ISRG JOURNAL OF CLINICAL MEDICINE AND MEDICAL RESEARCH [ISRGJCMMR]

ISRG PUBLISHERS
Abbreviated Key Title: ISRG J Clinic.Medici.Medica.Res.
ISSN: 3048-8850 (Online)
Journal homepage: https://isrgpublishers.com/cmmr/
Volume – II, Issue -I (January- February) 2025
Frequency: Bimonthly

A COMPARATIVE ANALYSIS OF THE COMPLICATIONS, AND REASONS FOR DISCONTINUATION OF ETONOGESTREL AND LEVONORGESTREL CONTRACEPTIVE IMPLANTS

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| **Received:** 10.02.2025 | **Accepted:** 15.02.2025 | **Published:** 24.02.2025

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Abstract

Background

Etonogestrel and levonorgestrel contraceptive implants, though safe, but exhibits adverse effects severe enough to necessitate discontinuation.

Objective

This study intends to compare the complication rates, and reasons for discontinuation of etonogestrel and levonorgestrel contraceptive implants, at Niger Delta University Teaching Hospital (NDUTH)

Method and materials

It was a retrospective cross-sectional study of 1232 women who used etonogestrel and levonorgestrel contraceptive implants, and discontinued during the study period. A total of 324 women used etonogestrel implants, while 908 used levonorgestrel.

Data collected was: Socio-demographic characteristics, the duration of contraceptive use, the complications experienced, and the reasons for implant removal.

DOI: 10.5281/zenodo.14916568

Results
The mean age of the women who took etonogestrel implants was significantly higher than that for levonorgestrel, t = 3.99(0.85, 2.49), p = 0.0001.

Regarding parity, significantly more women of very high parity (grand multiparous women) took etonogestrel p = 0.007. While more of nulliparous women took levonorgestrel implants p = 0.005.

The mean duration of contraceptive use was significantly higher among women who used levonorgestrel implant, t = 2.23, p = 0.02, and more women replaced etonogestrel implant than levonorgestrel, odds ratio = 17.43[10.83, 28.05], p = 0.001.

Compared to levonorgestrel implants, women who used etonogestrel significantly had more complications, p = 0.002, especially vaginal bleeding (p = 0.002), weight gain (p = 0.0001), and breast pain (p = 0.001).

Expired implant (44.7%) was the commonest reason for removal, and the rate was significantly higher among women who used levonorgestrel, p = 0.001.There was no difference in the discontinuation (from complications) between the two groups, except heavy vaginal bleeding, which was twice higher among those who used etonogestrel, odds ratio = 2.59[1.85, 3.63], p = 0.001.

Conclusion
Etonogestrel implant has more complications than levonorgestrel, especially irregular vaginal bleeding, weight gain, and breast pain.

Keywords: *etonogestrel, levonorgestrel, implants, complications.*

INTRODUCTION

The most common etonogestrel implants in Nigeria are implanon and nexplanon. Though implanon is as effective as nexplanon, it is being replaced globally with nexplanon. [1, 2] This is because it has the advantage of being radio-opaque, therefore it is radiologically detectable. [2] It is also designed to minimize insertion errors with a preloded applicator. [2] The insertion errors, most commonly encountered with implanon are: none release (insertion) of the implant, and insertion into the muscle tissue, instead of subdermally. [2, 3]

Pharmacologically, implanon and nexplanon are the same drug; they have the same dose of progestogen as active ingredient; 68ug of etonogestrel. They are easy to insert and remove because they are made of single rod polymer matrix. Their mechanisms of action are similar, so is their contraceptive effectiveness, and failure rates. The duration of action for both implants is 3 years. [1]

With respect to the mechanism, etonogestrel binds to the progesterone receptors in the ovaries (with high affinity), which triggers inhibition of luteinizing hormone, leading to ovulation suppression. [4] It also cause thinning of the cervical mucus, and inhibition of implantation. [4, 5]

Regarding contraceptive effectives (or failure rate), etonogestrel contraceptive implants are at the apex of contraceptive effectiveness; with very low failure rates (measured as pearl index). [6, 7] Whereas some studies reported the failure rate as zero, (Pearl Index, 0; 95% CI 0.0–0.2) [6] some other studies had pearl index of 0.02 (95% CI, 0.00–0.06), [7] and 0.34 pregnancies per 100 women in a year. [8]

