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Vaginal Bleeding Patterns in Women with Heart Disease Who Used Contraceptive Implants in Songklanagarind Hospital

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ABSTRACT

Objectives: The primary objective was to evaluate the vaginal bleeding patterns of women with heart disease who used contraceptive implants. The secondary objectives were to compare the results with healthy women (no underlying disease) and evaluate the rates and reasons for discontinuation.

Materials and Methods: A retrospective study was conducted at Songklanagarind Hospital from January 1, 2008 to December 31, 2017. The patients who used contraceptive implants were divided into two groups: women with heart disease and healthy women. The patterns of vaginal bleeding, discontinuation rate and reasons of discontinuation were recorded and compared.

Results: A total of 263 women who used contraceptive implants included 54 (20.5%) women with heart disease. Levonorgestrel implants were used most frequently (92.6%). The rate of abnormal vaginal bleeding was significantly higher in women with heart disease (94.4% vs 71.3%, $p < 0.01$). Abnormal vaginal bleeding patterns were irregular bleeding (33.3%), no bleeding (33.3%), and prolonged bleeding (14.8%). Women with heart disease (53.7%) who used anticoagulants had similar frequencies of overall abnormal vaginal bleeding patterns as the non-users of anticoagulants (95.8% vs 93.3%, $p = 1.00$). The discontinuation rates of contraceptive implants in women with heart disease were significantly lower than in healthy women (14.8% vs 29.7%, $p = 0.048$). The most common reason for discontinuation in women with heart disease was abnormal vaginal bleeding (62%).

Conclusion: The continuation rates of contraceptive implants in women with heart disease were high. The abnormal vaginal bleeding rate was 94.4%, especially irregular bleeding and no bleeding. Abnormal vaginal bleeding was the most common reason for discontinuation.

Keywords: Abnormal vaginal bleeding, contraceptive implants, discontinuation, heart disease.

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รูปแบบเลือดออกทางช่องคลอดของสตรีโรคหัวใจที่ใช้ยาฝังคุมกำเนิดในโรงพยาบาลสงขลานครินทร์

กล้า เจริญจิระตระกูล, สาธิต คลังสิน, ศรันญา วัฒนกำธรกุล, กรัณฑ์รัตน์ สุนทรพันธ์

บทคัดย่อ

วัตถุประสงค์: *วัตถุประสงค์หลักเพื่อศึกษารูปแบบของเลือดออกทางช่องคลอดของสตรีโรคหัวใจที่ฝังยาคุมกำเนิด เปรียบเทียบกับกลุ่มสตรีปกติ (ไม่มีโรคประจำตัว) ที่ฝังยาคุมกำเนิด วัตถุประสงค์รองเพื่อเปรียบเทียบอัตราการหยุดใช้ยาฝังคุมกำเนิดก่อนระยะเวลาจริง และเหตุผลที่หยุดใช้กับกลุ่มสตรีปกติ*

วัสดุและวิธีการ: *เป็นการศึกษาย้อนหลังในโรงพยาบาลสงขลานครินทร์ระหว่าง วันที่ 1 มกราคม 2551 ถึง 31 ธันวาคม 2560 ผู้ป่วยที่ใช้ยาฝังคุมกำเนิดถูกแบ่งเป็น 2 กลุ่มคือ สตรีโรคหัวใจและสตรีปกติ ทำการบันทึกและเปรียบเทียบรูปแบบเลือดออกทางช่องคลอด อัตราการหยุดใช้ยาก่อนเวลาจริง และเหตุผลที่หยุดใช้*

