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Article

Adverse events related to oral hormonal contraceptive use in undergraduate pharmacy students: a cross-sectional study

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We aimed to measure the prevalence of adverse events related to oral hormonal contraceptive (OHC) use and their associated factors in undergraduate pharmacy students. A cross-sectional study was conducted by using an online questionnaire for female students of the Faculty of Pharmaceutical Sciences of the University of São Paulo from July to August 2020. A descriptive analysis of the data was carried out, which was followed by determining the prevalence ratios to identify possible factors associated with adverse events resulting from OHC. A total of 269 valid responses were obtained, among which 50.2% (n = 135) of the students reported using OHC as a contraceptive method and 21.2% (n = 57) affirmed that they had at least one adverse event related to OHC use, which corresponds to 42.2% of those who had used OHC. The most common adverse event was headache (70.2%), and a period of less than one month was the most cited (49.1%). Only migraine comorbidity was associated with the occurrence of adverse events related to OHC. These findings reinforce the high incidence of adverse events among OHC users and the low rate of discontinuation due to these events. There is a need to provide more information on contraceptive methods to users, including its risks and contraindications.

Keywords: Oral hormonal contraceptive. Adverse events. Pharmacovigilance. Students. Pharmacy.

INTRODUCTION

The reproductive age of women includes the period between 15 and 49 years. In this phase, they are physiologically more propitious to the generation of a life compared to other ages, and the possibility of pregnancy declines as they age (OMS, 2011). Recent data point to a drop in the fertility rate from 2.39 children per woman in 2000 to 1.72 children per woman in 2015, which is possibly partially related to family planning (IBGE, 2015). This planning is defined by Brazilian Federal Law 9.236/1996 as "the set of fertility regulation actions that guarantee equal rights of constitution, limitation or increase in the number of offspring by women, men, or couples" (Brasil, 1996).

The use of contraceptive methods is strongly related to family planning and aims to prevent unwanted pregnancies. Currently, there are several contraceptive methods available on the market, such as oral hormonal contraceptives (OHC), intrauterine devices, male and female condoms, and vaginal rings. Among such methods, we can highlight OHC, which is intended for the female audience and is highly effective and easy to use (Bahamondes *et al.*, 2011). According to data from the "World Contraceptive Use 2019," OHC is the method most used by Brazilian women of reproductive age (United Nations, 2019).

OHC may contain a single hormone (isolated method) or a combination of more than one hormone (combined method). Both options are reversible, non-invasive, and usually available at an affordable cost. Depending on the hormones contained, these options may bring other advantages for users, such as the treatment of

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dysmenorrhea, premenstrual tension, acne, and ovarian cysts (Schindler, 2010). However, as with any drug treatment, there is the possibility of experiencing adverse events, defined as "any unwanted medical occurrences in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment" (Edwards, Biriell, 1994).

The use of OHC can bring some already known adverse events, from the most frequent ones, such as irregular bleeding, gastrointestinal, metabolic, and neurological effects, to more rare and serious adverse events, including cardiovascular and thromboembolic events (Vieira, Oliveira, Silva de Sá, 2007). The association between adverse events and contraceptive methods has been the subject of several studies. A systematic review estimated the risk of myocardial infarction and ischemic stroke, comparing non-users and users of combined OHC, in different doses, generations, and types, and report that the risk is 1.6 times higher for users versus non-users (Roach *et al.*, 2015). Moreover, other reviews have found no association between the use of OHC with low dosage and weight gain in users (Gallo *et al.*, 2014).

Although the OHC method is widely used, there is still a lack of knowledge about the possible adverse events resulting from its use. A study of 500 women was conducted in the United States to assess how much they knew about the effectiveness of the available methods and the risks associated with the use of combined OHC. About 2/3 of women overestimated the effectiveness of traditional contraceptive methods (male condoms and combined oral pills), and 56.2% of respondents believed that combined OHCs offer as much risk to a woman's health as a pregnancy. Unfortunately, the female population is still not well informed about the effectiveness and safety of contraceptives (Kakaiya, Lopes, Nelson, 2017).

