Acceptability, side-effects and discontinuation of second and third-generation oral contraceptive pills in Bangladesh: A quasi-experimental study

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Abstract

Background The third-generation oral contraceptive pill (3G-OCP) has improved side-effect profile compared to the second-generation (2G-OCP). In Bangladesh, comparative data on these two generations of OCPs is nonexistent. This study aimed to compare acceptability, side-effects and discontinuation rates between 3G- and 2G-OCPs. **Methods** This quasi-experimental study was conducted from October 2017 to June 2018 in two unions of one sub-district in Bangladesh. From each intervention and control unions, 1400 women were enrolled after screening for selection criteria. All the women in the intervention union received 3G-OCP while those in the control union had 2G-OCP. Women from both the groups were provided six cycles of OCPs, two at enrollment, and two each at two subsequent home-visits at 2-months apart by the health workers. Data was collected thrice: immediately after enrolment, and two subsequent follow-up visits at 2-months interval by the study interviewers. Life table analysis was done to compare cumulative discontinuation rates and Hazard Ratio (HR) was estimated for likelihood of discontinuation of 3G-OCP as compared to 2G-OCP due to side-effects. **Results** After 24-weeks of enrollment, 69.1% (n=967) of the women from the intervention and 58.0% (n=812) from the control group continued with the method. The major reason for discontinuation was pill use-related side-effects (3G-OCP: 20.4% vs. 2G-OCP: 19.5%). Initially, the reported side-effects for 3G-OCP were higher than those for 2G-OCP (47.3% vs. 33.2%). However, after 24-weeks of use, the corresponding figures became similar (9.5% vs. 8.7%). The cumulative discontinuation rate due to side-effects was 22.8% and 25.2% for 3G- and 2G-OCP respectively which was not statistically significant ($p=0.14$). After adjusting for potential covariates, the likelihood of discontinuation of 3G-OCP was 14% lower ($HR=0.86$, $p=0.075$) than 2G-OCP which was statically significant at 10% level. The study observed three deaths (one in intervention and two in control), of which one death in the control group was due to stroke. **Conclusion** The 3G-OCP was less likely to be discontinued than the 2G-OCP due to side effects. After 24-weeks of use the reported side-effects of the two types of OCPs was similar. However, one stroke-related-mortality due to use of 2G-OCP, demanded further larger studies.

Plain English Summary

This study was conducted to compare acceptability, side-effects and discontinuation rates between 2G- and 3G-OCPs. After checking for eligibility criteria, from each intervention and control area, 1400 married women of reproductive age were enrolled in the study by the health workers. Women in the intervention group were provided with 3G-OCP and those in the control group had 2G-OCP; 2 cycles at enrolment and 2 cycles at each of the 2 follow-up visits at home by the health workers. All the women in both the groups were interviewed three times: at enrollment and at two subsequent follow-up visits at home at 3-months apart by the study interviewers. Initially, the reported side-effects for 3G-OCP were higher than that by the 2G-OCP (47.3% vs. 33.2%); however, after 24-weeks of use the difference was eliminated (9.5% vs. 8.7%). After 24-weeks of use, 20.4% women from the intervention group and 19.5% from the control group discontinued the method due to pill use-related side-effects. Taking into account the duration of use, the cumulative discontinuation rate due to side-effects was 22.8% for 3G-OCP as compared to 25.2% for 2G-

OCP though the difference was not statistically significant. After adjusting for other potential socio-demographic characteristics, the likelihood of discontinuation of 3G-OCP was 14%, lower than 2G-OCP which was statistically significant at 10% level. The study observed three deaths, one in intervention and two in control groups of which one death occurring due to stroke in the control group was possibly related to the use of 2G-OCP. In conclusion, the study found relatively improved acceptance of the 3G-OCP than the 2G-OCP. Though the reported side-effects of the two types of OCPs was similar after 24-weeks of use, one mortality due to stroke, related to use of 2G-OCP, demands further studies in large populations.

Background

The first oral contraceptive pill (OCP) introduced in the 1960s marked a step into great progress for women's health and autonomy worldwide. The pill allowed women to be able to decide on the spacing of and the number of children they wished to have using a noninvasive method. Although this contraceptive method initiated several controversies at first, it was later strongly adopted and became the principal contraceptive method in the United States and other developed nations, used by approximately 8 to 10 million women in the US by 1970 [1].

While the OCP was very effective at controlling birth, its users reported several side effects. Research associated the high estrogen levels in the pill with increased risk of blood clots, strokes and myocardial infarction [2]. By 1962, about 132 reports of thromboembolism had been reported in OCP users and had resulted in 11 deaths [3]. In an effort to reduce these risks, second-generation OCP (2G-OCP) was developed. These pills contained a reduced dose of hormones – estrogens and progestin compared to the first-generation pills, and were meant to be safer for the women, cause fewer side effects and be overall more efficient than the former pill. Unfortunately, though successful at protecting against certain risky cancers [4], the 2G-OCP was still associated with risk of hypertension and presented daunting side effects such as dizziness, nausea, migraines and weakness. This discouraged women from staying on the pill, making its continuation rates low [5].

The third-generation OCP (3G-OCP) was hence developed to address the continuous low adherence of 2G-OCP. The 3G-OCP is an association of low-dose ethinylestradiol and potent testosterone-derived progestin, low in androgenic activity, making it less harmful for metabolism, weight gain, acne and other notable side effects [6] including a reduced risk of myocardial infarction [7]. When compared to 2G-OCP, 3G-OCP is associated with 29–45% lower rates of discontinuation due to weight gain [8]. The 3G-OCP also has shown potential improvements for a reduced risk of myocardial infarction and are more tolerated by the users. Findings from a transnational study conducted in 1997 showed that 3G-OCP users had approximately one-third of the risk of myocardial infarction when compared to 2G-OCP, the first pill to be associated with no risk of myocardial infarction [7].