With respect to complications of etonogestrel contraceptive implants, pain at the insertion site is quite common, and a systematic review reported the rate as 1.9%. [9] Redness and swelling are also common, and a study reported the rate as 4.7%. [10]

Majority of the complications of contraceptive implants are hormone related, and irregular vaginal bleeding is the most common. [11] Other reported complications of etonogestrel are: headache, loss of libido, weight gain, breast tenderness and acne. [8, 11] On the contrary, some women have absence of menses (amenorrhea) or scanty menses, instead of vaginal bleeding. [7]

Though the complications of etonogestrel contraceptive implants are many, only a few are troublesome to the extent that warrants implant discontinuation. The most frequently reported reason for discontinuation is heavy irregular vaginal bleeding, and reported rates were 18.4% at Abuja in Nigeria, [12] and 19.3% in Canada. [13] Other relatively common reasons are weight gain and headache. [7]

Regarding levonorgestrel contraceptive implants, the one most commonly used in Nigeria is Jadelle, [14] it is made of 2 silastique rods containing 75mg of levonorgestrel each. [14] Though insertion and removal are easy, it is more time consuming than etonogestrel implants because of the double rods. [15, 16] The duration of pharmacological effectiveness is 5 years, which is an advantage over etonogestrel implants [16]

Jadelle has been reported as a very potent contraceptive implant, whose effectiveness is comparable to that of implanon and nexplanon. [14, 15] Various studies in Nigeria have reported very low pregnancy rates: At Lagos University Teaching Hospital, the failure rate was 0.27 per 100 women-years.[17] In Port Harcourt, the pearl index was 0.002, [15] and at Ilorin, the pearl index was zero. [14]

The adverse effects (or complications) of jadelle are similar to that of nexplanon and implanon. A studies at llorin reported irregularity vaginal bleeding (60.9%) as the most common complication, [14] Similar studies reported 60.9 % in Port Harcourt, [15] and 31.1% at Uyo. [18] A study from another center in Port Harcourt reported amenorrhea (41.3%) as the most common complication of jadelle. [19] Other, but relatively less common complications are: breast tenderness, headache and dizziness. [18]

DOI: 10.5281/zenodo.14916568

With respect to discontinuation of jadelle implant, reported rates in Nigeria were: 11.1% in Ilorin, [14] and 13.7% in Calabar. [20] As it is with nexplanon and implanon, the most commonly reported reasons for discontinuation were irregular vaginal bleeding; 43.3% in Calabar, and 51.4% in Lagos. [17].

This study intends to bring to limelight the variations in complications between etonogestrel and levonorgestrel contraceptive implants. Our results are expected to boost contraceptive counseling, improve patients' knowledge, and make a better choice.

AIM AND OBJECTIVES

This study intends to compare the complication rates, and the reasons for discontinuation of etonogestrel and levonorgestrel contraceptive implants, at Niger Delta University Teaching Hospital (NDUTH).

METHODOLOGY

Study site

This study was carried out at the family planning unit, department of obstetrics and gynaecology, NDUTH.

Study design

It was a retrospective cross-sectional study of 1232 women who used etonogestrel and levonorgestrel contraceptive implants, and discontinued during the study period. The study was carried out from January 2019 to December 2023.

Inclusion criteria

Included in this study were women who used etonogestrel contraceptive implants (nexplanon, and implanon), and levonorgestrel implants (jadelle) in NDUTH, and discontinued either because of unbearable complications, or it has expired or they was to get pregnant.

Exclusion criteria

Excluded from this study were women still on the above contraceptive implants, and those who inserted the implants elsewhere, and were removed in NDUTH.

Data collection

During the study period, a total of 1232 women who used etonogestrel and levonorgestrel contraceptive implants, and discontinued were identified. Out of these, 324 women used etonogestrel implants, while 908 used levonorgestrel.

The case notes of these women were retrieved from the hospital record, and information extracted was: the socio-demographic characteristics of the women, the duration of contraceptive use (in months), the rank of the inserter (nurse or resident doctor), the rank of the remover, the complications experienced, and the reasons for implant removal.

Data analysis

Data was coded into (IBM) SPSS Statistical Package for Windows (version 25), and Epi Info Statistical Software (version 7) and analyzed. Results were presented in tables as rates, proportions, and mean with standard deviation. Test of significance was by odds ratio, and differences in mean was compared with independent Student's t-test. Using confidence interval of 95%, statistical significance was set as p values of ≤ 0.05.