Although new drugs undergo clinical trials before entering the market, studies have certain limitations and, therefore, some adverse events are only observed in the long term after the start of their commercialization. Pharmacovigilance is responsible for identifying, assessing, and monitoring the occurrence of possible adverse events related to the use of medications in order to ensure that the benefits provided by the medication are greater than the health risks. One problem, however, is that to be effective, pharmacovigilance depends on the spontaneous notification by health professionals of any suspected adverse event/reaction to medication, and it is estimated that only 5 %–10% are reported. The main reasons for this underreporting by the professionals are ignorance about how to make the notification and about the importance of notifying even the already known adverse reactions that appear in the package leaflet, lack of time to register the notification in the middle of other clinical activities, and fear of being implicated in some legal process (Varallo *et al.*, 2014).

In Brazil, there are still few epidemiological studies evaluating the association between OHC and the occurrence of adverse events, with the majority focusing on cardiovascular events (Steckert, Nunes, Alano, 2016; Magalhães, Morato, Santos, 2017; Siqueira, Sato, Santiago, 2017). In addition, the number of studies including female undergraduate students as a target audience is even lower, and most aim to evaluate the profile of the use of contraceptive methods and their knowledge about them (Alves, Lopes, 2008; Almeida *et al.*, 2015; Silva, Neto, 2017). However, few studies have focused on the evaluation of adverse events caused by the use of OHC in this population (Steckert, Nunes, Alano, 2016; Cabral *et al.*, 2018; Siqueira, Sato, Santiago, 2017). In view of the need for more data on the subject, the aim of this study was to measure the prevalence of adverse events related to the use of OHC and their associated factors in undergraduate pharmacy students.

MATERIAL AND METHODS

Study design and location

A cross-sectional study was conducted with female undergraduate students from the Faculty of Pharmaceutical Sciences of the University of São Paulo (FCF-USP) from July to August 2020. FCF-USP has an annual admission of 150 students, and during the study period, there were 586 women regularly enrolled in the program, distributed between full and night periods. The study was approved by the Human Research Ethics Committee of the Faculty (CAAE number: 30451720.0.0000.0067).

Population

All female students of reproductive age who were regularly enrolled in the pharmacy program at USP were invited to participate. All those who volunteered to participate signed the free and informed consent form electronically. The sample size was calculated considering a 95% confidence level (absolute precision of 5%), design of 1.0, population of 586 female students, and prevalence of 50% for the use of OHC – value estimated due to the absence of previous prevalence evidence for the public studied (Arya, Antonisamy, Kumar, 2012). Thus, the sample size was 233 pharmacy students.

Data collection

The data were collected through the application of an online questionnaire designed and hosted on the "Google Forms" platform, which was made available to students via the official undergraduate e-mail, obtained through contact with the undergraduate service. The disclosure was also carried out on the social platforms "Facebook" and "WhatsApp" to increase the reach and, consequently, the number of responses.

The online questionnaire included questions about age; year of admission to the pharmacy program and period of study (full or night); regular alcohol consumption (3 to 4 times a week); smoking (consumption of more than 100 cigarettes in lifetime and at least one cigarette in the last month); regular physical activity (150 minutes a week of light or moderate intensity, or at least 75 minutes a week of vigorous intensity); comorbidities; use of OHC in the last 30 days, occurrence of adverse events associated with OHC, who indicated the OHC; type of OHC; time of use; reason for starting use and reason for interruption (if applicable).

Data analysis

All collected data were organized and categorized in a Microsoft Excel® spreadsheet. First, descriptive statistics were performed to characterize the frequencies of variables related to the use of OHC and the occurrence of adverse events in the sample. Next, the prevalence ratios (PR) of the outcomes for independent variables were calculated using Poisson regression with 95% confidence intervals (95% CI). All independent variables were included in the adjusted multivariate analyses. The Wald test was used to assess the significance of variables with multiple categories. Statistical significance was set at $p < 0.05$. The analyses were conducted using Stata 14.2 software (Stata Corp., College Station, Texas, USA). In addition, OHCs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization (WHO, 2019).

RESULTS

A total of 280 responses were obtained, of which 11 were invalidated for not meeting the eligibility criteria: two responses by male students; and nine due to data inconsistencies, where three participants answered "no" for the use of contraceptive method followed by "yes" for information that the chosen method was OHC; two students did not indicate which OHC was used, and another four responded with more than one OHC brand, which has different classifications and/or different ATC codes, and it was not possible to identify which one was used in the last 30 days. Therefore, 269 responses were considered valid, corresponding to 45.9% of the female students regularly enrolled in the course.

