

Endometrial Assessment of Young Women Experiencing Abnormal Uterine Bleeding with The Use of a Single Rod-Levonorgestrel Implant.

Eka Rusdianto Gunardi¹, Yogi Pasidri^{1*}, Elizabeth Dian Novita¹, Herbert Situmorang¹, Hartono Tjahjadi²

Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Indonesia, Dr.Cipto Mangunkusumo Hospital, Jakarta¹

Department of Anatomical Pathology, Faculty of Medicine Universitas Indonesia, Dr.Cipto Mangunkusumo Hospital, Jakarta²

Corresponding Author: 1*



Keywords:

abnormal uterine bleeding,
endometrial atrophy, implants,
single rod implant

ABSTRACT

Contraceptive implants are subdermal capsules that release progestins over a 3 year period. The most common and frequent side effect of implants is abnormal uterine bleeding (AUB). Various diagnostic techniques are available to determine the cause of AUB. However, there have only been a few studies investigating endometrial pathology experienced by implant contraceptive acceptors. The aim of this study is to investigate endometrial etiologies of abnormal uterine bleeding on single-rod implant contraceptive acceptors. This observational descriptive study using cross sectional method was performed on acceptors of Monoplant® single rod implant containing 160 mg of Levonorgestrel who had abnormal uterine bleeding. A total of 20 subjects was recruited to the study. Women with cervical cancer, cervical stenosis, pelvic inflammatory disease, or abnormal uterus morphology were excluded. All the participants of the study had their endometrium assessed with a transvaginal ultrasound, hysteroscopy, and histopathology of an endometrial biopsy. Assessment of endometrium revealed that endometrial thinning and endometrial atrophy were found on 78.9% of subjects. Results of transvaginal ultrasound and hysteroscopy were compared to histopathologic results. Endometrial thinning and atrophy were found in majority of single rod implant acceptors having abnormal uterine bleeding. However, further examinations should be performed to eliminate additional etiologies.



This work is licensed under a Creative Commons Attribution Non-Commercial 4.0 International License.

1. INTRODUCTION

Contraceptive implants are subdermal rods that release progestins over a 3 year period. This type of contraception is very effective with the lowest implant contraceptive failure rate (<1%) and is rapidly reversible after removal [1- 3]. Over the past 35 years, implants have been approved by more than 60 countries and are currently used by millions of women worldwide, one of the various types of contraceptive implants is the Levonorgestrel (LNG) implant, varying in amount of implants and its contents [1], [2]. Further research was conducted in order to improve its effectiveness, including making a single-rod implants, such as

Monoplant®. The most common complaint of implant acceptors is abnormal uterine bleeding, which is frequently observed on days 9 to 30 after implant placement. Previous studies of Norplant®, a six rod LNG implant, showed changes in menstrual patterns would occur in about 80% in the first year of use, then decrease to about 40% on the third year, and further decrease to about 33% on the fifth year [1]. These changes include changes in the interval between bleeding, menstrual duration and volume, and bleeding in between menstruation [1- 4]. This irregular and prolonged bleeding was the main reason acceptors discontinued the implant method (ranging from 3.5% of all acceptors at 12 months to 11.9% at the fifth year). The cumulative continuation rate at the fifth and third year after insertion is 62-67% [5]. However, there is no study regarding abnormal uterine bleeding in single rod implant acceptors.

Various diagnostic techniques are available to determine the cause of AUB by further evaluating and visualizing the uterus and pelvic organs [6]. National Institute for Health and Care Excellence (NICE) guidelines recommend that assessment of the uterine cavity via transvaginal ultrasound or hysteroscopy may be indicated in patients with heavy menstrual bleeding having additional symptoms (such as intermenstrual or postcoital bleeding, pelvic pain, pelvic masses) suggesting structural abnormalities [7].

Transvaginal (TV) ultrasound is an initial and simple examination to see uterine cavity abnormalities with a very high sensitivity of 95.23%, a specificity of 94.82%, a positive predictive value of 93.01% and a negative predictive value of 96.49% to determine the presence of endometrial pathology. In some cases, the result of normal uterine cavity assessment on TV ultrasound examination requires a more reliable assessment by hysteroscopy. Found that about 21.8% of patients examined with TV ultrasound were also having other abnormality which can be found on hysteroscopy [6]. In some cases, despite no obvious pathology identified on transvaginal ultrasound, further evaluation of the endometrium is required via hysteroscopy.

