Etonogestrel Sub-Dermal Implant Side Effects and Treatment Length: A Retrospective Study

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Abstract

Study Objective: The Etonogestrel sub-dermal implant was approved in 2006 as a long acting, reversible contraceptive (LARC). The manufacturer study showed the contraceptive's side effects and treatment length in a sample population, but no long-term, large-scale, clinical, post-marketing study has been conducted in the US. The objective of this study is to provide clinical, post-marketing data to direct informed use of this implant. **Design**: Retrospective study. IRB approval was obtained; data were collected from the clinic's electronic medical record (EMR). **Setting**: University of Kentucky Adolescent Medicine Clinic Lexington, Kentucky. **Participants**: 800 female patients age 7-33 years who received an Etonogestrel sub-dermal implant from 2008-2019. **Main Outcome Measures**: implant failure rate; rates of side effects, premature rod removal, reasons for premature rod removal. **Results**: Implant failure rate was 0%. At the time of this paper, 35.5% of patients completed treatment. 304 patients had the LARC removed early. 39.1% had it removed due to bleeding; mood change and weight gain were the cause of removal in 4.3% and 3.6% of our patients respectively. The most common side effects reported among our patients were bleeding (49.5%), mood change (3.0%), and weight gain (2.8%) with a 6.9 (SD = $\pm$ 14.55) average percent change in BMI. **Conclusion**: Overall, a large percentage of our patients cited bleeding, mood change, and weight gain as common side effects and reasons for premature removal. However, the 0% implant failure rate demonstrates that the implant is still a successful contraceptive for adolescents.

Keywords: Contraceptive Agents, Hormonal; etonogestrel; Teen Pregnancy

Introduction

In 2006, the Implanon was introduced as one of the first widely-available Long-Acting Reversible Contraceptives (LARCs) in the United States[1]. Prior to this device, there were few options for women who desired long-acting contraception. The Norplant, approved in 1991, was the first of the implant variety of LARC; however, it was pulled off the market shortly after its introduction due to a myriad of unpleasant side effects[2]. In their 1998 review paper, Fraser et al complied the results of 400 studies including more than 55,000 women who had used the Norplant. Common side effects included irregular bleeding (affecting 40% of women), and weight change (affecting 30% of users); these were also the most common reasons for early removal[3]. Intrauterine devices (IUDs) of various forms had been on the market since the late 1960s, but more serious problems were associated with these devices, including pelvic inflammatory disease (PID) and increased morbidity if women became pregnant while the device was in place[2]. On the whole, then, short-acting contraceptives (e.g.,

oral contraceptive pills, Depo-Provera) were the only feasible option for most women. Individuals who struggled to remember to take a pill each day, experienced undesirable side effects from systemic hormones, or in whom hormonal contraception was contraindicated were unable to use these methods reliably, if at all. As a result, it was difficult to prevent pregnancy with near-certainty.

One group for which the LARCs are particularly useful is adolescents, since this group remains at persistently increased risk for unwanted pregnancy. According to the CDC, even in 2017 (the most recent year of data), the teen pregnancy rate for 15-19-year-olds is estimated at 18.8%[4]. However, this rate is decreased quite substantially from the 34.2% reported in 2010[4]. This sharp decline can be attributed to many factors including usage of LARCs and other forms of contraception[5]. Between the periods of 2006-2008 and 2008-2010, the percentage of teens aged 15-19 who used LARCs increased from 1.4% to 4.4%[5]. From 2011-2015, this figure increased slightly to 5.8%, split between implants such as the Implanon/Nexplanon (3.0%) and IUDs (2.8%)[6].

The LARCs are not without side effects. Multiple studies have reported drug-related effects from Etonogestrel implants including bleeding, mood changes, weight gain, and rod migration[7,8]. However, to the authors' knowledge at the time of this paper, no large-scale, long-term post-marketing studies exist that report the incidence of these adverse effects in clinical practice in the United States. Our objective, then, was to conduct a study analysing the side effects and efficacy of the implant among several hundred patients in a clinical setting.