These aforementioned, evidence-based characteristics of the 3G-OCP motivated the idea of its introduction in the National Family Planning Programme (NFPP) in Bangladesh. About 62% of the country's currently married women are using a contraceptive method and 25% of the women use OCP as

a primary method of contraception [9]. Oral contraception though widely accepted, also has a high stoppage rate which therefore affects its success in the country. In 2017 while the overall discontinuation rate of contraception was 37%, the OCP discontinuation rate was even higher (42%) [9].

As of 2014, among the women in Bangladesh who were using OCPs, 50% of them were using 2G-OCP, making it the most commonly used modern method of contraception in the country [10]. Yet, a study conducted in rural Bangladesh illustrated that approximately 50% of the women who were on the 2G-OCP, experienced side effects such as dizziness, nausea, blurring of vision and weakness [5]. The purpose of this study was to obtain evidence-based data on acceptability, side-effects and discontinuation rates of 3G-OCP adherence, as they compare to those of the 2G-OCP, as well as to identify reasons for discontinuation and compliance.

Methods

Study design and setting

This quasi-experimental study was conducted in two unions (one intervention and one control) of the Sarankhola sub-district of the Bagerhat district of Bangladesh where OCP discontinuation rate was high (30% during January-December, 2016) [11]. The study was conducted from October 2017 to June 2018.

Study population

All the married women of reproductive age (MWRA) in the two selected unions of Sarankhola sub-district (4096 in the intervention union and 3182 in the control union) represented the study population.

Specification of the 3G- and 2G-OCP

For this study, 3G-OCP was procured from a renowned pharmaceutical company, named, Renata Limited, Bangladesh, which was available in the market with the brand name 'Desolon'. Each Desolon pill contains Desogestrel BP (0.15mg) and Ethinylestradiol BP (0.03mg). Each cycle of 'Desolon' comes in a strip with only 21 pills and does not contain iron tablets. To make the strip similar to the 2G-OCP, the brand name of which is '*Sukhi*' and is available in the NFPP, customization of the strips of 'Desolon' was done by Renata Limited by adding seven additional iron tablets (each containing Ferrus Fumerates BP 75.0 mg) for the current study. For supplying six months' cycle among the 1400 clients of OCP, a total of 8,400 cycles of 3G-OCPs were procured from Renata Limited for this study purpose.

For the control area, Directorate General of Family Planning (DGFP), Bangladesh supplied the required number of 2G-OCP (*Sukhi*). Each 2G-OCP contained Levonorgestrel BP (0.15mg) and Ethinylestradiol BP (0.03 mg).

Sample selection and enrolment of women in the study

For enrollment in the study, a total of 2001 women from the intervention union and 2020 women from the control union were screened for selection criteria. The inclusion criteria were i) married women within 15 and 39 years of age; ii) not pregnant at the time of enrollment; iii) no desire for having a baby in next 1 year, and iv) willing to use OCP as a contraceptive method for the next 6 months. Exclusion criteria were: i) lactating mothers with a ≤ 6 -months-old baby; ii) known case of hypertension; iii) BMI ≥ 30 ; iv) migraine; v) blurring of vision; vi) varicose vein, and vii) known case of diabetes mellitus. The selection criteria were adapted in the local context using the WHO guideline [12]. Family Welfare Assistants (FWAs), a cadre of frontline government health workers, who were trained for 5 days to work in this study, screened and enrolled the subjects. From each intervention and control unions, 1400 women who passed the selection criteria and gave consent to participate in the study were enrolled. The study protocol was approved by the Institutional Review Board of International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b).

Distribution of OCPs

After enrollment, the FWAs provided two cycles of 3G-OCP to each woman in the intervention unions, and those in the control unions were provided with two cycles of 2G-OCP. The FWAs also oriented the women in both the groups about the process of using the OCPs and their tentative side-effects. In case of any major side-effect, the women were advised to communicate with the concerned FWAs or visit the satellite clinics or the nearest family planning clinic or health complex for necessary advice.

All the participants were visited twice by the FWAs, firstly at the 2nd month, and secondly at the 4th month as part of their regular home visit schedules. During each visit, in the intervention and control unions, the FWAs provided the women with 2 additional cycles of OCPs of the respective types after their health checking and necessary counselling.

Data-collection

Data was collected by 4 female Field Research Assistants (FRAs) who were provided with a 15-day training on the data collection tools, including interview techniques. A full-time field manager was engaged in the study area to monitor the entire field implementation process.

Within 2 days of enrolment, an FRA visited the participants at their homes and interviewed them for socio-demographic and reproductive characteristics including their previous contraceptive use history. Each participant was further followed-up at the 3rd and 6th months after enrollment for detailed information on the OCP use, side-effects and compliance. Women, who discontinued the method use, were asked about the time of, and reasons for discontinuation. A semi-structured pre-tested questionnaire was used for these follow-up interviews. All the completed questionnaires were regularly reviewed at the field for completeness and accuracy of the intervention under the supervision of the field manager. For internal constancy, necessary corrections were made after checking entered data with the questionnaire.