Hysteroscopy to directly view the uterine cavity followed by taking an endometrial biopsy is the gold standard examination of endometrial examination. The success of hysteroscopic diagnostic tests in AUB patients to detect endometrial pathology was 96.9% (SD 5.2%, range 83-100%) [8], [9]. However, it is not possible to carry out this examination on all patients given the invasive nature of the procedure and cost. There is still ongoing debate as to whether TV ultrasound alone is sufficient in assessing endometrial pathology or a hysteroscopy is required to assess the presence of endometrial pathology.

Until now, there have been no studies on the findings of endometrial pathology from transvaginal ultrasound and hysteroscopy confirmed by endometrial histopathology in single-rod implant contraceptive acceptors with AUB. This study aims to assess the etiologies of AUB in single-rod levonorgestrel implant contraceptive acceptors using transvaginal ultrasound, hysteroscopy, and endometrial histopathology result.

2. METHODS

This is an observational descriptive study using cross sectional method to assess the endometrial pathology found in single rod levonorgestrel implant acceptors using transvaginal ultrasound, hysteroscopy, and histopathology examination.

This study used 5% error bound and 95% confidence interval limit, with power of the test considered to be 90%. This study was done at dr. Cipto Mangunkusumo National General Hospital, Indonesia on January of 2019 to December of 2019. The inclusion criteria for this research were all acceptors of Monoplant® single rod levonorgestrel implant containing 160 mg of Levonogestrel having abnormal uterine bleeding during the course of the study aged 20-35 years old. Meanwhile, the exclusion criteria of this study were women with cervical cancer, cervical stenosis, pelvic inflammatory disease, or any abnormal uterine morphology. The

subjects were recruited consecutively.

All of the subjects in this study was examined using transvaginal ultrasound, hysteroscopy, and histopathology examination. Ultrasound and hysteroscopy examinations were done by obstetrics and gynecology consultants, while histopathology examinations were performed by histopathologic consultants. On ultrasound examination, all of the pathologies found were reported. On hysteroscopy examination, superficial vascular density pattern, morphology, and distribution were reported. Examination result was determined subjectively by each operator.

All human studies had been approved by the Research Ethics Committee of Faculty of Medicine, University of Indonesia. All patients who were included in this study had given their informed consent prior to their inclusion in the study. Collected data were then analyzed using SPSS for Macintosh ver. 20. Characteristics of subjects and examination results were analyzed descriptively.

3. RESULTS

Along the period of this study, the number of single rod implant acceptors with abnormal uterine bleeding symptoms was 20. However, 1 subject was excluded due to cervical stricture, rendering hysteroscopy impossible. Therefore, 19 subjects were recruited to the study and were further analyzed. Baseline characteristics of subjects can be found on Table 1.

Table 1. Characteristics of Subjects

Characteristics	N = 20
Age (years)	
21-25	2 (10%)
26-30	1 (5%)
31-35	17 (85%)
Body mass index (kg/m²)	
<i>Underweight</i>	1 (5%)
Normal	6 (30%)
<i>Overweight</i>	0
<i>Obese</i>	13 (65%)
Lactating	
Yes	5 (25%)
No	15 (75%)
Usage duration (months)	
0 – 6	4 (20%)
7 – 12	2 (10%)
13 - 18	4 (20%)
19 - 24	5 (25%)
25 – 30	5 (25%)
Intermenstrual bleeding episodes monthly (times)	1 (1-2)
Intermenstrual bleeding duration (days)	
1-7	12 (60%)
8-14	7 (35%)
>14	1 (5%)

It was found that all of our subjects were having intermenstrual bleeding episodes, ranging from 1 to 15 days.

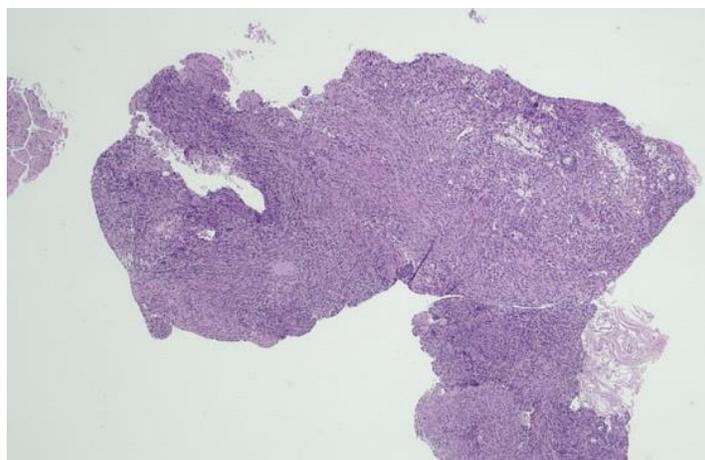


Figure 2. Histopathologic result of endometrial atrophy

4. DISCUSSION

Uterine bleeding is a common side effect of contraceptive use and is one of the most common reasons to default on using contraception. Irregular bleeding frequently occurs in the first few months of use. Following oral regimen of estradiol supplementation, this complaint would begin to lessen over time. Regular evaluation of uterine bleeding with contraceptive use can improve compliance with contraceptive use while reducing the incidence of unwanted pregnancy [10].