Materials and Methods

Ethical approval for the project was obtained from the ethical committee at the University of Kentucky. In 2008, the University of Kentucky Adolescent Medicine Clinic began offering Implanon/Nexplanon implant method of contraception to adolescents. Clinical records were searched for data relating to an Implanon/Nexplanon implant from 2008 to September 2019. Data items including name, date of birth, medical record number, insurance status, and dates of rod insertion and removal were collected. Records were excluded if from the study if there were no follow-up after rod insertion, if rod removal date was missing, or if the rod was defective (defined as rod removal the same day it was placed). A total of 800 records with valid data were selected for inclusion. Data extracted from these records were anonymised to ensure privacy and prevent client identification.

Based on the literature (e.g. see Merck pre-marketing study[9] and the 2016 study conducted by Obijuru et al[10]), information on the following side-effects were collected: dates of insertion/removal, side effects (heavy bleeding, spotting, mood change, migration, pregnancy, and weight gain), weights at insertion and removal, cause of removal if patients did not complete the full three years of treatment, and whether or not the rod was reinserted after expiration.

Of note, insurance status data was available for only half of the patient population. This was due to a variety of factors including incomplete chart data. Insurance status was not collected till finalisation of the transition to EMR at the adolescent clinic in 2012-2013. Therefore, this variable was dropped from the analysis. Similarly, due to large missing values, the variables race/ethnicity and geographical location were also dropped from the study.

Results

There were no implant failures recorded in our sample of 800 adolescents records. At the end of the data collection period (September 2019), 35.5% of patients had completed treatment, while 27.5% of patients were still in the process of completing treatment. Nearly

40% of patients had the LARC removed before completing three years of treatment. The most common causes for removal in our study included bleeding (39.1%), desiring pregnancy (6.9%), mood change (4.3%), and weight gain (3.6%) (Graph 1). The rates of all causes of removal from our study are listed in Table 1. The average length of treatment among patients in our study who had early removal was 635 (± 341.7) days.

Table 1: Causes of early removal (n=304)

Cause of Removal	UK Adolescent Clinic Rate
Unknown/other	42.1%
Bleeding	39.1%
Desiring pregnancy	6.9%
Mood change	4.3%
Weight gain	3.6%
Migration	2.0%
Medical co-morbidity	2.0%

The most common side effect reported during treatment among our patient population was bleeding, affecting 49.5% of patients. More than one-fourth (31.1%) of our patient population experienced spotting, while 18.4% reported heavy bleeding. The second and third most common side effects in our study were mood change (3.0%) and weight gain (2.8%). More than 60% of patients in our study did not report any side effects from the implant; 36.6% experienced one side effect, 2.8% reported two side effects, and only 0.25% patients experienced three or more side effects while the rod was in place. The rates of all side effects from our study are listed in Tables 2 and 3.

Table 2: Side effects and associated rates among all patients in our study (n=800)

Side Effect	Number of Patients Reporting Side Effect	UK Adolescent Clinic Rate
Bleeding	396	49.5%
Mood change	24	3.0%
Weight gain	22	2.8%
Migration	13	1.6%
Pregnancy	0	0%

The average percent change in BMI was 6.9 (SD = ± 14.55) % in our study. The average percent change in BMI among patients who cited weight gain as their primary reason for removal was 29.3 (SD = ± 20.23) %. The rate of rod reinsertion after completion of treatment among our patients was 26.4%. Common reasons for deciding against rod reinsertion included desiring pregnancy, unpleasant side effects (that were not significant enough to warrant early removal but did prevent reinsertion), and preferring to try another method of contraception.

Table 3: Number of side effects reported per patient (n=800)

Number of Side Effects	Number of Patients Reporting Side Effects	Percentage of Patients Reporting Side Effects
Zero	483	60.4%
One	293	36.6%
Two	22	2.8%

Three	1	0.13%
Four	1	0.13%

Discussion

The Etonogestrel sub-dermal implant is designed to be an easy, long-term, and effective form of contraception. Results from this study indicate that there were no recorded implant failures. Furthermore, with 60% of our sample reporting no side effects, this study provides some evidence to investigate this method of contraception further within a well-designed and rigorous study.

