Original Article

Preliminary Report on Comparative Study of Side Effects of Progestin-Only Contraceptive Methods between Thai Women Using DMPA and a Single-Rod Sub-Dermal Implant at Siriraj Hospital, Bangkok, Thailand

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Objective: To compare the side effects or specific adverse events except bleeding pattern reported between women using depo-medroxy progesterone acetate (DMPA) and a single-rod sub-dermal etonogestrel implant (Implanon).

Materials and Methods: This comparative study assessed women returning for follow-up visit at the Unit of Family planning, Siriraj Hospital between January and December 2019. Women aged 18 to 45 years old who used one of the progestin-only contraceptive methods, either DMPA or Implanon, as a birth control for six months were invited in the present study. Any adverse effects were recorded and analyzed.

Results: Fifty-nine women were in the Implanon group and 52 women were in the DMPA group. More women in the DMPA group were older [34.5 (27.5 to 38) versus 25 (22 to 31) years] and less single (26.9% versus 61.0%), p=0.001. The reported side effects in both groups were similar in degree and extent with no statistical significant difference except the symptom of flushing where more women in the Implanon group observed this event, p=0.004. There was borderline significance that women using Implanon had higher incidence of headache, gastrointestinal symptoms, and depression.

Conclusion: Both groups of women observed comparable adverse events except bleeding events. Flushing, headache, gastrointestinal symptoms, and depression were more reported by women using Implanon. Close method counseling during the course of use is essential to prolong continuing use to meet their contraceptive goal.

Keywords: DMPA, Implanon, Side effects, Thai women

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Hormonal contraceptive methods have their own advantages and disadvantages apart from protection against pregnancy. The combined oral contraceptive pill (COC) normally produces headache, nausea, vomiting, and weight gain. The intrauterine devices (IUDs) create abdominal pain or some spotting during use. Progestin-only contraceptive methods are a better alternative for breast-feeding women, women with thromboembolic disorder, women aged over 35 years, heavy smoker, obese women, or women who cannot tolerate the side effects of the COC. However, each progestin-only method induces certain side effects. For example, depo-medroxy progesterone acetate (DMPA) is more likely to create amenorrhoea during use. Progestin-only pills (POP) produce bloating abdomen and vaginal bleeding or spotting, and subdermal implants change the women's normal patterns of bleeding during use[1-3]. Weight gain has been notoriously reported to affect users while using the progestin-only method, DMPA has increased users' body weight at 6 or 12 months[4,5]. However, a recent report wrote that the use of etonogestrel, a single rod sub-dermal implant (Implanon) for up to

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two years has not increased the adolescents' body weight[6].

Although women are informed of these disadvantages before the initial use, still, some women cannot accept these bleeding events and eventually stop the use of the method of their preferences. Some women prefer a longer interval of menstrual cycle such as once within three months, while the other women still need monthly menstrual bleeding. Moreover, a rising number of women now want no menstrual bleeding while using a contraceptive method[7]. These have sometimes resulted in the low self-esteem of women in the method being used. Awareness of and understanding how women feel once these adverse events occur to them can help prolong the duration of the method used to meet the planned duration of pregnancy, as well as confidence of women in the contraceptive method. Mood change, especially depression, has been associated with the use of hormonal contraceptive pills[8] and DMPA, especially among adolescents[9,10]. However, there is inconsistent evidence of DMPA use and depression or mood change[11,12]. Progestin only contraceptive method, especially DMPA, has been used among women in Thailand for more than four decades. Their side effects on women during use have rarely been systematically assessed. Therefore, the present study aims to investigate the reported side effects of Thai women currently using a single-rod sub-dermal implant and DMPA and attending family planning services at the Siriraj Family Planning Siriraj Clinic.

Materials and Methods

This comparative study has been approved by the Institutional Review Board of the Faculty of Medicine Siriraj, Mahidol University (COA no. Si 243/2020).

Participants

Women aged 18 to 45 years old who used either DMPA or Implanon as a birth control between January 2019 and December 2019 and came for the six-month follow-up were included.