Abnormal uterine bleeding due to implant use is thought to be due to the transition of a relatively thick endometrium to a relatively thin endometrium as a result of the predominant progestin component, as in all types of hormonal contraceptives. Continuous use of hormonal contraceptives would transform the endometrium to become a dense tissue that has small, dilated, and fragile capillaries, susceptible to focal bleeding. This fragility of blood vessels is caused by changes in the basement membrane and pericytes, as well as reduced structural support from the altered stroma and endometrial glands. Changes in matrix metalloproteinase activity, changes in endometrial perfusion, local vascular hemostasis, pro and antioxidant processes, and cell migration also play an important role in remodeling [11].

Transvaginal ultrasound is the initial examination to evaluate abnormal uterine bleeding because it can detect endometrial pathology noninvasively [12]. Transvaginal ultrasound can be used to assess the thickness of thinning endometrium due to various reasons, as observed on a study by [14] which showed significant correlation between endometrial thickness measured by ultrasound and histopathology in women with abnormal uterine bleeding, either using contraception or not. In that study, ultrasound and histopathological examinations were performed on 350 Turkish women with abnormal uterine bleeding. Histopathological analysis showed that there were proliferative endometrium (36%), secretory endometrium (24.6%), decidualization (10.9%), endometrial polyps (8.3%), endometritis (6.8%), endometrial hyperplasia (4, 6%), irregular shedding (3.7%), endometrial atrophy (3.1%), endometrial cancer (1.1%), and retention of the placenta (0.9%). There was a significant correlation between ultrasound results and histopathology ($r = 0.215$, $p = 0.001$) [13].

On the other hand, hysteroscopy has the advantage that it can provide direct visualization of the uterine cavity and endometrium. This allows a biopsy to be performed during the procedure if an endometrial abnormality is suspected. Hysteroscopy is the standard test for evaluating the uterine cavity, but it is an invasive method, which might cause some discomfort [14]. However, in our study, we found that hysteroscopy in our subjects showed minimal changes despite the symptoms suffered. The only abnormality found was reduced superficial

vascular density, while vascular morphology and distribution pattern remained normal.

Assessed the utility of transvaginal ultrasound compared with hysteroscopy in evaluating abnormal uterine bleeding. The results showed that transvaginal ultrasound has high sensitivity and specificity (95.23% and 94.82%, respectively) and high positive and negative predictive values. The power of compatibility between transvaginal ultrasound and hysteroscopy was quite high (Kappa value 0.898) [15].

The contraceptive effects of progestogens can be divided into two main categories: changes in the structure of the endometrium and vascularization, and also changes in menstrual bleeding patterns [16]. Endometrial changes due to the influence of progestins vary widely and depend on the underlying condition of the endometrium, dose, potency, type of progestin, duration of therapy, degree of inhibition of follicular activity and occurrence of ovulation. Significant vascular changes due to the influence of progestin implants include changes in the superficial vessels to become more fragile (increased density of dilated, thin-walled and fragile vessels) leading to abnormal uterine bleeding [17], [18]. Based on our study, this phenomenon could be examined using either transvaginal ultrasound or hysteroscopy, with each having additional advantages.

Abnormal uterine bleeding remained as one of the most common side effects experienced by implants and other contraceptive acceptors. Discontinuation is also common among those suffering from it. Based on our research, we can conclude that endometrial atrophy is the main cause of abnormal uterine bleeding associated with contraceptive implants use. Furthermore, it can be inquired using ultrasound examination Hence, treatment for abnormal uterine bleeding cases in implants user should include treatment of endometrial atrophy.

5. CONCLUSIONS

It is concluded in this study that most of the cases of abnormal uterine bleeding in women using single rod levonorgestrel implant was attributed to endometrial atrophy. Therefore, ultrasound examination and conservative treatment using oral medication should be sufficient in decreasing the symptoms.

