Original Article

The Rate and Predictors of Abnormal Vaginal Bleeding Among Three Progesterone-Only Contraceptive Users: A Longitudinal Study

Mohammed Khairy Ali, Ali K. Elsaman, Ahmed M. Reyad and Mansour Khalifa

Department of Obstetrics & Gynecology, Faculty of Medicine, Assuit University, Egypt

ABSTRACT

Objectives: To identify the rate and predictors of abnormal uterine bleeding (AUB) related to the 1-year use of three progestin-only contraceptive methods (POCs).

Study Design: The study was a single-center 12-month longitudinal study.

Patients and Methods: It was conducted at Assiut Woman's Health Hospital; Egypt from the 1st of August 2018 to the 1st of August 2020 included women who wanted to use depot medroxyprogesterone acetate 150 mg injection (DMPA), etonogestrel (ENG) implant, or desogestrel pills for pregnancy prevention for at least 1 year. The rate of AUB associated with these methods during 1 year of use and the potential predictors associated with this bleeding were the study outcomes. The data was analyzed using a t-test, ANOVA test, Mann–Whitney U test, Chi-square, Fisher exact test, and multivariate logistic regression test.

Results: Three hundred and ninety women were included in the study. The rate of AUB during 1 year in the DMPA, ENG implant, and desogestrel pills group was 59.2%, 60.2%, and 53.2%; respectively. The predictive model found that high parity (cut-off >3), lactating women, women with AUB with previous hormonal contraception use, and women with a higher uterine volume (cut-off >42 ml) were significant predictors.

Conclusion: The ENG implant has a higher rate of AUB during 1 year of use followed by the DMPA group and desogestrel pills. The woman should be counseled if she is at risk for developing AUB during the first year of POCs use hopping to increase the continuation and satisfaction rate.

Key Words: Abnormal uterine bleeding; desogestrel; DMPA, etonogestrel Implant.

Received: 01 March 2024, **Accepted:** 27 July 2024

Corresponding Author: Mohammed Khairy Ali, Department of Obstetrics & Gynecology, Faculty of Medicine, Assuit University, Egypt, **Tel.:** +2 010 0553 7951, **E-mail:** mohammedelkosy@aun.edu.eg

ISSN: 2090-7265, 2025, Vol. 15

INTRODUCTION

The use of POCs has been increased obviously and progressively over the world in the last few years[1]. They are an option for breastfeeding women or for whom an estrogen-containing contraceptive is either contraindicated or causes additional health problems[2,3]. POCs are including progestin-only pills (POPs), DMPA, subdermal implants, and levonorgestrel intrauterine devices (LNG-IUS)[4].

Unscheduled vaginal bleeding among women using POCs is high and it responsible for dissatisfaction and discontinuation in the majority of the users[5]. These bleeding patterns include amenorrhea, vaginal spotting, pronged heavy bleeding, and sometimes normal monthly menses[6]. At one year of use, about 90 % of DMPA and Mirena users, 75% of Norplant, and 40 % of POPs users experience AUB[7,8].

The exact cause of this bleeding is not completely understood[9]. The fragility of superficial blood vessels within the endometrium, local changes in endometrial steroid response, and local angiogenic factors may be behind this bleeding[10].

Estimating the prevalence of AUB with POCs is difficult and the literature has not been in consensus. However; it is surely affected by type/dose of progestin, methods of progesterone provided, and duration of use[11].

Despite a high rate of AUB associated with POCs, there is still a small number of women who experience regular menstrual bleeding. The predictors associated with AUB with LNG-IUS were reported more than one time in the literature[12,13]. However, little is known about the predictors affecting menstrual pattern after using other types of POCs. So, the aim of our study was to identify the rate of AUB related to the 1-year use of three POCs; DMPA ENG implant, and desogestrel pills. Also, we explored

DOI:10.21608/EBWHJ.2024.273842.1307

the potential clinical and ultrasonographic predictors of AUB associated with these methods; to our knowledge, no previous studies addressed this issue.