Ethical approval

Approval to proceed with this study was granted by the NDUTH ethical committee, with registration number NDUTH/REC/0033/2024.

RESULTS

Table 1: Socio-demographic characteristics of the women

Socio-demographic factor	Type of implant		Total N = 1232	Odds ratio	Confidence interval	P value
	Etonogestrel N = 324(26.3%)	**Levonorgestrel N = 908(73.7%)**				
Maternal Age						
≤ 19 years	27(8.3%)	161(17.7%)	118(15.3%)	0.42	[0.27, 0.65]	0.003*
20-24 years	58(17.9%)	209(23.0%)	267(21.6%)	0.73	[0.53, 1.07]	0.003*
25-30 years	99(30.6%)	260(28.6%)	359(29.1%)	1.10	[0.83, 1.45]	0.51
30-34 years	70(21.6%)	138(15.2%)	208(16.9%)	1.54	[1.12, 2.12]	0.008*
≥ 35 years	70(21.6%)	140(15.4%)	210(17.1%)	0.28	[0.19, 0.39]	0.0001*
Mean maternal age	29.20 ± 6.48	27.53 ± 6.462		t= 3.99	[0.85, 2.49]	0.0001*
Parity						
Nulliparous (para 0)	40(12.3%)	174(19.2%)	214(17.4%)	0.59	[0.41, 0.86]	0.005*
multiparous (para 1-4)	220(67.9%)	610(67.2%)	830(67.4%)	1.03	[0.79, 1.36]	0.81
Grand multiparous (≥ para 5)	64(19.8%)	124(13.7%)	188(15.3%)	1.56	[1.12, 2.17]	0.007*
Marital status						
Married	200(61.7%)	555(60.1%)	755(61.3%)	1.03	[0.79, 1.33]	0.84
Single	124(38.3%)	353(38.9%)	477(38.7%)			

DOI: 10.5281/zenodo.14916568

Tribe						
Ijaw	234(72.2%)	688(75.8%)	922(74.8%)	0.83	[0.62, 1.11]	0.21
Igbo	39(12.0%)	120(13.2%)	159(12.9%)	0.90	[0.61, 1.32]	0.58
Yoruba	12(3.7%)	25(2.8%)	37(3.0%)	1.36	[0.67, 2.74]	0.38
Hausa/Fulani	1(0.3%)	5(0.6%)	6(0.5%)	0.56	[0.07, 4.80]	0.59
other tribes	39(12.0%)	70(7.7%)	109(8.9%)			
Occupation						
House wife	47(14.5%)	117(12.9%)	164(13.3%)	1.15	[0.08, 1.65]	0.46
Trader	102(31.5%)	298(32.8%)	400(32.5%)	0.94	[0.72, 1.23]	0.65
Farmer	43(13.3%)	58(6.4%)	101(8.1%)	2.24	[1.48, 3.40]	0.001*
civil servant	61(18.8%)	148(16.3%)	209(17.0%)	1.19	[0.86, 1.66]	0.29
Student	55(17.0%)	237(26.1%)	292(23.7%)	0.58	[0.42, 0.80]	0.0009*
Company staff	15(5.0%)	50(5.5%)	66(5.3%)	0.83	[0.46, 1.50]	0.54
Place of living						
Rural	273(84.3%)	656(72.2%)	929(75.4%)	0.96	[0.74, 1.21]	0.65
Urban	51(15.7%)	252(27.8%)	303(24.6%)			
Educational level						
Primary	31(9.6%)	107(11.8%)	138(11.2%)	0.70	[0.52, 1.21]	0.27
Secondary	133(41.0%)	320(35.2%)	453(36.8%)	1.28	[0.99, 1.66]	0.06
Tertiary	160(49.4%)	476(52.4%)	636(51.6%)	0.89	[0.89, 1.14]	0.34

The mean maternal age for women who took levonorgestrel was 27.53 ± 6.46 years and that for etonogestrel 29.20 ± 6.48 years. Women who took etonogestrel implants were significantly older, $t = 3.99(0.85, 2.49)$, $p = 0.0001$.