ผลการศึกษา: *สตรีทั้งหมด 263 คนที่ใช้ยาฝังคุมกำเนิด ประกอบด้วยสตรีโรคหัวใจ 54 คน (ร้อยละ 20.5) ส่วนใหญ่ร้อยละ 92.6 เลือกยาฝังคุมกำเนิดชนิด 5 ปี อัตราเลือดออกผิดปกติทางช่องคลอดของสตรีโรคหัวใจมากกว่ากลุ่มสตรีปกติอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 94.4 เปรียบเทียบกับร้อยละ 71.3)โดยรูปแบบของเลือดออกทางช่องคลอด เป็นเลือดออกกะปริดกะปรอยและไม่มีประจำเดือน ร้อยละ 33.3 ถัดมาเป็นเลือดออกเป็นระยะเวลานานร้อยละ 14.8 สตรีโรคหัวใจร้อยละ 53.7 ใช้ยาต้านการแข็งตัวของเลือดโดยมีรูปแบบเลือดออกผิดปกติทางช่องคลอดไม่แตกต่างจากกลุ่มที่ไม่ใช้ยาต้านการแข็งตัวของเลือด (ร้อยละ 95.8 เปรียบเทียบกับร้อยละ 93.3) อัตราการหยุดใช้ยาฝังคุมกำเนิดในสตรีโรคหัวใจต่ำกว่าในกลุ่มสตรีปกติอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 14.8 เปรียบเทียบกับร้อยละ 29.7) สตรีโรคหัวใจร้อยละ 62 หยุดใช้ยาฝังคุมกำเนิดเนื่องจากเลือดออกผิดปกติทางช่องคลอดมากที่สุด*

สรุป: *การใช้ยาฝังคุมกำเนิดในสตรีโรคหัวใจมีอัตราการใช้ต่อเนื่องสูง มีเลือดออกผิดปกติทางช่องคลอดหลังจากใช้ยาฝังคุมกำเนิดร้อยละ 94.4 ซึ่งส่วนใหญ่เป็น เลือดออกกะปริดกะปรอย และไม่มีประจำเดือน โดยอาการเลือดออกผิดปกติทางช่องคลอดเป็นสาเหตุสำคัญในการหยุดใช้ยาฝังคุมกำเนิดก่อนระยะเวลาจริง*

คำสำคัญ: *เลือดออกผิดปกติทางช่องคลอด, ยาฝังคุมกำเนิด, อัตราการหยุดใช้, โรคหัวใจ*

Introduction

A common cause of death in Thailand is heart disease, which consists of congenital heart disease including septal defect, valvular heart disease, and acquired heart diseases including rheumatic heart disease, myocarditis, and myocardial infarction. Although the mortality rate is decreasing[1], pregnancy causes increased blood volume and heart rates that lead to high morbidity and mortality rates during pregnancy, especially pregnancy with pulmonary hypertension that causes a mortality rate up to 30%[2]. In addition, 38% of all pregnancies with heart disease are categorized as high risk and 4% are contraindicated for pregnancy. Furthermore, the mortality rate is 1 in 100 compared with 7 in 100,000 in normal pregnancy[3]. In Songklanagarind Hospital, most pregnancies with heart disease are rheumatic heart disease. Morbidity and mortality during pregnancy were reported to be 24% and 3%, respectively[4]. Furthermore, some medications are teratogens such as warfarin that causes fetal warfarin syndrome and internal bleeding[5]. Therefore, contraception in women with heart disease is important.

A contraceptive method in women with heart disease requires many considerations such as long-acting, efficacy, and safety by medical eligibility criteria. In brief, categories 1 and 2 mean that a contraceptive method can be used in any circumstance or generally used and categories 3 and 4 mean a contraceptive method should not be provided[6].

Uncomplicated valvular heart disease has no limitations for contraception. Nevertheless, progestin therapy and an intrauterine device are suitable in complicated valvular heart disease, which includes pulmonary hypertension, atrial fibrillation, and subacute bacterial endocarditis[6]. Progestin only pills, contraceptive implants, and intrauterine device are suitable for patients with ischemic heart disease[7]. When considering the efficacy, contraceptive implants and intrauterine devices are suitable.

Three types of contraceptive implants are available: Implanon®, Jadelle®, and Levoplant®. In Songklanagarind Hospital we use Implanon® and Jadelle®. Implanon® is a single-rod implant that contains 68 mg of etonogestrel and Jadelle® is a double-rod implant that contains 150 mg of levonorgestrel. Both devices inhibit ovulation and produce a thick cervical mucus and have the highest efficacy of 1 pregnancy in 1,000 users[6]. However, the common side effect is abnormal vaginal bleeding as a consequence of endometrial thinning[8].