PATIENTS AND METHODS

It was a single-center; a 12-month longitudinal study. It was prospectively registered at Clinical trial. gov (NCT03398811). The study was conducted at Assiut Woman's Health Hospital, Assiut University, Egypt from 1st of August 2018 to 1st of August 2020. The protocol of the study was approved by The Assiut University Medical Ethical Review Board (IRB17100553).

Eligible participants

We included women aged between 18-40 years who wanted to use DMPA, ENG implant, or desogestrel pills only for pregnancy prevention for at least 1 year. All those women were more than 12 month postpartum and they had normal menstrual pattern before recruitment.

The exclusion criteria were women who were on any anticoagulant therapy or had a history of uterine, cervical, or ovarian pathology, women who had uterine bleeding disturbance (including amenorrhea) before recruitment, women who received DMPA injection within the previous 9 months or any hormonal treatments except they had three spontaneous regular menstrual cycles, severely anemic women (hemoglobin < 8gm/dl), women with any contraindications for POCs following the WHO eligibility[14] and women refused to participate in the study.

Enrollment

Written consent was obtained from all eligible participants after explaining the nature of the study. Then; women who met the entry criteria were subjected to detailed history included demographic/contraceptive data and systemic examination included BMI assessment. Then the uterine volume[15], endometrial thickness[16], and ovarian volume[17] were assessed by transvaginal ultrasound using the SONOACE X6 ultrasound device (Medison- United states). Moreover; uterine artery and subendometrial vessels were demonstrated by the color Doppler technique with real-time spectral analysis. The systolic/ diastolic ratio (S/D), resistance index (RI), and the pulsatility index (PI) were calculated when three similar consecutive waves were obtained[18,19].

After that; the participants were divided into three groups according to their choice: Group I "DMPA": women in this group choose to use Depot Medroxyprogesterone Acetate 150 mg (DMPA; Phrmcia, Egypt) injection every 3 months, group II "ENG implant": women in this group selected etonogestrel 68 mg implant (Implanon; Organon, USA Inc.) and group III "Desogestrel pills": women in this group opted to use desogestrel 75 µg pills (Cerazette; Organon, USA Inc); one pill every day at the same time for 28 days without pill-free interval.

The women were trained on how to fill the menstrual diary. The menstrual diary included information about days of bleeding and days of spotting. The principal investigator instructed them to record the menstrual pattern. They were provided with a diary to prospectively document their bleeding patterns for the next menstrual cycles. To increase the reliability of the menstrual diary; the participating women were asked to recall the bleeding pattern in the previous month.

Follow-up schedule

All women were instructed to come for follow-up at 1, 3, 6, 9, and 12 months. At each visit; the menstrual pattern was evaluated by the menstrual diary. Types of menstrual irregularities (if present) were reported at each visit. Most of the women brought their diaries during the follow-up visit which were seen by the principal investigator. Any women, who did not bring a diary, were asked to phone the principal investigator to complete the diary and they had to bring the missed diary at their next scheduled visit. BMI, endometrial thickness, uterine and ovarian volume, uterine artery, and subendometrial vessels Doppler indices were also documented. Any abnormalities in the ovary or the uterine cavity identified at any visit were recorded. The side effects of the method were also revised at each visit. Finally; any treatment (non-hormonal or hormonal) for controlling AUB with POCs use was reviewed.

Termination visit

At study termination, the final status of the participants was classified as “completed study", "lost from follow up" or "discontinued the POCs”. Additional 4 weeks were needed to allow for late visits and for trying to pick up participants who were lost from follow-up. Participants would continue the POCs and the follow-up visits at our Clinic if they wish so.

The study outcomes

The primary outcome was the rate of AUB during 1 year of DMPA, ENG implant, and desogestrel 75 µg pills use. While the secondary outcomes included the exploration of the potential predictors of AUB in the women using previously mentioned methods and to identify the changes in BMI, uterine volume, ovarian volume, endometrial thickness, uterine artery, and subendometrial vessels blood flow every month among these users

Sample size

Previous studies stated that about 68% of DMPA, 70%

of ENG implant users, and 40% of POPs users may have AUB during the first year of use[7,11,20]. Using population size 1000000 and hypothesized % frequency of outcome factor in the population equal to about 65% with confidence limits 5%, a total sample size of at least 390 patients was needed in this study assuming the rate of loss to follow-up of 10 % (Epi-info™, CDC, USA).