6. REFERENCES

- [1] Speroff, L.; Darney, P. D., *A Clinical Guide for Contraception*. 5th Ed ed.; Lippincott Williams & Wilkins: Philadelphia USA, 2011.
- [2] Shoupe, D.; Kjos, S. L.; SpringerLink *The handbook of contraception : a guide for practical management*, 1st 2006.; Humana Press: Totowa, N.J, 2006.
- [3] Gunardi, E.; Affandi, B.; Muchtar, A., *Monoplant® the Indonesian implant: the overview of implant and its development*. *Indonesian Journal of Obstetrics and Gynecology* 2011, 35, 40.
- [4] Gunardi, E.; Affandi, B.; Juliaan, F., *Levonorgestrel concentration in a single rod implant users for six months*. *Indonesian Journal of Obstetrics and Gynecology* 2011, 35, 122.
- [5] Tuladhar, J.; Donaldson, P. J.; Noble, J., *The introduction and use of Norplant implants in Indonesia*. *Stud Fam Plann* 1998, 29 (3), 291-9.
- [6] MOZHGAN, B.; S., M.; F., M.; SH., S., *Office hysteroscopy in patients with abnormal uterine bleeding and normal transvaginal sonography*. *INTERNATIONAL JOURNAL OF FERTILITY AND STERILITY* 2008, 1, 175-178.

- [7] Gynecologists, R. C. o. O. a., Management of unscheduled bleeding in women using hormonal contraception. Faculty of Sexual and Reproductive Healthcare Clinical Guidance: 2009; p Faculty of Sexual and Reproductive Healthcare Clinical Guidance.
- [8] Soguktas, S.; Cogendez, E.; Kayatas, S. E.; Asoglu, M. R.; Selcuk, S.; Ertekin, A., Comparison of saline infusion sonohysterography and hysteroscopy in diagnosis of premenopausal women with abnormal uterine bleeding. *Eur J Obstet Gynecol Reprod Biol* 2012, 161 (1), 66-70.
- [9] JS, P.; S, R.; S, P.; M, G.; M, P., A comparative diagnostic evaluation of hysteroscopy, transvaginal ultrasonography and histopathological examination in cases of abnormal uterine bleeding. *The Journal of Obstetrics and Gynecology of India* 2006, 56, 240-243.
- [10] A, E.; B, K. Evaluation and management of unscheduled bleeding in women using contraceptive. <http://uptodate.com>.
- [11] Gynecologists, R. C. o. O. a., Problematic bleeding with hormonal contraception clinical effectiveness unit. Faculty of Sexual and Reproductive Healthcare Clinical Guidance: England, 2015; pp 1-28.
- [12] Faúndes, A.; Alvarez, F.; Brache, V.; Cochón, L., Endometrial thickness and oestradiol concentration in women with bleeding complaints during use of Norplant implants. *Hum Reprod* 1998, 13 (1), 188-91.
- [13] RD, K.; AN, Z., Use of diagnostic hysteroscopy in abnormal uterine bleeding in perimenopausal age group and its clinicopathological co-relation with ultrasound and histopathology findings: experience in a tertiary care institute. *International Journal of Reproduction, Contraception, Obstetricsand Gynecology* 2015, 4, 413-418.
- [14] Ozer, A.; Ozer, S.; Kanat-Pektas, M., Correlation between transvaginal ultrasound measured endometrial thickness and histopathological findings in Turkish women with abnormal uterine bleeding. *J Obstet Gynaecol Res* 2016, 42 (5), 573-8.
- [15] Vitner, D.; Filmer, S.; Goldstein, I.; Khatib, N.; Weiner, Z., A comparison between ultrasonography and hysteroscopy in the diagnosis of uterine pathology. *Eur J Obstet Gynecol Reprod Biol* 2013, 171 (1), 143-5.
- [16] Goyal, B. K.; Gaur, I.; Sharma, S.; Saha, A.; Das, N. K., Transvaginal sonography versus hysteroscopy in evaluation of abnormal uterine bleeding. *Med J Armed Forces India* 2015, 71 (2), 120-5.
- [17] Dinh, A.; Sriprasert, I.; Williams, A. R.; Archer, D. F., A review of the endometrial histologic effects of progestins and progesterone receptor modulators in reproductive age women. *Contraception* 2015, 91 (5), 360-7.
- [18] Rogers, P. A., Endometrial vasculature in Norplant users. *Hum Reprod* 1996, 11 Suppl 2, 45-50.