Statistical analysis

Descriptive as well as analytical statistics were performed to report findings on compliance, side-effects and discontinuation by type of OCPs. To summarize various reported side-effects, findings are presented under four broad categories: i) direct pill use related problems; ii) probable pill use related problems; iii) possible pill use-related problems, and iv) other health problems in relation to the likelihood of side-effects of OCP use. Life table technique was used to compute rates of method discontinuation due to side-effects by taking into account the varying length of time for which the subjects remained in the study with the Log-Rank test (Mantel-Cox) to compare the intervention to control. The Cox's Proportional Hazard model was used to estimate the Hazard Ratio (HR) for assessing the likelihood of discontinuation of 3G-OCP as compared to 2G-OCP after adjusting for selected socio-demographic variables. All the statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows version 20.0 (Chicago, IL, USA).

Results

The similarities and differences in socio-demographic characteristics of the OCP acceptors in the two study groups are shown in Table 1. Mean age of each of the 3G-OCP and 2G-OCP acceptors was 29 years. When comparing the educational status, about 60% of the OCP acceptors in both the groups had at least incomplete secondary or higher education. Only 4% of the acceptors in the intervention group and 6% in the control group had no education. About 47% of the husbands from each group of OCP acceptors had incomplete secondary or higher education. About 10% of the husbands of 3G-OCP users as compared to 14% of those accepting 2G-OCP had no education. For the employment status of the OCP acceptors, only about 5% in each intervention and control group were involved with any income-generating activities. The OCP acceptors in the control group had relatively higher monthly family expenditure as compared to that in the intervention area (Taka 11,644 vs. Taka 11,575 equivalent to USD 137 vs. USD 136). About 2–3% of the OCP acceptors had a monthly family expenditure less than or equal to Taka 5,000 (equivalent to USD 59). Almost all of the women (over 99%) in each intervention and control group reported using a contraceptive method previously. Only 0.1% of the women in the intervention group and 0.3% in the control group did not use any contraceptive method previously. Among the women who mentioned using a contraceptive method, about 97% in both the intervention and control groups had taken oral pills previously. A substantial proportion of women (51% in the intervention and 41% in control union) had used injectable contraceptive. Among the other types of contraceptive methods, in the intervention area, about 20% reported using both the condom and maintaining safe period methods. On the other hand, in the control area, 45% of the women practiced safe period and 11% used condom.

Table 1
Variations in socio-demographic characteristics of the of the OCP acceptors by type

Socio-demographic characteristics	% of OCP acceptors by type		
	Total n = 2800	3G-OCP n = 1400	2G-OCP n = 1400
Age (in years) of the clients			
<= 19	8.4	8.8	8.0
20–24	21.2	20.4	22.1
25–29	20.0	18.9	21.1
30–34	20.6	22.4	18.8
35–39	29.8	29.6	30.0
Mean (SD)	29.1(6.7)	29.1(6.7)	29.0(6.7)
t = 0.58 p = 0.559			
Educational status of the clients			
No education	4.8	4.1	5.5
Incomplete primary	10.1	13.9	6.3
Completed primary	25.6	22.4	28.9
Incomplete secondary	44.0	45.1	42.9
Completed secondary	8.8	8.0	9.5
Higher than secondary	6.7	6.4	7.0
$\chi^2 = 56.77$ p < 0.001			
Employment status of the clients			
Nothing	95.4	94.9	95.9
Formal Job	1.9	1.4	2.4
Informal Job	2.7	3.6	1.7
$\chi^2 = 12.98$ p < 0.001			
Education of husband of the clients			
No education	11.7	9.6	13.7

OCP = Oral Contraceptive Pill, 3G-OCP = Third Generation Oral Contraceptive Pill, 2G-OCP = Second Generation Oral Contraceptive Pill, SD = Standard Deviation, IUD = Intra Uterine Device

Socio-demographic characteristics	% of OCP acceptors by type		
	Total n = 2800	3G-OCP n = 1400	2G-OCP n = 1400
Incomplete primary	12.5	17.4	7.6
Completed primary	28.7	26.0	31.5
Incomplete secondary	27.8	29.0	26.6
Completed secondary	9.1	8.3	9.9
Higher than secondary	10.2	9.6	10.8
$\chi^2 = 75.89$ p < 0.001			
Monthly family expenditure of the clients (in Taka)			
<= 5000	2.2	1.9	2.6
5001–10000	52.7	52.4	53.0
10001–15000	30.2	30.4	30.1
15001–20000	9.7	9.4	10.0
20000+	3.6	3.1	4.1
Didn't know	1.6	2.9	0.3
$\chi^2 = 34.041$ p < 0.001			
Mean (SD)	11610.5 (4836.3)	11575.4 (4649.9)	11644.7
Ever used any contraceptive method			
Yes	99.8	99.9	99.7
No	0.2	0.1	0.3
$\chi^2 = 1.80$ p = 0.179			
Type of method ever used (Multiple Response)	n = 2794	n = 1399	n = 1395
Oral pill	96.8	96.8	96.8
Injectables	46.0	51.0	40.9
Condom	15.5	19.7	11.3
IUD	1.4	0.9	1.8

OCP = Oral Contraceptive Pill, 3G-OCP = Third Generation Oral Contraceptive Pill, 2G-OCP = Second Generation Oral Contraceptive Pill, SD = Standard Deviation, IUD = Intra Uterine Device

Socio-demographic characteristics	% of OCP acceptors by type		
	Total	3G-OCP	2G-OCP
	n = 2800	n = 1400	n = 1400
Implant/Norplant	2.6	3.4	1.9
Safe period	32.4	19.9	44.9
Refuse to answer	0.1	0.0	0.1
Withdrawal	2.4	4.2	0.6
OCP = Oral Contraceptive Pill, 3G-OCP = Third Generation Oral Contraceptive Pill, 2G-OCP = Second Generation Oral Contraceptive Pill, SD = Standard Deviation, IUD = Intra Uterine Device			

Profile of side effects of 3G-OCP and 2G-OCP users

The incidence of different reported side-effects between the 3G-OCP and 2G-OCP acceptors at different time points during the 6-month follow-up period of the study is shown in **Table 2**. Initially, the 3G-OCP acceptors reported a higher incidence of side-effects (47.3%) as compared to the 2G-OCP acceptors (33.2%). However, at the end of 6 months of use, the incidence of reported side-effects of the two types of OCPs in the study convened to about 9%.