Statistical Analysis

The data was collected and entered into Microsoft Excel Database to be analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 21). Normally distributed variables were expressed in means ± standard deviation and compared either by t-test or Anouva. While abnormally distributed variables were presented by medians and compared using means of non-parametric tests. Chi-square and Fisher-exact tests were used to compare proportions. Multivariate logistic regression was conducted to test for predictors of AUB among POCs users. The sensitivity, specificity, positive predictive value, negative predictive value, the accuracy of the potential predictors revealed by logistic regression were also expressed. The *p-value* <0.05 was considered statistically significant.

RESULTS

Four hundred thirty-seven women were counseled for participation. However; 47 women were excluded from the study. The eligible women were divided into three groups; group I (DMPA group; 168 women), group II (ENG implant group; 140 women) while group III (desogestrel pills group; 82 women). However; only 155 women in the group I, 132 women in group II, and 72 women in group III completed the 1-year follow-up visits (Figure 1, the study flow chart).

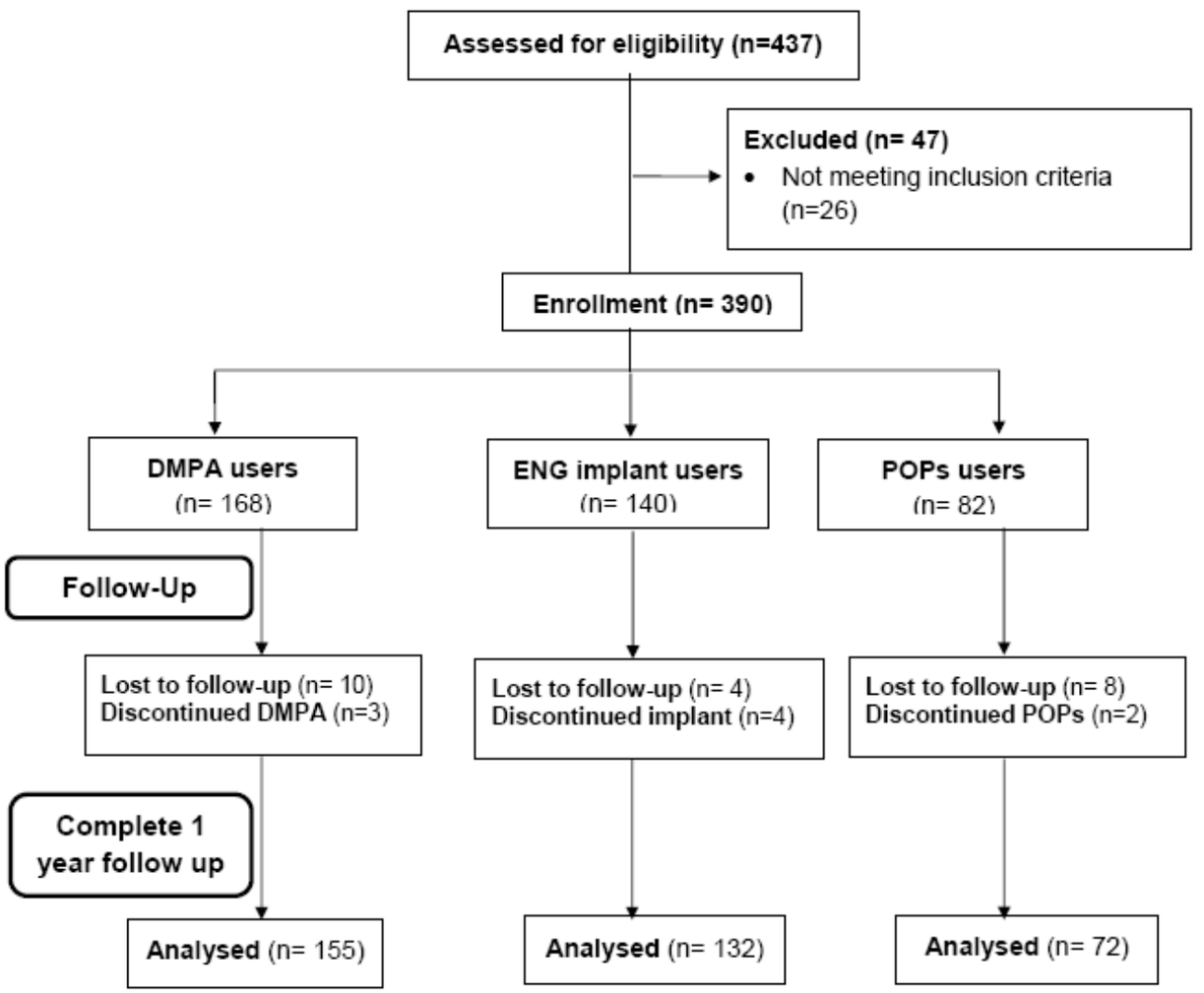

Fig. 1: The study flow chart

All groups were similar in baseline socio-demographic data without statistically significant differences except for duration from the last pregnancy that was higher in the DPMA group (p=0.000) (Table1).

Table 2 shows that the higher rate of AUB during 1 year was detected in the ENG implant group (60.2%) followed by the DMPA group 59.2% and a lower rate was found in the desogestrel pills group 53.2% but without statically significant differences (p>0.05) (Table 2).