Since only 5.8% of teenage patients aged 15-19 use a LARC as their primary method of contraception[4], it is clear that many adolescents are not aware of contraceptive options. This lack of awareness is supported by a 2014 analysis of the National Survey of Reproductive and Contraceptive Knowledge which reported that only 40% of teenagers aged 18-19 were familiar with the implant as a contraceptive option compared to 56% of young adults aged 20-29[11]. Another possible explanation for the low rate of LARC use among teenagers is limited access to providers. This is partly due to external factors influencing access, such as differences in funding allocation for family planning services among various states[12]. However, this can also be attributed to individual, self-imposed avoidance of providers if adolescents are concerned about the confidentiality of their visit. In a 2017 paper, the Guttmacher Institute reported that among sexually active females aged 15-17 who possessed doubts about the privacy of visits to reproductive health providers, only 22% utilized these services[13]. Therefore, it is advisable that clinicians assist adolescent clients to make an informed decision about their choice of contraceptives.

More than 40% of the patients in our study cited bleeding as a side effect. Bleeding while using the implant has been reported as a common side effect in existing literature[9,10,14]. For example, in a 2016 study conducted by Obijuru et al, 48% of participants reported bleeding as a side effect; in a 2019 study published by Lazorwitz et al, 59.4% of women experienced this effect[10,14]. The consistency of our data with that of other publications strongly supports the conclusion that this method of contraception is associated with relatively high rates of abnormal or nuisance bleeding; additionally, it supports the exigency of providing patients with robust, clinically-based information about the implant's side effect profile. This is of particular relevance for the adolescent patient population, whose bleeding profile is more variable—especially in the first three years after menarche[15].

Nearly 2 in 5 patients (38%) in our study had the rod removed prematurely. This figure was very close to the 35% reported by the Obijuru study[10]. Interestingly, our figure was higher than the 25% reported by Beesham et al in their 2019 paper[16] and the 23.4% reported by Nageso and Gebretsadik in their 2018 study[17]. The average age of patients in our study (17.3 $\pm$ 2.8 years) could be an explanation for the high rate of premature implant removal; the similar average age of patients in the Obijuru study (17 $\pm$ 1.8 years)[10] supports this, especially when considered in the context of the older average age of the patients in the Beesham study (28 years)[16] and the Nageso paper (24.5 $\pm$ 4.8 years)[17]. Adolescents—and even adults until age 25—do not have fully matured prefrontal cortices; this predisposes them to make more impulse decisions without necessarily considering the long-term consequences[18,19,20].

One interesting result of this study was the relatively large average percent change in BMI among our patient population: 6.9% (SD = $\pm$ 14.55) among all users and 29.3% (SD = $\pm$ 20.23) among patients who cited weight gain as their primary reason for removal. According to Gallo et al (2016), the definition of clinically significant weight gain observed with progestin-containing implants is a weight gain of 2kg or an BMI increase of 1.0[21]. Therefore,

by these standards, our results seem to suggest that the implant is associated with weight gain. However, some of the weight gain may be due to growth during puberty[22,23], and this certainly helps to explain the positive percent change in BMI observed among our patient population.

It is important that adolescents are provided with unbiased and valid information during counselling session to enable them to make an informed decision. This includes discussing rates of side effects, and medical and non-medical options for managing side effects. Although none of the 800 adolescents in our study experienced pregnancy while the implant was in place, the records have not provided us any quality of life measure including physical and mental health to explore rate of full-term compliance. Therefore, a broader view of contraceptives options is recommended in developing future research, in particular designs that allow within and between individual variations, e.g. population-based sampling to include contraceptive users and non-users and their choices.

Limitations

The results from this study cannot be generalised to the general population because this study is not population-based and is restricted to one adolescent clinic. Results could improve with a multi-centre study design. Large volume of missing data due to poor record keeping also limited the study to a small number of variables and led to the exclusion of variables, such as insurance status and geographical location, from the study.

Disclosure/Conflicts of Interest

None declared. The authors received no sources of funding for this project.