Direct pill use related problems

The analysis noted a significantly higher incidence of any direct pill use related problem among the 3G-OCP users as compared to 2G-OCP users in the first four months of follow-up. However, in the 5th and 6th months this variation deteriorated. Nevertheless, in the 6th-month follow-up, the 2G-OCP users reported a higher incidence of vertigo and nausea as compared to the corresponding figures by 3G-OCP users. In the 6th-month, any direct pill use related problem by the 3G-OCP users was even lower (4.7%) than the reported figure by the 2G-OCP users (6.0%), though the difference was not statistically significant (**Table 2**).

Table 2: Comparison of side-effects related to use of OCP type at different time points of use						
	% of OCP acceptors by type had side-effects after use of months					
Type of side effects	At 1 month		At 3 month		At 6 month	
	3G-OCP n=1315	2G-OCP n=1205	3G-OCP n=1022	2G-OCP n=913	3G-OCP n=970	2G-OCP n=816
Direct pill use related						
Headache	2.0	3.3	0.5	0.4	0.0	0.1
Vertigo	35.6	26.4	11.3	6.1	2.6	4.4
Nausea	17.9	19.5	3.2	3.0	2.0	4.7
Weight gain	0.4	1.2	0.0	0.3		
Acne in face	0.2	0.0	0.0	0.0	0.1	0.0
Growth of unwanted hair	0.0	0.0	0.0	0.0		
Spottings	0.4	0.1	0.1	0.0		
Menstrual bleeding less than normal	1.0	1.3	1.0	1.3	1.0	0.2
Cessation of menstruation	0.8	0.5	0.6	0.1		
Migraine	2.1	0.8	0.0	0.0		
Prolonged duration of menstruation	0.8	0.4	0.1	0.0		
High blood pressure	0.5	1.4	0.2	0.1	0.2	0.0
Excessive vomiting	1.9	0.7	0.3	0.0		
Any direct pill use related	41.0	31.0	14.9	8.9	4.7	6.0
Probable pill use related						
White discharge	5.6	3.2	4.3	2.5	2.7	1.3
Excessive bleeding during menstruation	2.4	0.2	1.4	0.1	0.7	0.0
Blurred vision	3.5	4.4	0.6	0.2	0.8	0.1
Varicose vein	0.2	0.2	0.0	0.0		
Dried breast milk	0.3	0.2	0.1	0.2		
Yellowish eyes/urine	0.1	0.0	0.0	0.0		
Any probable pill use related	11.1	7.4	6.2	3.0	3.9	1.5
Possible pill use related						
Weakness	11.4	8.3	2.7	1.5	2.4	3.6
Lower abdominal pain	0.9	1.2	0.1	0.1	0.2	0.6
Heaviness on foot/pain in leg	0.4	0.0	0.0	0.0	0.1	0.0
Frequent urination	0.8	0.4	0.4	0.0	0.0	0.1
Acidity/Gastric	1.8	0.3	1.6	0.1	1.2	0.1
Varicose vein	0.2	0.2	0.0	0.0		
Chest pain	0.1	0.2	0.0	0.0		
Any possible pill use related	13.8	9.6	4.5	1.8	3.9	4.3
Other health problems						
Back pain	0.2	0.1	0.0	0.1	0.0	0.0
Breathing difficulties	0.3	0.2	0.3	0.0	0.0	0.0
Others	1.1	0.9	0.2	0.4	0.0	0.0
Any other health problem	1.7	1.2	0.5	0.5	0.0	0.0
Any side-effect or health problem	47.3	33.2	21.6	11.5	9.5	8.7
Significant at 5% level for t test for proportions between 3G-OCP and 2G-OCP						

OCP=Oral Contraceptive Pill, 3G-OCP=Third Generation Oral Contraceptive Pill, 2G-OCP=Second Generation Oral Contraceptive Pill

Probable pill use related problems

Comparison of reported probable pill use related problems showed an overall decline in reported side-effects in both groups of OCP users (reduced from 11.1–3.9% in 3G-OCP and 7.4–1.5% in 2G-OCP users). However, overall, there was a persistent higher incidence of related side-effects among the 3G-OCP users than the 2G-OCP users. When analyzed by types of side-effects, white discharge, excessive bleeding and blurred vision were significantly higher in the 3G-OCP users than those using 2G-OCP (Table 2).

Possible pill use related problems

Our analysis demonstrates a higher incidence of any possible pill use related problem in 3G-OCP users than those using the 2G-OCP in each of the first four-month time points consecutively. However, at the 5th and 6th month time point this variation was eliminated (Table 2).

Other health problems

Overall reporting of other health problems was low (ranging from 1.2–1.7%) in the first follow-up that gradually reduced to 0% at 6 months of use (Table 2). No variation in other reported health problems between 3G-OCP and 2G-OCP users was observed over time.