The rate of uterine bleeding irregularities (UBI), including amenorrhea, at 1, 3, 6, 9, 12 months in DMPA was 10.8%, 62.2%, 68.3%, 45.9%, and 19.4%; respectively. While the figures related to ENG implant group were 15.7%, 61.6%, 67.6%, 56.0%, and 25.8%; respectively. For desogestrel pills; the rate of UBI was 10.0%, 59.5%, 62.3%, 43.2%, and 23.6%; respectively. The rate of amenorrhea was progressively increased in all groups with time. No statistically significant differences were noted between groups regards the rate of UBI at each visit (p>0.05) (Table 3).

It was noted that about 30% of women were received non-hormonal treatment for controlling AUB (the mean duration of the treatment was about ± 2.5 months), while about 17% of them were received hormonal treatment (the mean duration of treatment about ± 3.70 months). No statistically significant differences were noted between groups regards the received treatment for AUB (p>0.05).

There were statistically significant differences in the BMI, the ultrasonographic parameters from baseline to 12 months in all groups (p=0.000) (Table 4).

No statistically significant differences were observed between the groups regards the side effects (breast tenderness, headaches, nausea, ovarian cysts, decreased female sexual function, and stomach cramping) of POCs at each month (p>0.05).

The baseline data of women who had AUB and women without AUB during 1- year use of the three POCs were compared. The reveled significant factors (lactation; p=0.000, bleeding with previous hormonal contraception use; p=0.007, BMI; p=0.007, uterine volume; p=0.001 and uterine artery PI; p=0.002) and other factors which seemed to affect our outcome were entered in the multiple logistic regression model.

The multiple logistic regression model found that high parity (cut-off >3), lactating women, women with AUB with previous hormonal contraception use, women with a higher uterine volume (cut-off >42 ml) were significant predictors for development of AUB during the first year of DMPA, ENG implant and desogestrel pills use (Table 5). The sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and AUC of these potential predictors were shown in table 6 (Table 6).

