 1.62			
12 months	4.71 ± 1.34			
Uterine artery PI				
Baseline	2.65 ± 0.70	0.000*	0.000*	0.000*
6 months	3.91 ± 0.63			
12 months	4.35 ± 0.60			

BMI body mass index, **mL** milliliter, **PI** Pulsatility index
P-value[1] between baseline and 6 months
P-value[2] between baseline and 12 months
P-value[3] between 6 months and 12 months
* Statistical significant difference ($P < 0.05$)
The data did not include women who lost from follow up or stopped using the method.

Table 4: Reported side effects of ESI method at 6 months and 12 months

Side effects	No.	%
At 6 months: (n= 269)		
Breast tenderness	34	12.6%
Headache	31	11.5%
Nausea	35	13.0%
Ovarian cysts	14	5.2%
Acne	17	6.3%
Stomach cramping	22	8.2%
Dizziness	17	6.3%
No side effects	171	63.6%
At 12 months: (n= 254)		
Breast tenderness	33	13.0%
Headache	32	12.6%
Nausea	39	15.4%
Ovarian cysts	17	6.7%
Acne	16	7.5%
Stomach cramping	19	6.3%
Dizziness	17	6.7%
No side effects	157	61.8%

ESI etonogestrel subdermal implant

Table 5: Multiple logistic regression analysis for risk factors of amenorrhea at 12 months among ESI users

Variables	P-value	OR	95% C.I.	
			Lower	Upper
Bleeding days	**0.020***	2.079	1.121	3.858
Cycle length	**0.002***	2.647	1.421	4.930
Uterine volume baseline	**0.000***	0.949	0.925	0.974
Ovarian volume baseline	**0.002***	0.756	0.633	0.904
Uterine artery PI. baseline	**0.000***	2.544	1.637	3.955

OR Odds ratio, **CI** confidence interval

Table 6: Sensitivity, Specificity, +PV, -PV, accuracy and AUC of the potential predictors for amenorrhea at 1-year among ESI users

Risk factors	Cut-off	Sensitivity	Specificity	+PV	-PV	Accuracy	AUC
Bleeding days	≤ 3	68.37	54.49	48.6	73.3	59.8	0.614
Cycle length	≤ 28	71.43	53.21	49.0	74.8	60.2	0.623
Uterine volume	≤ 44	86.73	55.77	55.2	87.0	67.7	0.699
Ovarian volume	≤ 5	69.39	61.54	53.1	76.2	64.6	0.666
Uterine artery PI	> 2.62	65.31	71.15	58.7	76.6	68.9	0.666

AUC area under the curve, **ESI** etonogestrel subdermal implant, **+PV** positive predictive value, **-PV** negative predictive value