Status of continuation with 3G-OCP and 2G-OCPs

Among the enrolled women in both intervention and control groups, 967 (69.1%) and 812 (58.0%) continued with taking the OCPs respectively at the end of 6-month follow-up (Fig. 1). The crude discontinuation rates due to side-effects were 20.4% (n = 285) and 19.5% (n = 273) for 3G-OCP and 2G-OCPs respectively. A substantial proportion of subjects in each intervention (9.0%, n = 126) and control (18.1%, n = 254) group, discontinued the method due to various social reasons (husband's disapproval, husband away, wanted child were the top three reasons for method discontinuation) (Table 3). During the 6-month follow-up period, 4 women in the intervention group and 7 in the control group reported getting pregnant. When these women were asked about the reasons for becoming pregnant, the majority (75.0% in the intervention and 57.1% in the control group) said about stopping the pill due to side-effects. About one-fourth of the women in each intervention and control group mentioned forgetting taking the pill as a reason for becoming pregnant (Table 3).

Table 3
Reasons for discontinuation of OCP by type at different follow-up visits

Reasons for discontinuation	% (number) discontinued by at different follow-up visits by type of OCP used					
	At 3 month follow-up		At 6 month follow-up		Overall	
	3G-OCP n = 1400	2G-OCP n = 1400	3G-OCP n = 1015	2G-OCP n = 906	3G-OCP n = 1400	2G-OCP n = 1400
Side-effects	18.0 (252)	17.8 (249)	3.3 (33)	2.6 (24)	20.4 (285)	19.5 (273)
Social reasons	8.4 (118)	14.6 (205)	0.8 (8)	5.4 (49)	9.0 (126)	18.1 (254)
Became pregnant due to stopped taking pill	0.2 (3)	0.5 (7)	0.1 (1)	0.0 (0)	0.3 (4)	0.5 (7)
Death	0.0 (0)	0.1 (1)	0.1 (1)	0.1 (1)	0.1 (1)	0.1 (2)
Lost to follow-up	0.9 (12)	2.3 (32)	0.5 (5)	2.2 (20)	1.2 (17)	3.7 (52)
Any reason	27.5 (385)	35.3 (494)	4.7 (48)	19.4 (94)	30.9 (433)	42.0 (588)
OCP = Oral Contraceptive Pill, 3G-OCP = Third Generation Oral Contraceptive Pill, 2G-OCP = Second Generation Oral Contraceptive Pill						

Life table analysis for discontinuation of OCP

The discontinuation rate of the 3G-OCP was 2.4% lower than that of 2G-OCP. Results from the life table analysis, after taking into account the duration of OCP use revealed that by the end of 24 weeks, discontinuation rate attributed to side-effects of the 2G-OCP was 25.2% as compared to 22.8% for the 3G-OCP. However, this difference was not statistically significant (Fig. 2). The same analysis also showed that the major share of these discontinuations occurred within the first 4 weeks of OCP adherence (14.6% for 3G-OCP and 19.6% for 2G-OCP).

Reasons for discontinuation of OCP due to side-effects

Table 4 demonstrates the proportion of women who discontinued OCP due to various side-effects. Most of the side-effect related discontinuations occurred within the first follow-up visit for both the groups of women. At the end of the first follow-up visit, among the women who discontinued OCP, over 90% in both intervention and control groups discontinued the method use due to direct pill use related problem in which vertigo, nausea, excessive vomiting and migraine were the major reasons for discontinuation. At the end of the first follow-up visit, about a quarter of the participants (25.0% in the intervention and 27.7% in the control group), reported discontinuing the OCP due to a probable pill use related problem in which blurred vision, excessive bleeding during menstruation and white discharge were major reported reasons. At the end of the first follow-up visit, 13.1% and 14.5% of the discontinuations for the 3G-OCP and 2G-OCP respectively were due to any possible pill use related problem in which lower abdominal pain, acidity/gastric, weakness, and frequent urination were the main problems. Other health problems such as loss of appetite, breathing difficulties, back pain etc. were reported by around 4% of the women from in each intervention and control group as reasons for discontinuing the method use.

Table 4
Reasons for discontinuation due to side-effects by type of OCP used by follow-up visits

Reasons for discontinuation	% discontinued at follow-up visits by type of OCP used			
	At 3 month follow-up		At 6 month follow-up	
	3G-OCP n = 252	2G-OCP n = 249	3G-OCP n = 33	2G-OCP n = 24
Direct pill use related				
Vertigo	86.9	84.3	93.9	66.7
Nausea	63.9	72.3	84.8	70.8
Excessive vomiting	11.1	6.0	3.0	0.0
Migraine	9.5	8.0	6.1	0.0
Prolonged duration of menstruation	5.2	2.4		
High blood pressure	2.0	5.6		
Weight gain	1.2	4.8	0.0	16.7
Cessation of menstruation	1.2	2.0	3.0	0.0
Irregular menstrual bleeding	0.0	1.2		
Menstrual bleeding less than normal	0.0	0.8		
Any direct pill use related	94.4	97.2	100.0	87.5
Probable pill use related				
Blurred vision	15.1	20.9	18.2	4.2
Excessive bleeding during menstruation	5.6	1.6		
White discharge	5.2	5.2	15.2	4.2
Dried breast milk	1.2	1.2		
Insomnia	0.4	0.0		
Dementia/Depression	0.0	0.4		
Jaundice	0.0	0.4		
Any probable pill use related	25.0	27.7	27.3	4.2
Possible pill use related				

OCP = Oral Contraceptive Pill, 3G-OCP = Third Generation Oral Contraceptive Pill, 2G-OCP = Second Generation Oral Contraceptive Pill