From a literature review, no explanation has been published on whether or not heart disease changes the bleeding patterns in women who use contraceptive implants. However, some women with heart disease in this study needed an anticoagulant. Previous studies evaluated bleeding patterns in women on warfarin therapy while using levonorgestrel containing contraceptives. They found drug interaction between warfarin and the levonorgestrel-containing contraceptives. They concluded that progestin binds to the F1-S variant of human α1-acid glycoprotein which is the protein transport of warfarin[9, 10].

Recently, no study has evaluated vaginal bleeding patterns in the specific group of women with heart disease who use only contraceptive implants. Therefore, our primary objective was to evaluate the vaginal bleeding patterns of women with heart disease who used contraceptive implants. The secondary objectives were to compare the results with healthy women who used contraceptive implants and evaluate discontinuation rates and reasons of discontinuation.

Materials and Methods

A retrospective study was conducted after the protocol approval by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC.61-246-12-4). The medical records were reviewed of all patients from the database of the Unit of Family Planning, Department of Obstetrics and Gynecology at Songklanagarind Hospital between 1 January 2008 and 31 December 2017. The exclusion criteria were incomplete data (i.e. no data of vaginal bleeding patterns or reasons for discontinuation) or lost to follow-up (i.e. no follow-up before implant removal or incomplete contractive implant use), women with

underlying diseases other than heart disease, and women with abnormal menstruation before using a contraceptive implant. In our institute, guidance for choices of contraception in women with heart disease follows a global handbook from World Health Organization (WHO)[6]. In women with uncomplicated valvular heart disease and WHO class I/II, the choice of contraception depends on fertility desire, and the needed duration of contraception. Women with complicated valvular heart disease and WHO class III/IV are counseled the irreversible contraceptive methods. If they refuse an irreversible contraceptive method, long-acting reversible methods are offered based on the medical eligibility criteria.

Patients using contraceptive implants were divided into two groups: women with heart disease and women with a healthy status (no medical condition). The demographic data, pattern of abnormal bleeding, discontinuation rate, and reasons of discontinuation were recorded and compared between the two groups. The medical records of all eligible patients were retrospectively reviewed by the investigator.

Two types of contraceptive implants were available for the study: etonogestrel containing contraceptive implant (Implanon®, Merck & Co., Inc, Whitehouse Station NJ, USA) and levonorgestrel containing contraceptive implants (Jadelle®, Bayer Healthcare, Berlin, Germany).

Abnormal vaginal bleeding was defined as prolonged bleeding, irregular bleeding, lighter bleeding, infrequent bleeding, and no bleeding according to the International Federation of Gynecology and Obstetrics (FIGO) recommendation of 2011[11] and the WHO family planning guidelines of 2018[6] (Table 1).

Table 1. Definition of abnormal vaginal bleeding patterns[6, 11].

Abnormal vaginal bleeding patterns	Definition
No bleeding	No days of bleeding/spotting entered throughout the reference period
Lighter bleeding	Lighter bleeding and fewer days of bleeding
Prolonged bleeding	≥ 10 days in one episode
Infrequent bleeding	< 2 episodes in one 90-day reference period
Irregular bleeding	A range of varying lengths of bleeding-free interval > 17 days within one 90-day reference period

Data are presented as mean ± standard deviation or n (%). BMI: body mass index

In our institute, when a patient needs removal of a contraceptive implant because of side effects, the attending physician advises, reassures, and manages the side effects. If the patients maintain their desire to discontinue using the implant, the other contraceptive methods are offered.

The data were collected using EpiData Version 3.1 and used the R-program for the statistical analysis. Descriptive statistics were used. Univariate analysis was done to compare the difference of vaginal bleeding from a contraceptive implant between women with heart disease and normal women using the chi square or Fisher's exact test for nominal variables and the student's t-test or Wilcoxon's rank sum test for continuous variables. A multiple logistic regression analysis was performed to identify independent risk factors. Statistical significance was set at $p < 0.05$.