Outcome measures

All side effects reported by the participant were noted. They were headache, androgenic effects i.e., oily face, acne, hair loss, weight gain, gastrointestinal (GI) symptoms i.e., nausea or vomiting, breast engorgement, depression, loss of libido, flushing (red face due to capillary complex vasodilatation), skin rash, vaginal symptoms i.e., vaginal discharge or dryness, sleepiness, and loss of appetite. They were graded as no side-effect, mild, moderate, and severe side-effect.

Statistical analysis

Number (percentage) and median with interquartile range (interquartile range) were used for descriptive statistics. Chi- square or Fisher's exact test was used to compare categorical data. Student t-test and Mann-Whitney U test were used to compare parametric and non-parametric data, respectively. A p-value of less than 0.05 was considered statistically significant.

Results

There were 59 women in the Implanon group and 52 women in the DMPA group of the present preliminary report. Their age ranged from 22 to 38 years old. It appeared that women in the DMPA group were much older than those of their counterparts, $p<0.001$. More women in the DMPA group had higher family income than those of their counterparts, $p=0.040$. In addition, women in the Implanon group were more likely to be single than those in the DMPA group with statistically significance, $p=0.001$ (Table 1). However, there were no difference of women in both groups in terms of blood pressure, education, allergy, underlying diseases, and currently receiving medication.

Table 2 shows the reported side effects or specific adverse events of women in the DMPA and Implanon groups. It is interesting to note that there were no statistically significant differences in each reported side effects that occurred in both groups of women except that more women in the Implanon group reported flushing than those women in the DMPA group, 72.4% and 58% in the Implanon and DMPA groups, respectively, $p=0.004$. There was borderline significance that women using Implanon had higher incidence of headache, GI symptoms, and depression. Around half of women in both groups reporting vaginal symptoms had abnormal vaginal discharge but none required medical treatment. The comparison of frequency of complaints of women in the both groups is shown in Figure 1.

Discussion

This descriptive preliminary report aims to comparatively assess adverse events or side effects of current users between the single-rod sub-dermal implant (Implanon) and the injectable DMPA. Women using DMPA are older with more body mass index (BMI) and body weight, and more income than

Table 1. Demographic data (n=111)

	Implanon (n=59) n (%)	DMPA (n=52) n (%)	p-value
Age (years); median (IQR)	25 (22 to 31)	34.5 (27.5 to 38)	<0.001*
Body mass index			0.180
Underweight	12 (20.4)	4 (7.7)	
Normal	33 (55.9)	29 (55.8)	
Overweight	10 (16.9)	15 (28.8)	
Obese	4 (6.8)	4 (7.7)	
Systolic blood pressure; median (IQR)	110 (104 to 117)	114 (107 to 121)	0.152
Diastolic blood pressure; median (IQR)	70 (65 to 76)	72 (68 to 80)	0.249
Highest education			0.915
Primary/secondary school	14 (23.7)	12 (23.1)	
Vocational certificate/ diploma	3 (5.1)	3 (5.8)	
Bachelor's degree	38 (64.4)	31 (59.6)	
Master's degree or higher	4 (6.8)	6 (11.5)	
Family income (Baht)			0.040*
No income	3 (5.1)	3 (5.8)	
≤20,000	38 (64.4)	18 (34.6)	
20,000 to 25,000	8 (13.6)	12 (23.1)	
25,001 to 30,000	5 (8.5)	10 (19.2)	
>30,000	5 (8.4)	9 (17.3)	
Marital status			0.001*
Single	36 (61.0)	14 (27.0)	
Married	22 (37.3)	36 (69.2)	
Divorce	1 (1.7)	2 (3.8)	
Underlying disease			0.519
Yes	8 (13.6)	5 (9.6)	
No	51 (86.4)	47 (90.4)	
Receiving medication			0.445
Yes	5 (8.5)	2 (3.8)	
No	54 (91.5)	50 (96.2)	
Allergy			1.000
Yes	3 (5.1)	3 (5.9)	
No	56 (94.9)	48 (94.1)	

DMPA=depo-medroxy progesterone acetate; IQR=interquartile range

those using the Implanon. This may be because more women in DMPA group are likely to have complete family size with older age. DMPA becomes much more popular among the women with no fertility need. It is very interesting to observe that those women using Implanon were more likely to be younger. They expect a high contraceptive efficacy and long-term