Reasons for discontinuation	% discontinued at follow-up visits by type of OCP used			
	At 3 month follow-up		At 6 month follow-up	
	3G-OCP n = 252	2G-OCP n = 249	3G-OCP n = 33	2G-OCP n = 24
Lower abdominal pain	4.0	4.8	3.0	8.3
Acidity/Gastric	2.8	1.2	9.1	0.0
Weakness	2.4	6.0		
Frequent urination	2.4	1.6	3.0	0.0
Chest pain	0.8	0.4		
Pain in leg	0.8	0.0		
Tumor in uterus	0.0	0.4		
Difficulty in urination	0.0	0.4		
Heaviness on foot	0.4	0.0		
Any possible pill use related problem	13.1	14.5	12.1	8.3
Other health problems				
Loss of appetite	1.2	0.8		
Breathing difficulties	0.0	2.0	0.0	4.2
Back pain	2.0	0.0		
Allergy	0.4	0.4		
Tumor in hand	0.0	0.4		
Any other health problem	3.6	3.6	0.0	4.2
OCP = Oral Contraceptive Pill, 3G-OCP = Third Generation Oral Contraceptive Pill, 2G-OCP = Second Generation Oral Contraceptive Pill				

The study also observed 3 deaths, 1 in the intervention area and 2 in the control group. The death in the intervention group was due to diarrhoea and therefore not likely to be related to the use of 3G-OCP under this study. Of the two death cases in the control group, one was due to a stroke that was likely to be related to the use of 2G-OCP. The other death case in the control group had pre-existing kidney and heart disease and a history of taking 2G-OCP. Despite being enrolled in the study, the latter woman did not use the 2G-OCP in the current study thus this death was not related to the study intervention.

Cox-Hazard model for discontinuation of OCPs

In this study, we fitted Cox's Proportional Hazard model to estimate the Hazard Ratio (HR) for discontinuation of type of OCP adjusted for selected socio-demographic covariates (client's age, educational status, employment status, previously used OCP as a contraceptive method, women's husbands' educational level and monthly family expenditure). Table 5 demonstrates that after adjusting for socio-demographic covariates, the 3G-OCP users were 14% less likely to discontinue the method as compared to those using the 2G-OCP (HR = 0.86, $p = 0.075$) which was statistically significant at 10% level of error. We also observed that women with increasing age, low education level, previous use of OCP, and low family income were more likely to discontinue OCP (Table 5).

Table 5

Crude and adjusted HRs with 95% CIs for discontinuation of 2G-OCP as compared to 3G-OCP adjusted for different covariates

Covariates	n	Crude			Adjusted		
		HRs	95.0% CI	p- value	HRs	95.0% CI	p-value
Type of OCP used							
2G-OCP	1085	1.00	-	-	1.00	-	-
3G-OCP	1252	0.89	0.75–1.05	0.15	0.86	0.72–1.02	0.08
Age (in years) of the clients							
<= 19	168	1.00	-	-	1.00	-	-
20–24	487	0.78	0.56–1.08	0.14	0.78	0.56–1.09	0.14
25–29	457	0.74	0.53–1.04	0.08	0.75	0.53–1.06	0.10
30–34	507	0.71	0.51–0.99	0.04	0.73	0.52–1.02	0.06
35–39	718	0.70	0.51–0.96	0.03	0.74	0.53–1.03	0.07
Educational status of the clients							
No education	116	1.00	-	-	1.00	-	-
Incomplete primary	248	1.57	0.91–2.70	0.11	1.59	0.91–2.77	0.10
Primary	622	1.83	1.11–3.03	0.02	1.77	1.06–2.95	0.03
Incomplete secondary	990	1.78	1.09–2.92	0.02	1.69	1.00-2.85	0.05
Secondary	204	1.56	0.89–2.72	0.12	1.43	0.78–2.61	0.25
Higher	157	2.03	1.16–3.55	0.01	2.02	1.06–3.86	0.03
Employment status of the clients							
Nothing	2225	1.00	-	-	1.00	-	-
Formal job	48	0.84	0.45–1.57	0.58	0.62	0.30–1.26	0.18
Informal job	64	0.98	0.59–1.64	0.94	1.04	0.62–1.74	0.90
Education status of the husbands of the clients							
No education	282	1.00	-	-	1.00	-	-
Incomplete primary	307	1.22	0.87–1.71	0.26	1.19	0.84–1.69	0.33
Primary	688	1.18	0.88–1.59	0.28	1.06	0.78–1.45	0.69
HRs = Hazard Ratios, CIs = Confidence Intervals, 2G-OCP = Second Generation Oral Contraceptive Pill, 3G-OCP = Third Generation Oral Contraceptive Pill, OCP = Oral Contraceptive Pills							

Covariates	n	Crude			Adjusted		
		HRs	95.0% CI	p-value	HRs	95.0% CI	p-value
Incomplete secondary	628	1.12	0.83–1.52	0.46	1.01	0.73–1.40	0.95
Secondary	201	1.15	0.78–1.68	0.49	1.05	0.69–1.59	0.84
Higher	231	1.32	0.92–1.88	0.13	1.20	0.78–1.85	0.41
Monthly family expenditure (in Taka)							
<= 5000	54	1.00	-	-	1.00	-	-
5001–10000	1226	1.72	0.85–3.46	0.13	1.81	0.89–3.65	0.10
10001–15000	713	1.60	0.79–3.26	0.19	1.69	0.83–3.44	0.15
15001–20000	224	1.72	0.82–3.62	0.15	1.75	0.83–3.69	0.14
20000+	81	2.28	1.03–5.07	0.04	2.38	1.06–5.34	0.04
Didn't Know	39	3.10	1.33–7.24	0.01	3.25	1.38–7.64	0.01
Previously used OCP							
Yes	2258	1.00	-	-	1.00	-	-
No	79	1.28	0.84–1.94	0.25	1.29	0.85–1.97	0.23
HRs = Hazard Ratios, CIs = Confidence Intervals, 2G-OCP = Second Generation Oral Contraceptive Pill, 3G-OCP = Third Generation Oral Contraceptive Pill, OCP = Oral Contraceptive Pills							