With respect to age specific variations, younger women (≤ 24 years) took more of levonorgestrel implants, $p = 0.003$. On the contrary, women who took etonogestrel were significantly older (≥ 30), $p = 0.008$

Regarding parity, significantly more nulliparous women took levonorgestrel implants $p = 0.005$, while women of very high parity (grand multiparous women) took more of etonogestrel $p = 0.007$.

With respect to occupation, significantly more students (p = 0. 0009) took levonorgestrel implants, and more farmers (p = 0, 0001) took etonogestrel.

Table 2: Insertion, removal and duration of use of the contraceptive implants

Variable	Type of implant		Total N = 1232	Odds ratio	Confidence interval	P value
	Etonogestrel N = 324(26.3%)	Levonorgestrel N = 908(73.7%)				
Rank of inserter						
Nurse	315(97.2%)	875(96.4%)	1190(96.6%)	1.28	[0.60. 2.70]	0.31
Resident doctor	9(2.8%)	33(3.6%)	42(34.0%)			
Rank of remover						
Nurse	265(81.8%)	767(84.5%)	1032(83.8%)	0.83	[0.59, 1.15]	0.26
Resident doctor	59(18.2%)	141(15.5%)	200(16.2%)			
Number of times implant was inserted						

DOI: 10.5281/zenodo.14916568

1	222(68.5%)	885(87.7%)	1107(89.9%)	0.06		0.0002*
2	101(31.2%)	23(12.3%)	124(10.1%)	17.43	[10.83, 28.05]	0.0001*
3	1(0.3%)	0(0.00%)	1(0.3%)			
Duration of use (in months)						
< 12 months	70(21.6%)	99(10.9%)	169(13.7%)	2.29	[1.63, 3.21]	0.0001*
12-24 months	38(11.7%)	92(10.1%)	130(10.6%)	1.18	[0.79, 1.77]	0.40
25-36 months	80(24.7%)	211(23.2%)	291(23.6%)	1.10	[0.82, 1.49	0.52
37-48 months	111(34.3%)	354(39.0%)	465(37.7%)	0.82	[0.83, 1.06]	0.13
49-60 months	24(7.4%)	129(14.2%)	153(12.4%)	0.48	[0.30, 0.75]	0.001*
> 60 months	1(0.3%)	23(2.5%)	24(1.9%)	0.12	[0.02, 0.89]	0.001*
Mean duration	28.9 ± 14.9	31.0 ± 13.6		t=2.33	[0.33, 3.87]	0.02

Regarding the number of times the implants were inserted (or changed), significantly more women used levonorgestrel implants just once, odds ratio = [0.04, 0.09], p = 0.002. For etonogestrel implants, significantly more women used it twice, odds ratio = 17.43 [10.83, 28.05], p = 0.0001.

With respect variation in the duration of contraceptive use, the mean duration was significantly higher among women who used levonorgestrel implants, t = 2.23, p = 0.02. However, within the first 12 months (3 years) significantly more women used etonogestrel, but above 48 months (4 years), the use of levonorgestrel implants was significantly higher, p = 0.001.

Table 3: Complications experienced by the women

Complications	Type of implant		Total N = 1232	Odds ratio	Confidence interval	P value
	Etonogestrel N = 324(26.3%)	Levonorgestrel N = 908(73.7%)				
No complications	161(49.7%)	541(59.6%)	702(56.9%)			
Complications present	163(50.3%)	367(40.4%)	530(43.1%)	0.67	[0.52, 0.86]	0.002*
Complications	**N = 163(50.3%)**	**N = 367(40.4%)**				
Vaginal bleeding	84(25.9%)	148(16.3%)	232(18.8%)	1.80	[1.33, 2.44]	0.0001*
Headache	26(8.0%)	66(7.3)	92(7.5%)	1.01	[0.63, 1.62]	0.95
weight gain	12(3.7%)	31(3.4%)	43(3.5%)	0.30	[0.15, 0.58]	0.0002*
Pain at injection site	10(3.1%)	45(5.0%)	54(4.4%)	0.61	[0.30, 1.23]	0.16
Hypertension	3(0.9%)	17(1.9%)	20(1.6%)	0.49	[0.14, 1.68]	0.24
Breast pain	6(1.9%)	1(0.1%)	7(0.6%)	17.11	[2.01, 142.70]	0.001*
Amenorrhea	6(1.9%)	7(0.8%)	13(1.1%)	2.43	[0.81, 7.28]	0.10
Acne	5(1.5%)	7(0.8%)	12(0.9%)	2.02	[0.64, 6.40]	0.22
Nausea	5(1.5%)	0(0.0%)	5(0.4%)			
Mood change	4(1.2%)	12(1.3%)	16(1.3%)	0.93	[0.30, 2.91]	0.90
Contraceptive failure	1(0.3%)	1(0.1%)	2(0.2%)	2.81	0.18, 45.03]	0.44
Loss of libido	1(0.3%)	11(1.2%)	12(0.9%)	0.25	[0.03, 1.96]	0.15
Malaise	0(0.9%)	22(2.4%)	22(2.4%)			