Table 2. Percentage of women reporting specific adverse events (n=111)

	Implanon (n=59) n (%)	DMPA (n=52) n (%)	p-value
Headache			0.054
No	26 (44.1)	31 (62.0)	
Mild	19 (32.2)	15 (30.0)	
Moderate/severe	14 (23.7)	4 (8.0)	
Androgenic effects			0.211
No	9 (15.3)	14 (28.0)	
Mild	26 (44.0)	16 (32.0)	
Moderate/severe	24 (40.7)	20 (40.0)	
Weight gain			0.767
No	29 (49.2)	26 (52.0)	
Yes	30 (50.8)	24 (48.0)	
GI symptoms			0.080
No	28 (48.3)	34 (68.0)	
Mild	20 (34.5)	13 (26.0)	
Moderate/severe	10 (17.2)	3 (6.0)	
Breast engorgement			0.364
No	39 (66.1)	38 (76.0)	
Mild	15 (25.4)	7 (14.0)	
Moderate/severe	5 (8.5)	5 (10.0)	
Depression			0.083
No	35 (59.3)	40 (80.0)	
Mild	17 (28.8)	7 (14.0)	
Moderate/severe	7 (11.9)	3 (6.0)	
Loss of libido			0.129
No	33 (56.9)	23 (46.0)	
Mild	9 (15.5)	16 (32.0)	
Moderate/severe	16 (27.6)	11 (22.0)	
Flushing			0.004*
No	16 (27.6)	21 (42.0)	
Mild	17 (29.3)	22 (44.0)	
Moderate/severe	25 (43.1)	7 (14.0)	
Rash			0.377
No	38 (65.5)	39 (78.0)	
Mild	13 (22.4)	8 (16.0)	
Moderate/severe	7 (12.1)	3 (6.0)	
Vaginal symptoms			0.283
No	22 (38.6)	25 (50.0)	
Mild	19 (33.3)	17 (34.0)	
Moderate/severe	16 (28.1)	8 (16.0)	
Sleepiness			0.329
No	44 (74.6)	39 (78.0)	
Mild	11 (18.6)	5 (10.0)	
Moderate/severe	4 (6.8)	6 (12.0)	
Loss of appetite			0.189
No	24 (40.7)	16 (32.0)	
Mild	13 (22.0)	19 (38.0)	
Moderate/severe	22 (37.3)	15 (30.0)	

DMPA=depo-medroxy progesterone acetate; GI=gastrointestinal

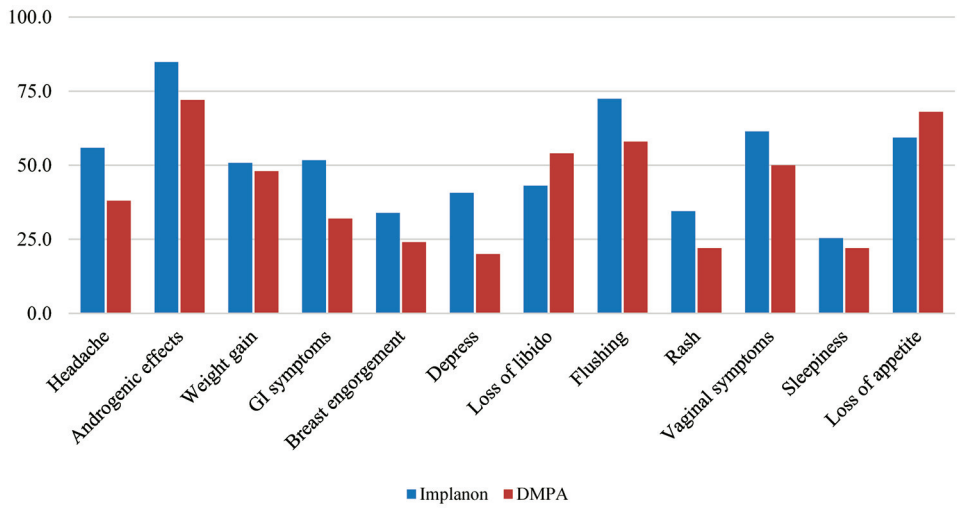

Figure 1. Comparison of frequency of complaints between Implanon (n=59) and DMPA (n=52) users.

effect of contraception because higher frequency of sexual relations is likely in this age group.