The characteristics of female students are described in Table I. Most participants were between 20 and 24 years old (60.0%). The most mentioned years of entry into the course were 2015 and 2016, with a frequency of approximately 17.0% for both. Most students who attended the course at night (61.7%), did not engage in regular physical activity (55.0%), did not consume regular alcohol (90.3%), and declared themselves as non-smokers (94.8%). Migraine was the most common comorbidity among the sample (20.8%).

Among the respondents, 50.2% (n = 135) reported having used OHC as a contraceptive method in the 30 days prior to the survey, and 21.2% (n = 57) indicated having had an adverse event associated with the use of this method, which corresponds to 42.2% of those who used OHC (Table I). The most commonly used active ingredients were drospirenone and gestodene, both in

combination with ethinyl estradiol, as shown in Table II. In addition, 85.2% (n = 115) reported using a single-phase combined OHC.

Regarding the reasons for using the OHC (Table III), the most mentioned was "avoiding an unplanned pregnancy," with a frequency of 77.0% (n = 104), followed by "treatment of hormonal disorders" (39.3%). Most reported using this type of contraceptive method for more than 5 years, totaling 38.0% (n = 51). For 95.6% (n = 129) of OHC users, the indication for use was made by the physician. However, two users reported that OHC was indicated by a pharmacist.

Among the users who reported an adverse event related to the use of the OHC (Table I), most (44.2%) were aged between 20 and 24 years, did not perform regular physical activity (45.7%), did not consume regular alcohol (42.7%), and declared themselves as non-smokers (42.0%). Among those who reported having comorbidities, migraine was the most cited (62.9%). Table IV describes the profile of adverse events related to the use of oral hormonal contraceptives among pharmacy students. The most cited adverse event was headache (70.2%), and time less than one month was the most cited as the duration of the event (49.1%). Most students consulted a physician due to the occurrence of an adverse event (52.6%), but they did not discontinue the method due to the event (75.4%). Those who discontinued did so, mainly on their own (64.3%). Only the presence of migraine comorbidity was associated with the occurrence of adverse events with the use of OHC in the unadjusted analyses (PR = 1.80 [95% CI 1.05–3.06]; p = 0.036) and adjusted (PR = 2.14 [95% CI 1.06–4.35); p = 0.035, as can be seen in Table V.

TABLE I - Characteristics of pharmacy students (n = 269)

Variables	Total		Use of OHC		Adverse event*	
	n	%	n	%	n	%
Age range						
<20 years	34	12.6	17	50.0	7	41.2
20–24 years	161	60.0	86	53.4	38	44.2
25–29 years	60	22.3	28	46.7	10	35.7
>30 years	14	5.2	4	28.6	2	50.0
Year of entry						
2013 or less	32	11.9	14	43.8	6	42.9
2014	26	9.7	11	42.3	4	36.4
2015	46	17.1	21	45.7	9	42.9
2016	47	17.5	26	55.3	11	42.3
2017	35	13.0	15	42.9	5	33.3
2018	33	12.3	17	51.5	8	47.1
2019	26	9.7	17	65.4	10	58.8
2020	24	8.9	14	58.3	4	28.6
Course Period						
Full time	103	38.3	49	47.6	19	38.8
Night	166	61.7	86	51.8	38	44.2

TABLE I - Characteristics of pharmacy students (n = 269)

Variables	Total		Use of OHC		Adverse event*	
Regular physical activity						
No	148	55.0	70	47.3	32	45.7
Yes	121	45.0	65	53.7	25	38.5
Regular alcohol consumption						
No	243	90.3	124	51.0	53	42.7
Yes	26	9.7	11	42.3	4	36.4
Smoker						
No	255	94.8	131	51.4	55	42.0
Yes	14	5.2	4	28.6	2	50.0
Health conditions**						
Arterial hypertension	2	0.7	1	50.0	1	100.0
Hypercholesterolemia	27	10.0	18	66.7	7	38.9
Overweight	40	14.9	20	50.0	8	40.0
Obesity	10	3.7	8	80.0	3	37.5
Migraine	56	20.8	35	62.5	22	62.9
Total	269	100	135	50.2	57	42.2

* Among the participants who reported using OHC.
** Answers were not mutually exclusive; percentages do not add up to 100%.