Table 1: Demographic data of the participants

	DMPA (n= 168)		ENG implant (n= 140)		Desogestrel pills (n= 82)		*P-value*
Age (years), mean ± SD	28.30 ± 6.44		26.67 ± 7.54		27.45 ± 8.16		0.143
Residence, n (%)							
Urban	73	43.5%	72	51.4%	37	45.1%	0.359
Rural	95	56.5%	68	48.6%	45	54.9%	
Education, n (%)							
Illiterate	29	17.3%	25	17.9%	15	18.3%	
Basic education	80	47.6%	59	42.1%	36	43.9%	0.901
Secondary or more	59	35.1%	56	40.0%	31	37.8%	
Women work, n (%)	88 (52.4%)		67 (47.9%)		38 (46.3%)		0.596
History of previous abortion, n (%)	14 (8.3%)		9(6.4%)		7(8.5%)		0.781
Parity, median (range)	4.0 (1.0-7.0)		5.0 (2.0-7.0)		4.0 (1.0-8.0)		0.480
No. of NVDs, median (range)	2.0 (0.0-5.0)		2.0 (0.0-6.0)		2.5 (0.0-7.0)		0.876
No. of CSs, median (range)	1.0 (0.0-6.0)		2.0 (0.0-6.0)		1.5 (0.0-6.0)		0.582
Number of living children, median (range)	4.0 (1.0-8.0)		5.0 (1.0-6.0)		4.5 (1.0-7.0)		0.372
Duration from the last pregnancy (month), median (range)	25 (13-81)		22.5 (13-81)		22 (13-52)		0.000*
Lactation, n (%)	80 (47.6%)		75 (53.6%)		50 (61.0%)		0.133
Previous use of hormonal contraception	63 (37.5%)		51 (36.4%)		28 (34.1%)		0.875
AUB with previous hormonal contraception use	52(82.5%)		42(82.4%		23 (82.1%)		0.999
BMI (Kg/m^2), mean ± SD	26.79 ± 4.47		26.89 ± 4.70		27.10 ± 4.89		0.883

AUB abnormal uterine bleeding, BMI body mass index, CSs caesarian sections, DMPA depot medroxyprogesterone acetate, ENG etonogestrel, Kg kilogram, M^2 meter square, NVDs normal vaginal deliveries, n (%) number and percentage, SD standard deviation

* Statistical significant difference (P < 0.05)

Table 2: Number of women with AUB during 12 month of three POCs use [+]

AUB	DMPA (n= 130)		ENG implant (n= 108)		Desogestrel pills (n= 62)		*P-value*[1]	*P-value*[2]	*P-value*[3]	*P-value*[4]
	No.	%	No.	%	No.	%				
Yes (175)	77	59.2%	65	60.2%	33	53.2%	0.653	0.881	0.432	0.377
No (125)	53	40.8%	43	39.8%	29	46.8%				

AUB abnormal uterine bleeding, DMPA depot medroxyprogesterone acetate, ENG etonogestrel, n (%) number and percentage [+] Ninety women were excluded from this analysis (18 women lost from follow up, 8 women stop the method before development of AUB and 64 women had amenorrhea at 12 month). *P-value* [1] is the comparison between all groups, *p-value* [2] is the comparison between the first group and second group, *p-value* [3] is the comparison between the first group and third group, *p-value* [4] is the comparison between the second group and third group, *p-value* [5] is the comparison between baseline data and data at each month in every group.

Table 3: The rate and types of UBI during each visit in the first year of three POCs use