Compared to levonorgestrel implants, women who used etonogestrel significantly had more complications, odds ratio = 0.67[0.52, 0.86], p = 0.002, and these manifested as vaginal bleeding (p = 0.002), weight gain (p = 0.0001), and breast pain (p = 0.001).

DOI: 10.5281/zenodo.14916568

Table 4: Reason for removal of contraceptive implants

Reason for removal	Type of implant		Total N = 1232	Odds ratio	Confidence interval	P value
	Etonogestrel N = 324(26.3%)	Levonorgestrel N = 908(73.7%)				
Implant has expired	130(40.1%)	458(50.4%)	588(44.7%)	0.66	[0.51, 0.85]	0.001*
Desire to get pregnant	102(31.5%)	270(29.7%)	372(30.2%)	1.09	[0.83, 1.43]	0.55
Heavy vaginal bleeding	74(22.8%)	93(10.2%)	167(13.6%)	2.59	[1.85, 3.63]	0.001*
Headache	10(3.1%)	40(4.4%)	50(4.1%)	0.69	[0.34, 1.40]	0.30
Weight gain	4(1.2%)	19(2.1%)	23(1.9%)	0.58	[0.20, 1.73]	0.32
Hypertension	2(0.6%)	15(1.7%)	17(1.4%)	0.37	[0.08, 1.63]	0.17
Contraceptive failure	1(0.3%)	1(0.1%)	2(0.2%)	2.81	[0.18, 45.03]	0.44
Amenorrhea	1(0.3%)	6(0.6%)	7(0.6%)	0.47	[0.06, 3.88]	0.46
Loss of libido	0(0.0%)	3(0.3%)	3(0.2%)			
Malaise	0(0.0%)	3(0.3%)	3(0.2%)			

The commonest reason for implants removal in NDUTH (44.7%) was expired implant. However, the rate was significantly higher among women who used levonorgestrel, odds ratio = 0.66[0.51, 0.85], p = 0.001.

Regarding implant removal due to complications, the commonest reason for removal (13.6%) was severe irregular vaginal bleeding. Comparatively, etonogestrel implants were twice more likely to be removed because of heavy vaginal bleeding than levonorgestrel implants, odds ratio = 2.59[1.85, 3.63], p = 0.001.

DISCUSSION

Women in need of contraceptive implants have a limited range of choice, as only few products are available globally. In most countries, only 4 types are available; nexplanon, implanon, jadelle and Sino-implant. [21, 22] While nexplanon and implanon are made of etonogestrel synthetic progestogens, Jadelle and Sino-implant are composed of levonorgestrel. [21, 22]

In Nigeria (including NDUTH), the contraceptive implants currently in use are implanon, nexplanon and jadelle. Sino-implant, a product of Shanghai Dahua Pharmaceutical Company in China is not yet popular in Nigeria [23]. Though the use of nexplanon is gaining momentum in Nigeria, and it is gradually replacing implanon, it is not always available in NDUTH. This explains why it is difficult to completely phase it out.

Despite the fact that levonorgestrel and etonogestrel implants have been in use for a long time globally, literature search has revealed that there is just a handful of publications on studies comparing the two sets of drugs, in terms of effectiveness (or failure rates), complications, and reasons for discontinuation.