TABLE II - Use of oral hormonal contraceptives by pharmacy students according to the ATC classification (n = 135)

5th level of ATC *	Active ingredient(s)	n	%
G03AA07	Levonorgestrel + Ethinylestradiol	10	7.4
G03AA09	Desogestrel + Ethinylestradiol	4	3.0
G03AA10	Gestodene + Ethinylestradiol	19	14.1
G03AA12	Drospirenone + Ethinylestradiol	53	39.3
G03AA14	Nomegestrol + Estradiol	1	0.7
G03AA15	Chlormadinone + Ethinylestradiol	5	3.7
G03AB03	Levonorgestrel + Ethinylestradiol	2	1.5
G03AB05	Desogestrel + Ethinylestradiol	3	2.2
G03AB08	Dienogeste + Estradiol	11	8.2
G03AC09	Desogestrel	3	2.2
G03DB08	Dienogeste	1	0.7
G03HB01	Cyproterone + Ethinylestradiol	23	17.0

* The difference in codes for the same combination of active ingredients is due to the fact that some are single-phase and others are multi-phase.

TABLE III - Profile of the use of oral hormonal contraceptives among pharmacy students (n = 135)

Variables	Use of OHC	
	n	%
Type of OHC		
Mini pill	4	3.0
Single-phase combined	115	85.2
Biphasic combined	4	3.0
Combined three-phase	1	0.7
Combined four-phase	11	8.1
Reasons for use *		
Avoid an unplanned pregnancy	104	77.0
Treatment of hormonal disorders	53	39.3
Improvement of symptoms of premenstrual tension	51	37.8
Reduction of menstrual flow	52	38.5
Acne	9	6.7
Endometriosis	4	3.0
Regulation of the menstrual cycle	3	2.2
Cyst treatment	3	2.2
OHC usage time		
<1 year	14	10.4
1 year	23	17.2
2 years	25	18.7
3 years	10	7.5
4 years	11	8.2
>5 years	51	38.0
OHC indication*		
Physician	129	95.6
Friends/family	9	6.7
Internet	1	0.7
Pharmacist	2	1.5

* Answers were not mutually exclusive; percentages do not add up to 100%.

TABLE IV - Profile of adverse events related to the use of oral hormonal contraceptives among pharmacy students (n = 57)

Variables	Adverse Event	
	n	%
Adverse event *		
Headache	40	70.2
Weight gain	17	29.8
Nausea	25	43.9
Vomiting	4	7.0
Increased blood pressure	0	0.0
Thromboembolic event	0	0.0
Abnormal vaginal bleeding	8	14.0
Decreased libido	4	7.0
Mood swings	3	5.3
Others	7	12.3
Adverse event duration		
<1 month	28	49.1
1 month	9	15.8
> 1 month	20	35.1
Consultation with the health professional about the adverse event		
No	27	47.4
Yes	30	52.6
OHC suspension due to adverse event		
No	43	75.4
Yes	14	24.6
Who guided the suspension of the OHC **		
Physician	5	35.7
Own account	9	64.3

* Answers were not mutually exclusive; percentages do not add up to 100%.
** Among the participants who discontinued the use of OHC due to an adverse event.

TABLE V - Unadjusted and adjusted prevalence ratios (PR) with 95% confidence intervals (95% CI) for the occurrence of adverse events among pharmacy students who used oral hormonal contraceptives (n = 135)

Variables	Adverse events associated with the use of OCH			
	Unadjusted PR (95% CI)	P value	Adjusted PR (95% CI)	P value
Age range		0.934		0.815
<20 years	1.00		1.00	
20–24 years	1.07 (0.48–2.40)		1.33 (0.41–4.31)	
25–29 years	0.87 (0.33–2.28)		0.85 (0.16–4.64)	
>30 years	1.21 (0.25–5.85)		0.67 (0.05–8.27)	
Year of entry		0.949		0.944
2013 or less	1.00		1.00	
2014	0.85 (0.24–3.01)		0.77 (0.16–3.61)	
2015	1.00 (0.36–2.81)		0.58 (0.11–2.98)	
2016	0.99 (0.37–2.67)		0.71 (0.17–3.01)	
2017	0.78 (0.24–2.55)		0.37 (0.06–2.14)	
2018	1.10 (0.38–3.16)		0.57 (0.11–3.10)	
2019	1.37 (0.50–3.78)		0.78 (0.15–4.12)	
2020	0.67 (0.19–2.36)		0.43 (0.06–3.10)	
Course Period		0.640		0.356
Full time	1.00		1.00	
Night	1.14 (0.66–1.98)		1.42 (0.67–3.01)	
Regular physical activity		0.516		0.242
No	1.00		1.00	
Yes	0.84 (0.50–1.42)		0.65 (0.32–1.34)	
Regular alcohol consumption		0.750		0.692
No	1.00		1.00	
Yes	0.85 (0.31–2.35)		1.30 (0.35–4.79)	
Smoker		0.813		0.344
No	1.00		1.00	
Yes	1.19 (0.29–4.88)		2.25 (0.42–12.15)	
Health conditions*				
Arterial hypertension	2.39 (0.33–17.29)	0.448	3.27 (0.11–98.94)	0.496
Hypercholesterolemia	0.91 (0.41–2.01)	0.813	0.85 (0.28–2.64)	0.784
Overweight	0.94 (0.44–1.98)	0.867	0.79 (0.28–2.20)	0.651
Obesity	0.88 (0.28–2.82)	0.829	0.42 (0.08–2.19)	0.305