		DMPA		Implanon		Desogestrel pills		*P-value*[1]	*P-value*[2]	*P-value*[3]	*P-value*[4]
		No.	%	No.	%	No.	%				
1 month	Menstrual irregularities:	167		140		80					
	Yes	18	10.8	22	15.7	8	10.0	0.326	0.201	0.852	0.235
	No	149	89.2	118	84.3	72	90.0				
	Type of irregularities:										
	Amenorrhea	2	11.1	1	4.5	0	0.0				
	Spotting	9	50.0	12	54.5	6	75.0	0.734	0.620	0.560	0.755
	Heavy prolonged bleeding	5	27.8	4	18.2	1	12.5				
	Hypomenorrhae	2	11.1	5	22.7	1	12.5				
3 months	Menstrual irregularities:	164		138		79					
	Yes	102	62.2	85	61.6	47	59.5	0.920	0.915	0.685	0.760
	No	62	37.8	53	38.4	32	40.5				
	Type of irregularities:										
	Amenorrhea	5	4.9	5	5.9	3	6.4				
	Spotting	47	46.1	40	47.1	25	53.2	0.414	0.185	0.518	0.848
	Heavy prolonged bleeding	11	10.7	12	14.1	6	12.7				
	Hypomenorrhae	39	38.3	28	32.9	13	27.7				
6 months	Menstrual irregularities:	161		136		77					
	Yes	110	68.3	92	67.6	48	62.3	0.636	0.901	0.360	0.433
	No	51	31.7	44	32.4	29	37.7				
	Type of irregularities:										
	Amenorrhea	7	6.4	6	6.5	4	8.3				
	Spotting	59	53.6	50	54.3	25	52.1	0.251	0.550	0.061	0.385
	Heavy prolonged bleeding	8	7.3	10	10.9	15	31.3				
	Hypomenorrhae	36	32.7	26	28.3	4	8.3				
9 months	Menstrual irregularities:	157		134		74					
	Yes	72	45.9	75	56.0	32	43.2	0.122	0.086	0.709	0.079
	No	85	54.1	59	44.0	42	56.8				
	Type of irregularities:										
	Amenorrhea	22	30.6	14	18.7	4	12.5				
	Spotting	28	38.9	34	45.3	15	46.9	0.299	0.232	0.143	0.819
	Heavy prolonged bleeding	4	5.5	8	10.6	2	6.2				
	Hypomenorrhae	18	25.0	19	25.4	11	34.4				
12 months	Menstrual irregularities:	155		132		72					
	Yes	30	19.4	34	25.8	17	23.6	0.421	0.194	0.461	0.735
	No	125	80.6	98	74.2	55	76.4				
	Type of irregularities:										
	Amenorrhea	27	90.0	26	76.5	11	64.7				
	Spotting	2	6.7	5	14.7	4	23.5	0.205	0.494	0.061	0.359
	Heavy prolonged bleeding	0	0.0	1	2.9	2	11.8				
	Hypomenorrhae	1	3.3	2	5.9	0	0.0				

DMPA depot medroxyprogesterone acetate, ENG etonogestrel, n (%) number and percentage * Statistical significant difference ($P < 0.05$) *P-value* 1 is the comparison between all groups, *P-value* 2 is the comparison between the first group and second group, *P-value* 3 is the comparison between the first group and third group, *P-value* 4 is the comparison between the second group and third group, *P-value* 5 is the comparison between baseline data and data at each month in every group.

Table 4: The changes in BMI and ultrasonographic parameters from baseline to 12 month among DMPA, ENG implant and desogestrel pills users

Outcome+	DMPA (n= 168)	ENG implant (n= 140)	Desogestrel pills (n= 82)	*P-value*[1]	*P-value*[2]	*P-value*[3]	*P-value*[4]
	Mean ± SD	Mean ± SD	Mean ± SD				
BMI							
Baseline	26.79 ± 4.47	26.89 ± 4.70	27.10 ± 4.89	0.883	0.851	0.618	0.743
12 months	27.77 ± 4.52	27.80 ± 4.90	28.08 ± 4.78	0.890	0.970	0.646	0.677
P-value[5]	0.000*	0.000*	0.000*				
Endometrial Thickness(mm)							
Baseline	3.77 ± 1.17	3.80 ± 1.16	3.82 ± 1.17	0.944	0.810	0.754	0.916
12 months	3.37 ± 1.18	3.23 ± 1.07	3.22 ± 1.12	0.521	0.321	0.367	0.939
P-value[5]	0.000*	0.000*	0.000*				
Uterine volume (ML)							
Baseline	45.96 ± 13.14	44.86 ± 13.68	42.59 ± 11.95	0.162	0.466	0.057	0.212
12 months	39.88 ± 14.60	37.70 ± 13.32	37.92 ± 13.18	0.361	0.185	0.320	0.917
P-value[5]	0.000*	0.000*	0.000*				
Ovarian volume (ML)							
Baseline	6.35 ± 1.76	6.31 ± 1.77	6.32 ± 1.71	0.981	0.850	0.905	0.968
12 months	4.80 ± 1.39	4.62 ± 1.32	4.61 ± 1.45	0.461	0.273	0.336	0.960
P-value[5]	0.000*	0.000*	0.000*				
Uterine artery PI							
Baseline	2.34 ± 0.67	2.29 ± 0.62	2.32 ± 0.59	0.818	0.527	0.844	0.742
12 months	2.94 ± 0.52	2.83 ± 0.52	2.80 ± 0.52	0.080	0.072	0.053	0.668
P-value[5]	0.000*	0.000*	0.000*				
Sub-endometrial uterine artery PI							
Baseline	1.31 ± 0.29	1.34 ± 0.30	1.35 ± 0.32	0.514	0.374	0.308	0.797
12 months	1.46 ± 0.24	1.49 ± 0.23	1.48 ± 0.22	0.449	0.213	0.498	0.728
P-value[5]	0.000*	0.000*	0.000*				