Regarding the reported adverse events during method use, there was no statistically significant difference between women using Implanon and DMPA, except that flushing was more reported in women using Implanon. Flushing is the uncontrollable condition of vasodilation that can be partly explained by deprivation of estrogen level. Whether or not Implanon has more negative impact on hypothalamus-pituitary-ovary axis needs to be further explored. Headache is more likely to be reported among women using Implanon, 55.9% against 38.0%. In other implant studies, headache accounted for 15.5%, 16.0%, 11.6%, and 7.8% of implanon users[3,12-14]. Headache was reported at different levels of different category of subdermal implant use, at 26.5%, 23.5%, 21.2%, and 28.3% for Norplant-6, Jadelle, Implanon, and Norplant-2, respectively[15]. Moreover, Brache et al stated that headache and acne are related to the method use, subdermal implant. Furthermore, weight gain is possibly related[16].

Women using implanon reported higher symptom of depression, at 40.7% against 20.0%. Depression during hormonal progestogen use has periodically been reported among users. However, studies are inconsistent of this adverse event among users, especially DMPA users[3,13-16]. Loss of appetite is more reported in women using DMPA, at 68.0% than those of their counter parts, at 59.3%, which is one of the interesting outcomes that is different from the previous report. This may be because the difference of race, culture, and lifestyle. In general, Asian women, especially Thai older women with DMPA are much more concerned over their figure and this may affect their eating habit.

The strength of the study is the comparative study conducted in the specialized clinic where the follow-up system and data record are very good. However, small sample size is one of the limitations of the present study. This, as the preliminary report, has resulted in limited data for generalization. The second limitation is that the study should be extended to collect women's adverse events at 12 months of use or beyond to obtain more solid data for representation. Last, the present study was initially planned and designed to be a prospective, randomized controlled trial. However, due to the request of women in family planning service who did not accept the method planned and were allocated by computer randomization.

Conclusion

Androgenic effects or male side effects i.e., oily face, acne, and hair loss are common adverse events occurring during hormonal contraceptive use of progestin-only contraceptives. Despite a high percentage of complaint about headache, no discontinuation resulted from this adverse event among women at six months of use. Headache is a subjective event where many women may perceive and report the event at different levels. Moreover, method counselling during use is also essential for tolerance and understanding of the method being used

to fulfill the duration of use. Information gained from this small descriptive report can help improve the quality of contraceptive counselling, for progestin-only methods. There is no statistically significant difference of adverse events reported among women using Implanon and DMPA. Both methods are equally safe and be used as effective contraceptive methods protecting against pregnancy. The side effects or specific adverse events of progestin-only contraceptives needs to be looked at to promote the use, continuation rate, and avoidance of the unwanted side effects particularly in Thai and Asian women.

What is already known on this topic?

Progestin-only contraceptive methods having different modalities than oral pills. Injectable, and sub-dermal implant, or even Progestin-only intrauterine insertion (Mirena) have been developed to provide alternatives to women or method of choices for woman who cannot tolerate the methods with combined estrogen hormone. However, its popularity of use among women has been very low due to its outstanding adverse events such as irregularity of bleeding and change in bleeding patterns during its use. Moreover, some common side effects such as headache, weight gain, hair loss, breast engorgement, greasing face, and depression also cause the unacceptability among women. These adverse events are major reasons for early method discontinuation.

What this study adds?

This preliminary report has observed comparison of side effects occurring to women using the three-monthly injectable method, DMPA, and the single-rod sub-dermal implant (Implanon). It is noted that women of both methods have no significantly statistical difference of the side effects, except flushing. Apart from the irregularity of bleeding, the adverse effects normally occur during the method initiation and become less over time of use. Close counseling from the initiation of the method use is essential to prolong continuing use of the method.

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Conflicts of interest

The authors declare no conflict of interest.

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