Discussion

The study found that the cumulative discontinuation rate due to side effects for the 3G-OCP at 22.8% while that for the 2G-OCP at 25.2% with most discontinuation happening within the first 4 weeks of intervention. The attained results were favourable for the 3G-OCP which is in corroboration with previous studies [6, 13]. Kulier et al. in a study in 2004 expressed that the 3G-OCP had a less negative impact on participants' weight gain, metabolism, acne and other side effects [6]. In addition, results from the Cox-Hazard model of this study revealed that after 6 months of the OCP adherence, the 3G-OCP was 14% less likely to be discontinued when compared to the 2G-OCP in Bangladesh (HR = 0.86, p = 0.075). This figure also supports the above premise.

Although overall results are advantageous, the measured discontinuation rates of 25.2% and 22.8% for 2G-OCP and 3G-OCP respectively are still relatively high. In addition to displaying relatively high rates of discontinuation, the study also expressed similarities with other previous studies [13]. Side effects were one of the main reasons for OCP discontinuation causing approximately 20% of discontinuation amongst participants in both groups. The second reason for discontinuation was social reasons. In a setting like Bangladesh, social factors can frequently play direct roles in health outcomes as the

community is very homogenous and traditional; therefore, immediate change is not easy. Social factors contributed to 9% of discontinuation among the intervention group and 18% in the control group by the end of the study.

The major reason for OCP discontinuation in this study was various side effects, causing 20% of discontinuation in the intervention group and 19% in the control group. These results reflect similar findings from previous studies conducted in 2006 in Bangladesh, that listed side effects as one of the three major reasons for method discontinuation [5]. Unlike some past studies, this study asked participants what specific side effects they experienced while on the pills, to identify the side effects that were most connected to discontinuation. The relevant side effects in the research were categorized into 4 different groups: direct pill related problems, probable pill use-related problems, possible pill use related problem and other health problems. The most reported side effects leading to discontinuation were direct pill use-related problems. These problems included, most frequently identified vertigo, nausea, blurred vision, excessive vomiting, migraine and others. In 2G-OCP and 3G-OCP groups, vertigo and nausea caused more than 30% of direct pill related discontinuation. In 2G-OCP acceptors, vertigo and nausea caused about 35% of discontinuation, which was 33% in 3G-OCP acceptors.

Side effects being a primary reason that led to OCP discontinuation motivated the review of the variances between reported side effects amongst the intervention and control groups. Regarding the timing of reported side effects, as shown in the results, within the first four months of follow-up, more participants from the intervention group ended OCP adherence. However, a significant shift happened in the fifth month. The number of women, from the intervention group, who were discontinuing the pill, started reducing more rapidly than of the women in the control group. By the end of the study, at 6 months, more OCP acceptors from the control group were discontinuing the pill. The fact that approximately 97% of the women in this study had been on a contraceptive pill prior to this study may serve as a potential explanation to the dynamic timing of the discontinuation due to side effects trend. The Rosenberg et al. 1998 study articulated in their study that, recent pill use was the only significant variable in predicting discontinuation, meaning that prior exposure to an OCP made a difference on if the women stayed on the pill or not [14]. In 2017, the NFPP released their 2018–2020 prioritized actions and listed as commitment 7 to provide free and adequate contraceptives to NGOs, private clinics and hospitals and garment factory clinics with trained family planning personal [15]. This effort was meant to increase the accessibility of contraceptives to women all over the country; hence more women were taking the 2G-OCP. The 3G-OCP, however, was yet to be introduced in the NFPP in Bangladesh, therefore, most of these women were probably using the 2G-OCP as their contraception method prior to participating in this study. This means that most women in the control group had already been exposed to the 2G-OCP and had a chance to adapt to its potential side effects the first time they took the method. Most of the OCP acceptors from the intervention group, however, were getting exposed to the 3G-OCP for the first time and therefore experiencing these side effects for the first time leading to more initial discontinuation.

Inversely, while former studies report clear favourable trends between higher educational status and OCP discontinuation rates, this study's results challenge those previous findings. Women in the intervention

group who had no educational background or incomplete primary education, in this study, reported lower discontinuation rates than women with higher education. Also, women in the intervention group, from families with high monthly expenditure (20,000 + BDT, equivalent to USD 235+) also showed significantly higher discontinuation rates in comparison to women from other expenditure brackets in both groups. Both of these findings are different from the results shown in previous studies [16, 17]. Muhindo et al., in 2015, reported that lower education level was an indicator for poor contraceptive adherence in Uganda [16] and Mahumud et al., in 2015 reported that significantly higher rates of discontinuation were pronounced among married Bangladeshi women who were less educated [17]. These new results could consequently be due to the presence of the health workers who provided thorough and personal counselling to each participant during the study implementation period by making all the women, especially the less privileged ones, well aware that some side effects would be apparent as a result of being on the pill. A 1998 study on oral contraception continuation by Rosenberg et al., expressed that pill discontinuation is especially likely if the side effects come as a shocker to the pill acceptors [14]. Hence, understanding the origin and possibility of side effects onset prior to taking the pill could have been one of the reasons that kept the less educated OCP acceptors on the pill even after the inception of side effects. A 2006 study on OCP discontinuation in rural Bangladesh found that women who had consulted a trained worker prior to getting on the pill had a minimum use period of twelve months while women who did not have proper counselling from a trained worker had a minimum use time of one month [5]. A more recent study aimed at identifying the practices that led to unintended pregnancies in Bangladesh, recommended after its findings, to increase trained field workers who can ensure distribution of OCP supplies and provide counselling and support for the families, through the family planning program [18].