BMI body mass index, DMPA depot medroxyprogesterone acetate, ENG etonogestrel, ML milliliter, PI pulsatility index, SD standard deviation *P-value*[1] is the comparison between all groups, *P-value*[2] is the comparison between the first group and second group, *P-value*[3] is the comparison between the first group and third group, *P-value*[4] is the comparison between the second group and third group, *P-value*[5] is the comparison between baseline data and data at each month in every group. * Statistical significant difference ($P < 0.05$). + the data did not include women who lost from follow up or stopped the method.

Table 5: Multiple logistic regression analysis for risk factors of AUB during 1st year of DMPA, ENG implant and desogestrel pills

Variables	*P-value*	OR	95% C.I.	
			Lower	Upper
Age	0.463	0.976	0.914	1.042
Parity	0.018*	1.411	1.061	1.875
Lactation	0.014*	3.403	1.284	9.016
BMI (kg/m^2)	0.143	0.927	0.837	1.026
AUB with previous hormonal contraception use	0.004*	6.481	1.810	23.212
Uterine volume (ml)	0.038*	1.040	1.002	1.079
Uterine artery PI	0.326	0.694	0.335	1.439

AUB abnormal uterine bleeding, BMI body mass index, C.I. confidence interval, DMPA depot medroxyprogesterone acetate, ENG etonogestrel, Kg kilogram, M^2 meter square, ml milliliter, OR odds ratio, PI pulsatility index * Statistical significant difference ($P < 0.05$)

Table 6: Sensitivity, Specificity, +PV, -PV, accuracy and AUC of the potential predictors for AUB with 1 year use of three POCs

Risk factors	Sensitivity	Specificity	+PV	-PV	Accuracy	AUC
Parity Cut-off(> 3)	57.14	48.00	60.6	44.4	55.3	0.505
Lactation	62.86	60.80	69.2	53.9	62.0	0.618
UBI with previous hormonal contraception use	91.67	28.00	60.4	73.7	62.7	0.598
Uterine volume Cut-off(> 42 ml)	66.86	53.60	66.9	53.6	61.3	0.610

AUB abnormal uterine bleeding, AUC area under the curve, +PV positive predictive value, -PV negative predictive value, UBI uterine bleeding irregularities

DISCUSSION

The present work demonstrated that more than half of women who used DMPA, ENG implant, and desogestrel pills had AUB during the 1- a year of use. Again; we found a significant increase in the BMI, decrease in endometrial thickness, uterine and ovarian volume beside decrease in the uterine artery and sub-endometrial vessels blood flow from baseline to 12 months in all groups. Moreover; our results revealed that the high parity (>3), lactating women, women with AUB with previous hormonal contraception use, women with a higher uterine volume (>42 ml) were risk factors to develop AUB during 1-year of these POCs use.

Disturbances of uterine bleeding patterns are almost unavoidable in POCs users, and there is no method that can promise regular bleeding[21]. These bleeding disturbances are not usually affecting the health of users, but they may dislike by users and lead to refusal or discontinuation of these methods[22].

In our study; the rate of AUB during the 1-year of DMPA use was 59.2%, 60.2% for ENG implant, and 53.2% for desogestrel pills users. Taneepanichskul S *et al*. found that the rate of AUB in the first year of DMPA use was 58.3% in women aged more than 35 years[23]. Despite our study included women aged from 18-40 years; we almost all reported the same figure. Another study demonstrated that the rate of AUB at 1-month of use of DMPA was 93.5% and the figure became 42.4% at one year of use[24]. Schrager S *et al*. reported that AUB occurs during the 1-year in 70 % of women who used DMPA[25]. Kaunitz *et al*. found that only 5.7 % of women who used DMPA had AUB. The long period of follow up in their study (2 years) may be behind this much lower figure[26].