Regarding the contraceptive effectiveness of etonogestrel and levonorgestrel implants, they are rated as the most effective contraceptives globally. Their failure rates are extremely low, and evidence indicates that they are of equal potency. [13,15] Studies have reported the pearl index of etonogestrel implants as 0.02, [6] and 0.34, [17] which is comparable to that of levonorgestrel; 0.02, [15] and 0.27. [17] Some studies actually reported complete suppression of ovulation, with a zero pearl index for both. [13, 14]

Result from this study has substantiated the findings above; we did not find any significant difference between the 2 groups, this implies that they have similar contraceptive effectiveness. This was also substantiated by a (WHO) randomized controlled trial comparing levonorgestrel to etonogestrel, where similar pearl index was found (in both group) after follow-up for 3, and 5 years. [24]

The reason why the mean duration of contraceptive use in this study was higher among women who used levonorgestrel implant (jadelle) is most probably because the duration of contraceptive effectiveness is 5 years, which is longer than that for etonogestrel (3 years). The shorter duration also partly explains why significantly more women on etonogestrel (in this study) replaced their implants. However, the higher rate of discontinuation because of etonogestrel complications is another factor.

As stated in the introduction above, the complications of levonorgestrel and etonogestrel contraceptive implants are similar, and this has been verified by the pattern of the types of complications observed in this study. However the rates are expected to vary, as levonorgestrel and etonogestrel are pharmacologically different drugs.

With respect to contraceptive complications in this study, there are significant variations; the overall rate was higher in the women who received etonogestrel implants. In addition, the rate of irregular vaginal bleeding, weight gain, and breast pain were higher among the women who used etonogestrel implants. At the moment, there is no satisfactory explanation why these complications were more in women who received etonogestrel, compared to those that received levonorgestrel. However, further studies are recommended.

Regarding the other complications of contraceptive implants (stated in the introduction), we did not observed any significant difference between the two groups. This was however similar to results obtained from a randomized controlled trial (on etonogestrel vs. levonorgestrel), where it was reported that there was no significant difference in the rates of acne, headache, and mood swing. [24]

DOI: 10.5281/zenodo.14916568

The reason why the women on etonogestrel implants (in this study) had more irregular vaginal bleeding than their counterparts (on levonorgestrel) is not clear. However, the reason why women on subdermal implants bleed has been explained pathologically as multi-factorial.

It has been reported that etonogestrel and levonorgestrel implants cause increased endometrial vascular fragility, with dilatation and congestion of endometrial vessels, which could precipitate bleeding. [25, 26] There is also the theory of increased vascular permeability, with tendency to bleed from expression of angioproteins. [25, 27]

As a matter of fact, the above reasons could not explain why some women on these drugs bleed, and others don't. However, a study has attributed it to the gene expression theory; it reported that women with low chemokinine C-X-C motil 1 (CXCL1), also known as growth regulatory oncogene alpha, has 6.8 fold increased risk of vaginal bleeding when using etonogestrel and levonorgestrel implant, odds ratio = 6.8[2.21, 20.79], p = 0.001. [27]

Weight gain is another important complication of subdermal implants, and in this study, the rate was significantly higher among the women who received etonogestrel. However, our result was different from that of a similar study which reported that there was no significant difference in the rate of weight gain between the two groups. [28] Weight gain was said to increase by 3.0kg [2.5, 3.5] in the women that used etonogestrel, and 2.9[2.4, 3.4] in the levonorgestrel group after follow-up for 36 months. [28]

The mechanism of weight gain in women on subdermal contraceptive implants has been linked to hormonal changes on lipid metabolism, which leads to increase deposition of fats in the hips, thigh and abdomen. [29, 30] However, this also does not satisfactorily explain why some women on these drugs gain weight, and others don't. A study has however linked the explanation to be genetic in origin. That it is caused by variations in expression of ESR1 gene, a variant of estrogen receptor gene. [31]

Regarding the reasons for discontinuation of the implants secondary to complications (in this study), there was no significant difference between the 2 groups, except irregular vaginal bleeding. This evidence suggests that though subdermal implants have adverse effects, only few are severe enough to warrant discontinuation.

An important observation in this study is that far more women 908(73.7%) took levonorgestrel implants, and only 324(26.3%) had etonogestrel (during the study period) in NDUTH. Though levonorgestrel last up to 5 years, which is a desirable factor, it is possible that the complications of etonogestrel (which were significantly higher in this study) could have played a role in modifying the choice of the contraceptive implants. Therefore, further studies on this subject matter are required.

Conclusion

Etonogestrel implant has more complications than levonorgestrel, especially irregular vaginal bleeding, weight gain, and breast pain. Irregular vaginal bleeding was the commonest complication of subdermal implants that leads to discontinuation, and the rate is higher with etonogestrel.

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