Results

A total of 327 women used contraceptive implants that were prescribed at the Unit of Family Planning during the study period. Sixty-four women were excluded because of abnormal vaginal bleeding before application of an implant and underlying diseases such as diabetes, hypertension, autoimmune disease and human immunodeficiency virus (HIV) (Fig. 1). Finally, 263 women were enrolled in the study that included 54 (20.5%) women with heart disease and 209 (79.5%) healthy women.

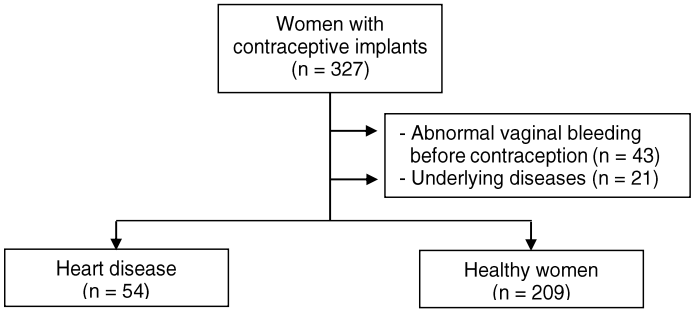

Fig. 1. Patient Flow Chart.

The demographic data of women with heart disease and healthy women who used contraceptive implants are shown in Table 2. Women with heart disease had a significantly higher nulliparity rate (32.8% vs 15.5%, $p < 0.05$) and lower body mass index (21.4 vs 22.4 kg/m^2, $p < 0.05$).

The median (interquartile range) age of women with heart disease was 28 (25, 34.8) years. Thirty-eight patients had acquired heart disease. According to the modified WHO classification of maternal cardiovascular risk, the most common was WHO class III (48.1%) followed by WHO class IV (27.7%), which has a high mortality rate during pregnancy. The 54 women were categorized according to the modified WHO classification: class I included repaired ventricular septal defect[1] and mild pulmonary stenosis/tricuspid regurgitation[2]; class II included atrial/ventricular septal defect (7) and repaired tetralogy of Fallot[3]; class III included mechanical valve[22], moderate mitral stenosis[1], and tetralogy of Fallot[3]; and class IV included pulmonary arterial hypertension[10], severe mitral valve stenosis[3], and dilated cardiomyopathy[2]. According to the New York Heart Association Functional Classification, most women were class I (54.4%) and class II (43.9%) at the time of implant insertion.

Table 2. Demographic data of women with heart disease and healthy women who used contraceptive implants.

Characteristics	Women with heart disease (n = 54)	Healthy women (n = 209)
Age (years), median (IQR)	28 (25, 34.8)	30 (24, 36)
Nulliparity	15 (28.8)*	24 (15.5)
BMI (kg/m^2), median (IQR)	21.4 (19.4, 23.8)*	22.4 (20.7, 24.9)
Type of contraceptive implants		
Etonogestrel	4 (7.4)*	87 (41.6)
Levonorgestrel	50 (92.6)*	122 (58.4)
Type of heart disease		
Congenital	20 (37)	
Acquired	34 (63)	
WHO classification		
Class I	3 (5.5)	
Class II	10 (18.5)	
Class III	26 (48.1)	
Class IV	15 (27.7)	
Anticoagulant users	29 (53.7)	

Data are presented as n (%) unless otherwise indicated. IQR: interquartile range, BMI: Body mass index, WHO: World Health Organization. *$p < 0.05$

Most women with heart disease chose levonorgestrel (92.6%), while 7.4% chose etonogestrel containing contraceptive implants. The percentage of women who used the levonorgestrel implant was greater than the group of healthy women (92.6% vs 65.4%, $p < 0.05$) (Table 2).

After using contraceptive implants, 51 (94.4%) women with heart disease had a significantly higher overall rate of abnormal vaginal bleeding compared with the healthy women (149/209, 71.3%). Abnormal vaginal bleeding patterns in women with heart disease were irregular bleeding (33%), no bleeding (33%), prolonged bleeding (14.8%), infrequent bleeding (13%), and lighter bleeding (13%) (Fig. 2). Some patients had more than one abnormal vaginal pattern. However, the timing of having the episode of any abnormal bleeding pattern was similar between the two groups: 1-8 months in women with heart disease and 1-7 months in healthy women.