Despite bleeding patterns with the ENG implant may reach up to 78% in a 3-month period, 50% of women will improve with continuous use and 30% of users will be amenorrheic by one year of use[27]. Most implant users will experience a reduction in the frequency of menstrual bleeding with time[28]. Harvey C *et al*. mentioned that more than 50 % of ENG implant users requested premature discontinuation (removal of Implanon before 3 years) due to associated AUB[29].

In women using POPs; nearly 40% of users will have AUB and approximately 10% have amenorrhea during 1st year of use[30]. Palacios S *et al*. mentioned that the rate of AUB with desogestrel pills was 58.0 % at the 1st cycle of use which decreased to 45.3% after 9 months[31]. We reported almost a similar number.

We think that the great variation of AUB rate in literature with POCs use is due to the absence of a comprehensive understanding of the primary mechanisms leading to AUB. Social and cultural factors were hypothesized by many investigators.

Our results found that the highest incidence of AUB occurred during the first 6 months of POCs use and decreasing over time. The amenorrhea rate was higher in DMPA followed by ENG implant then desogestrel pills during in the 1- a year of use.

A primary cause of AUB with initiation may be due to the significant endometrial thinning properties of progestins[11]. With sustained use of the method, inhibition of ovulation will occur resulting in the development of amenorrhea especially with DMPA and ENG implant[21]. Our results are in consensus with these facts.

Weight gain is a common side-effect of hormonal contraceptives[32]. A systematic review in 2013 found limited evidence of weight gain when using POCs[33]. We are also on the same track with the results of this systematic review.

The thinning of the endometrium during POCs use is one of the accepted mechanisms for the development of AUB[10,11]. Our results also showed significant thinning in endometrial thickness from before to 12 month of POCs use.

A significant decrease in the uterine and ovarian volume had been observed in our study at 12 month of POCs use. This is due to a decrease in uterine artery blood flow and suppress of FSH and LH with continued use[10,34,35]. The uterine artery and sub-endometrial blood flow decreased significantly in all groups at 12 month of use. Prolonged use of POCs associates with a pseudogestational status and hypoestrogenemia which causes a significant decrease in blood flow to and inside the uterus[35,36].

Despite the presence of many studies in the literature[37-39] that cared about the continuation rate with POCs methods but we failed to find any study pointing to the predictors associated the AUB with these methods.

In our study; a high parity was a risk for the development of AUB with POCs. It can be explainable because multipara has a higher uterine size more than nulliparous women and the involution process after delivery lasts longer in the multiparous women[40].

A second risk factor was lactation. Almost all breastfeeding mothers are menstruation-free for the first six months postpartum but some of them may experience spotting and irregular periods[41]. So; in those women, lactation adds more risk for AUB.

The AUB with previous hormonal contraception use was the most significant risk factor observed in our study. This was unsurprising; because the same cause may be still present and lead to AUB.

The high rate of AUB with large uterine volume may be explained by increases in the surface area of the endometrial cavity besides an increase in the blood flow to the uterus[42].

In the end; this study has both strengths and weaknesses. Up to our knowledge; this is the first study that addressed the predictors for development to AUB with POCs use. The reporting of events every month during POCs use for 12 month is very few in literature. Furthermore, the ultrasound assessment was performed by a single investigator.

However, the present work had some limitations. Randomization of the participants to the intervention arm was not possible. Subjective rather than objective evaluation for the bleeding pattern by the menstrual diary was another limitation. We tested only the clinical effect of contraception methods but we did not test any chemical markers like estradiol. Long-term follows up (more than 12 month) is essentially needed. The studying of predictors associated with amenorrhea was not addressed in our study due to the small number of women who had amenorrhea at 12 month.

CONCLUSION

Most of women will have AUB during first year of DMPA, ENG implant and desogestrel pills use. The DMPA and ENG implants are associated with the greatest rate of AUB and amenorrhea. High parity, lactating women, women with AUB with previous hormonal contraception use, women with a higher uterine volume (>42 ml) are significant predictors for AUB during the first year of DMPA, ENG implant and desogestrel pills use.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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