In addition, the discrepancy between women's educational background and discontinuation rates could be explained by the notion of self-authorization and exposure to more contraceptive options. Women with higher education levels are likely to be employed which makes them more financially capable, enabling them to seek different contraceptive methods if side effects become too discomforting. It could also be inferred that these women are more empowered to make independent decisions on their bodies and OCP continuation, leading them to stop if they are displeased with the side effects.

From the results, we also observed three death cases during the implementation of the OCP intervention. One of the deaths was of a participant in the intervention group and the 2 others from participants in the control group. The death case in the intervention group had previously been on the 2G-OCP for over 15 months and even after starting the 3G-OCP, did not report any major health changes. This individual suffered and died from diarrhoea therefore her death was not associated with the 3G-OCP. One of the 2 deaths in the control group had no previous use of OCP. She, however, was hypertensive, was not taking her antihypertensive drug regularly and subsequently died of a stroke. Although the 2G-OCP can protect against some cancers [4], previous research has also linked it with increased risks of hypertension, migraines and other side effects [5]. Subsequently, this death could be identified as likely to be related to 2G-OCP use. The other death in the control group was of a woman who had been on the NFPP 2G-OCP for 3 years prior to the start of the study. Immediately after her enrollment in this study, this woman was diagnosed as having kidney and heart complication and spent 2 months in the hospital, during which she

was not taking the 2G-OCP. Although she made it out of the hospital, her complications caused her death which therefore cannot be connected to the 2G-OCP use in this study. Yet, it is important to mention that her prior 3 years on the 2G-OCP might have played a role in the status of her overall health.

Limitations

A major limitation of this study was the short duration of study implementation period (6 months only). This prevented observation of long-term effects of each type of OCP used in this study. Because the first adherence months of OCP have been proven to be a more sensitive period for pill initiators than pill switchers [14], a longer follow up time was necessary to allow the 3G-OCP acceptors to get comfortable with the pill.

Also, the short timing of study implementation did not allow for a 'wash out-period' for those study participants who had previously been using other hormonal contraceptive methods, prior to being enrolled in this study. The fact that some participants might have had a different hormonal balance than their natural balance while other were at natural balance, might have affected the findings especially when the study had measured a variable closely related to hormonal configuration. Alongside, only two unions were used for patient recruitment. Both the unions were in the same sub-district and under the same district. Participants for the 3G-OCP were recruited from one union and participants for the 2G-OCP were from the other union, resulting in small and similar sample groups. Nonetheless, during the analysis, discontinuation rates of OCP types were adjusted for previous contraceptive use history and other socio-demographic characteristics of the participants.

Conclusion

Like previous research suggested, this study also found that the 3G-OCP in compared to the 2G-OCP would be a better method of contraception to administer to women of Bangladesh. Although a study with a larger sample size and longer implementation period might show the results more clearly, this study serves some evidence-based findings in recommending the addition of 3G-OCP in the National Family Planning Programme (NFPP) in Bangladesh.

Efforts should be ensured through quality counselling so that women stay on the pill for the first four to six months, that they will be less likely to discontinue the method. It will also be essential for the NFPP to have targeted strategies for the different strata of women that it caters to. Although Bangladesh can be described as a country that holds culture and tradition very highly, it is also important to note that advancements in health, education and several other sectors are encouraging people and more significantly women to find ways to protect and aid their personal health, sometimes despite cultural norms. For example, targeting those women who have a history of using OCP and who have a low socio-economic and or educational background may help improve the continuation rate of the 3G-OCP, as the study showed that this population is less likely to discontinue this pill. Nonetheless, the study observed three death cases, of which at least one was likely to be associated with the use of 2G-OCP, no inference

could be drawn on the association of the use of OCP type with mortality under this study, for which further studies are recommended.

Abbreviations

OCP: Oral Contraceptive Pill; CI = Confidence Interval; 2G-OCP = Second Generation Oral Contraceptive Pill; 3G-OCP = Third Generation Oral Contraceptive Pill; HR = Hazard Ratio; NFPP = National Family Planning Programme; MWRA = Married Women of Reproductive Age; WHO = World Health Organization; FRA = Field Research Assistant.

Declarations

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Availability of data statement

The detailed dataset is available with Mahbub Elahi Chowdhury (MEC), the Principal Investigator of the main study. A copy of the original data is also stored in the data archive of icddr,b. These data are not publicly available. However, non-identifiable data can be accessible upon request subject to the approval of the Research Administration (RA) Department of icddr,b.

Authors' contributions

MEC conceptualized the main study, substantially contributed to writing and critically reviewing the manuscript. AYW developed the first draft of the paper. SIS analyzed the data and interpreted the findings. MMUA and MNR critically reviewed the manuscript and gave substantial inputs in writing. FAH substantially contributed to writing and critically reviewing the manuscript.

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Ethical approval and consent to participate

Ethical approval to conduct the study was obtained from the Ethics Review Committee of International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b). Informed written consents were obtained from each subject before enrollment in the study.

Consent for publication

Consent for publishing non-identifiable data was obtained from the clients.

Competing interests

We declare that none of the authors has any competing interest.

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Figures

Figure 1

Enrollment and follow-up status of the subjects in the study

Hazard Function

Figure 2

Cumulative hazard function for discontinuation of OCPs due to side-effects by OCP users by type