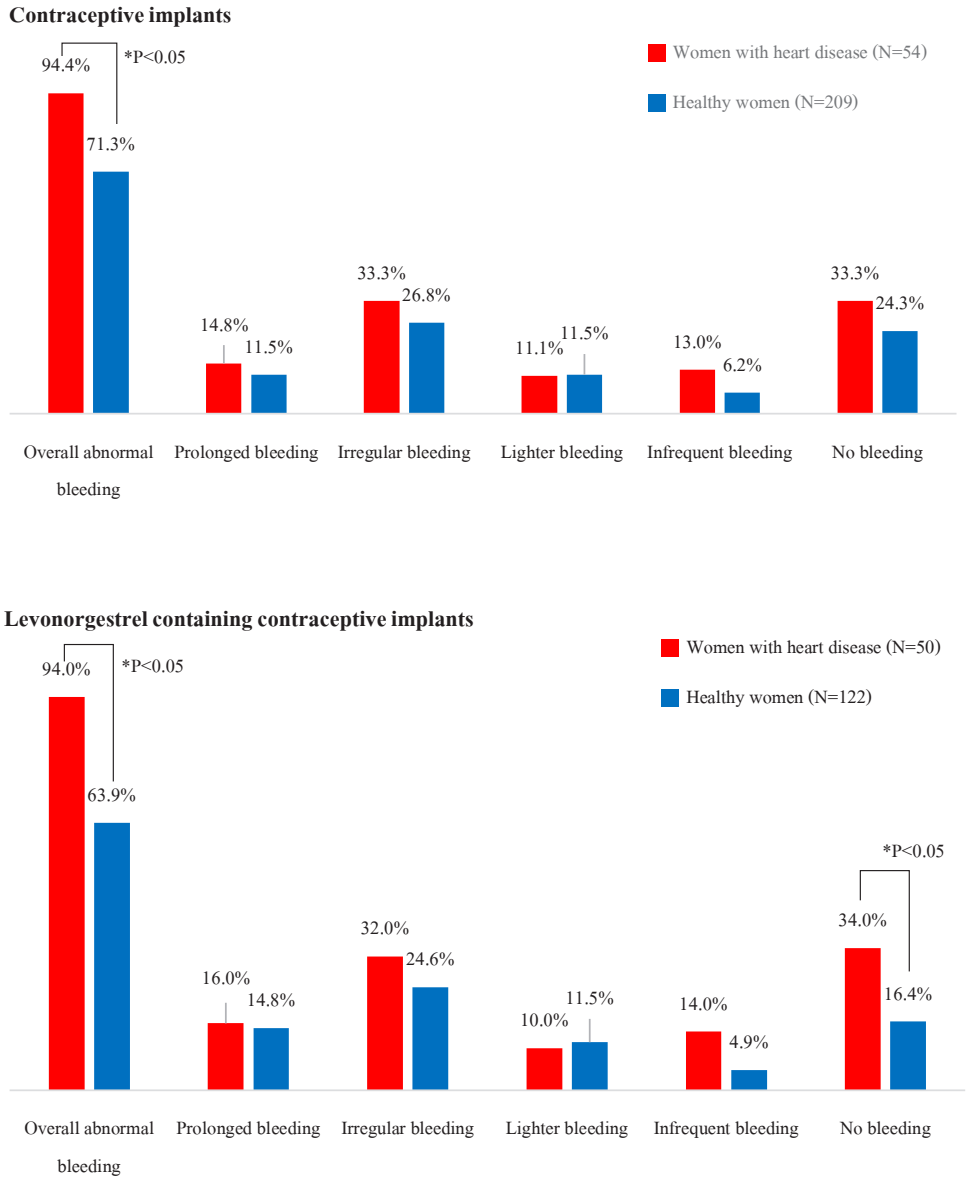

Fig. 2. Comparison of frequency of abnormal vaginal bleeding patterns between women with heart disease and healthy women who used contraceptive implants

When focusing on women who used only levonorgestrel containing contraceptive implants, women with heart disease had a significantly higher overall rate of abnormal vaginal bleeding compared with the healthy women (94% vs 63.9%, $p < 0.05$) (Fig. 2).