References

1. Feisullin K, Westhoff, C: Contraception. In: Principles of Gender-Specific Medicine (2nd ed.). Edited by MJ Legato. Academic Press, 2010, pp 357-365.
2. Strasser J, Borkowski L, Couillard M, et al: Long-acting reversible contraception: overview of research & policy in the United States. The George Washington University Jacob's Institute of Women's Health 2016 Jun.
3. Fraser I, Tiitinen A, Affandi B, et al: norplant consensus statement and background review. Contraception 1998; 57:1.
4. Martin JA, Hamilton BE, Osterman MJK, et al: Births: final data for 2017. National Vital Statistics Reports; vol 67 no 8. National Center for Health Statistics 2018 Nov 7.
5. Boonstra HD: What is behind the declines in teen pregnancy rates? Guttmacher Institute 2014 Sept 3.
6. Abma JC, Martinez GM: Sexual activity and contraceptive use among teenagers in the United States, 2011–2015. National Health Statistics Reports no 104. National Center for Health Statistics 2017 Jun 22.
7. Darney P, Patel A, Rosen K, et al: safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials. Fertil Steril 2009; 91:1646.
8. Villas-Boas J, Vilodre LC, Malerba H, et al: metabolic safety of the etonogestrel contraceptive implant in healthy women over a 3-year period. Eur J Obstet Gynecol Reprod Biol X 2016; 202:51.
9. Merck Sharp, Dohme B.V.: Highlights of prescribing information. Merck & Co., Inc.; rev Nov 2019. https://www.merck.com/product/usa/pi_circulars/n/nexplanon/nexplanon_pi.pdf. Accessed March 19, 2020.
10. Obijuru L, Bumpus S, Auinger P et al: etonogestrel implants in adolescents: experience, satisfaction, and continuation. J Adolesc Health 2016; 58:284.

11. Craig A, Dehlendorf C, Borrero S, et al: exploring young adults' contraceptive knowledge and attitudes: disparities by race/ethnicity and age. Womens Health Issues 2014; 24:e281.
12. State Family Planning Funding Restrictions. Guttmacher Institute 2020 May 1.
13. Hasstedt K: Ensuring Adolescents' Ability to Obtain Confidential Family Planning Services in Title X. Guttmacher Institute Policy Review 2018; 1:48.
14. Lazorwitz A, Aquilante C, Dindinger E, et al: relationship between etonogestrel concentrations and bleeding patterns in contraceptive implant users. Obstet Gynecol 2019; 134:807.
15. American College of Obstetricians and Gynecologists: menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Obstet Gynecol 2015; 126:e143.
16. Beesham I, Smit J, Beksinska M, et al: reasons for requesting removal of the hormonal implant, implanon nxt, at an urban reproductive health clinic in kwazulu-natal, south africa. S Afr Med J 2019; 109:750.
17. Nageso, A, Gebretsadik, A: discontinuation rate of implanon and its associated factors among women who ever used implanon in dale district, southern ethiopia. BMC Womens Health 2018; 18:189.
18. Arain M, Haque M, Johal L, et al: maturation of the adolescent brain. Neuropsychiatr Dis Treat 2013; 9:449.
19. McKinney E: Health promotion for the adolescent. In: Maternal-Child Nursing (5th ed.). Canada, Wiley & Sons, Ltd, 2018, pp 150-169.
20. Leshem, R: brain development, impulsivity, risky decision making, and cognitive control: integrating cognitive and socioemotional processes during adolescence—an introduction to the special issue. Dev Neuropsychol 2016; 41:1.
21. Gallo M, Legardy-Williams J, Hylton-Kong T: association of progestin contraceptive implant and weight gain. Obstet Gynecol 2016; 127:573.
22. Rogol A, Clark P, Roemmich J: growth and pubertal development in children and adolescents: effects of diet and physical activity. Am J Clin Nutr 2000; 72:521S.
23. Rosenbaum M: Special considerations relevant to pediatric obesity. In: Endotext. Edited by KR Feingold, B Anawalt, A Boyce, et al. South Dartmouth, MDText.com, 2018.
24. Romano M, Braun-Courville D: assessing weight status in adolescent and young adult users of the etonogestrel contraceptive implant. Adolesc Ped Gynecol 2019; 32:409.
25. Wolf R, Long D: pubertal development. Pediatr Rev 2016; 37:292.
26. Stoddard A, McNicholas C, Peipert JF: efficacy and safety of long-acting reversible contraception. Drugs 2011; 71:969.

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