Anticoagulants were used in 29/54 (53.7%) women with heart disease who used contraceptive implants. When we compared vaginal bleeding patterns in women with heart disease who used and those who did not use anticoagulant medications, we found no significant differences (95.8% vs 93.3%, $p = 1.00$) (Table 3). Among the 29 anticoagulant users, the mean international normalized ratio (INR) level before using a contraceptive implant was 2.5 ± 0.9, while the mean INR level was 2.2 ± 0.7 after insertion of an implant.

The discontinuation rates of contraceptive implants in women with heart disease were significantly lower than in the healthy women (14.8% vs 29.7%, $p = 0.048$). The reasons for discontinuation in the women with heart disease were abnormal vaginal bleeding (62.5%) and personal reasons (37.5%), while the reasons for discontinuation in the healthy women were personal reasons (53.2%) and abnormal vaginal bleeding (25.8%). The details of personal reasons are shown in Table 4.

Table 3. Comparison of frequencies of abnormal vaginal bleeding patterns of women with heart disease and healthy women (n = 263) between anticoagulant and non-anticoagulant users.

Abnormal vaginal bleeding patterns	Anticoagulant users (n = 24)	Non-anticoagulant users (n = 30)	p value
Overall abnormal bleeding	23 (95.8)	28 (93.3)	1.000
Heavy bleeding			
Prolonged bleeding	6 (25)	2 (6.7)	0.12
Irregular bleeding	8 (33.3)	10 (33.3)	1
Non-heavy bleeding			
Lighter bleeding	2 (8.3)	4 (13.3)	0.682
Infrequent bleeding	4 (16.7)	3 (10)	0.687
No bleeding	7 (29.2)	11 (36.7)	0.771

Data are presented as n (%).

Table 4. Comparison of discontinuation rates and reasons of discontinuation between women with heart disease and healthy women who used contraceptive implants.

	Women with heart disease (n = 54)	Healthy women (n = 209)
Discontinued	8 (14.8)*	62 (29.7)
Reasons of discontinuation		
Abnormal vaginal bleeding	5 (62.5)	16 (25.8)
Personal reasons	3 (37.5)	33 (53.2)
Fertility needed	3 (37.5)	22 (35.5)
Divorce	0	3 (4.8)
Switch to other method	0	8 (12.9)
Increased body weight	0	7 (11.3)
Acne	0	3 (4.8)
Headache	0	3 (4.8)

Data are presented as n (%). *$p < 0.05$

Discussion

Songklanagarind Hospital is a super-tertiary care university hospital in southern Thailand. Therefore, most cases of pregnancy in the region with heart disease are referred to this hospital. Based on a study by Suwanrath et al[4], pregnancy was contraindicated in one out of four of patients with heart disease and the occurrence of maternal cardiovascular events increased significantly with a higher WHO classification. A highly effective contraceptive method with a long-acting mechanism is the preferred choice, especially when considering contraceptive implants.

The purpose of this retrospective study, which evaluated the vaginal bleeding patterns in women with heart disease compared with healthy women, was to inform the women regarding bleeding patterns and prevent them from implant discontinuation. Most women with heart disease (92.6%) used levonorgestrel containing contraceptive implants because of the prolonged duration for contraception. Based on the WHO classification, most of them were class III (48.1%) and class IV (27.7%). These results were similar to a previous study that used a long-acting reversible method in high severity cases according to the WHO classification because these groups were contraindicated for pregnancy and the long-acting method was suitable for them[12].

In this present study, abnormal vaginal bleeding from contraceptive implants was significantly higher in women with heart disease (94.4% vs 71.3%, $p < 0.05$). Most women used levonorgestrel containing contraceptive implants. Therefore, a subgroup analysis was conducted to compare bleeding between women with heart disease and healthy women who used only levonorgestrel containing contraceptive implants. We found that the incidence of abnormal vaginal bleeding was still significantly higher in women with heart disease. Based on previous studies, we suspected this result was possibly explained by drug interaction between warfarin and levonorgestrel. Zingone et al described the mechanisms of interaction that were: i) inhibition or induction of cytochrome P450 enzymes, ii) alteration of the coagulation cascade by hormonal contraceptives, and iii) protein binding displacement[9]. A study by Laine et al found that etonogestrel and levonorgestrel inhibited CYP2C9, 2C19, and 3A4[13].

A previous study reported that etonogestrel containing contraceptive implants affected the coagulation cascade, especially factors II, X, XI, and protein C but did not affect the prothrombin time[14]. Levonorgestrel might affect factor IX by displacing the protein binding of warfarin along with an elevated INR[10, 15]. We considered that an abnormal INR level might have an effect on bleeding patterns. However, a subgroup analysis in women with heart disease who used anticoagulant medications were found to have no increased INR levels after contraceptive implant insertion. Even though all anticoagulant users had normal INR values, no data were available on anticoagulant dosage changes and some data of the INR were missing during the use of contraceptive implants. In our institute, the cardiologists and cardiovascular thoracic surgeons have a target INR range of 2.0-3.5. However, when we conducted a subgroup analysis in women with heart disease to compare women who used anticoagulant medications with those who did not use anticoagulants, we found no significant difference of abnormal vaginal bleeding patterns. Therefore, we could not conclude that anticoagulants had any effect on vaginal bleeding patterns. This was possibly due to the small sample size.

Based on the comparison of patterns of vaginal bleeding between women with heart disease and healthy women who used contraceptive implants, no significant differences between the two groups were observed. In women with heart disease, most bleeding patterns were irregular bleeding (33%) and no bleeding (33%). Due to the lack of data in women with heart disease, we compared the present study with a previous study in a normal population. We found that the most common pattern was also irregular bleeding (48.5%)[16].

Overall, the continuation rate in women with heart disease was significantly higher than in the healthy group (85.2% vs 70.3%, $p = 0.048$). The continuation

rate in women with heart disease in the present study was higher compared with a previous study that reported 52% in a normal population[16]. The high continuation rates in contraceptive implants revealed that women with heart disease realized their heart disease was a contraindication for pregnancy as most of these women were WHO class III and class IV. They were possibly aware of the benefits of this method and were knowledgeable of the complications if they got pregnant. Abnormal vaginal bleeding was the most common reason to discontinue a contraceptive implant in women with heart disease (62.5%) which was similar to a previous study (54%)[16]. However, in healthy women, personal reasons were the most common for discontinuation (53.2%). Only one previous study by Bahamondes et al also reported personal reasons as the most common (16.4%)[16]. An in-depth analysis found that the personal reasons included fertility desire, divorce, and switch to another method.

This study has some strengths and limitations. One strength was this study provided the first descriptive data in women with heart disease using contraceptive implants. The important point in these patients is how to continue the method to prevent unintended pregnancy. The data on abnormal vaginal bleeding patterns and the reasons of discontinuation can assist health care providers with more confidence in prescribing contraceptive implants in women with heart disease. The retrospective nature of this study was a limitation. Some specific data could not be collected, especially changes in the dosage of an anticoagulant medication, duration of use, and the level of coagulation. However, the medical records were collected from a computer-based hospital information system.

Although the discontinuation rate was low in the present study, abnormal vaginal bleeding was still the most common reason to discontinue a contraceptive implant in women with heart disease. In-depth counseling is preferred in these patients to perceive the benefits of this method beyond the side effects.

Conclusion

The continuation rates of contraceptive implants in women with heart disease were high (85.2%) even though abnormal vaginal bleeding from contraceptive implants in women with heart disease was found to be in 94.4%. The two most common patterns of abnormal vaginal bleeding were irregular bleeding and no bleeding. These two reasons were the most common reasons to discontinue using a contraceptive implant.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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