TABLE V - Unadjusted and adjusted prevalence ratios (PR) with 95% confidence intervals (95% CI) for the occurrence of adverse events among pharmacy students who used oral hormonal contraceptives (n = 135)

Variables	Adverse events associated with the use of OCH			
	Unadjusted PR (95% CI)	P value	Adjusted PR (95% CI)	P value
Migraine	**1.80 (1.05–3.06)**	**0.036**	**2.14 (1.06–4.35)**	**0.035**
Type of OHC		0.713		0.883
Mini pill	1.00		1.00	
Single-phase combined	0.80 (0.19–3.30)		0.57 (0.09–3.77)	
Biphasic combined	1.00 (0.14–7.10)		1.08 (0.10–11.45)	
Combined three-phase	-**		-**	
Combined four-phase	1.27 (0.26–6.13)		0.81 (0.11–6.21)	
Reasons for use*				
Avoid an unplanned pregnancy	1.01 (0.54–1.87)	0.978	1.09 (0.46–2.61)	0.841
Treatment of hormonal disorders	0.90 (0.53–1.55)	0.708	1.16 (0.54–2.52)	0.699
Improvement of symptoms of premenstrual tension	0.96 (0.56–1.65)	0.884	1.10 (0.52–2.35)	0.806
Reduction of menstrual flow	0.93 (0.54–1.59)	0.794	1.07 (0.53–2.19)	0.845
Acne	1.35 (0.54–3.37)	0.542	1.84 (0.63–5.36)	0.263
Endometriosis	1.82 (0.57–5.82)	0.355	3.80 (0.60–24.23)	0.158
Regulation of the menstrual cycle	0.79 (0.11–5.68)	0.804	0.82 (0.07–9.79)	0.876
Cyst treatment	2.44 (0.76–7.82)	0.185	3.63 (0.67–19.73)	0.135
OHC usage time		0.591		0.372
<1 year	1.00		1.00	
1 year	0.74 (0.31–1.80)		0.63 (0.21–1.97)	
2 years	0.75 (0.31–1.77)		1.04 (0.37–2.92)	
3 years	0.47 (0.13–1.72)		0.51 (0.11–2.35)	
4 years	0.71 (0.24–2.11)		0.80 (0.21–3.06)	
>5 years	0.49 (0.22–1.10)		0.38 (0.13–1.12)	
OHC indication*				
Physician	0.84 (0.26–2.68)	0.771	1.52 (0.12–18.92)	0.745
Friends/family	0.51 (0.12–2.09)	0.296	0.93 (0.18–4.92)	0.930
Internet	-**		-**	
Pharmacist	2.42 (0.59–9.91)	0.281	6.73 (0.26–172.67)	0.249

* The absence of variables was considered as a reference because the categories were not mutually exclusive.
** Excluded from the analysis due to the collinearity resulting from the number of respondents (n = 1).

DISCUSSION

This study showed a high use of OHC among undergraduate pharmacy students, since more than half of the respondents reported having used it in the 30 days prior to the study, which is consistent with other studies conducted with university students (Bryden, Fletcher, 2001; Coetzee, Ngunyulu, 2015; Steckert, Nunes, Alano, 2016; do Nascimento Chofakian *et al.*, 2019). Most students reported using single-phase combined OHC, which is composed of more than one hormone (progestogen and estrogen) in constant amounts throughout the cycle. Compared to multiphasic OHC (i.e., biphasic, triphasic, or quadriphasic), monophasic can be preferentially chosen, as the former requires more rigorous adherence regarding the need to follow a specific sequence in taking the pills, increasing the possibility of misuse and reduction effectiveness (Dragoman, 2014).

In this study, the most frequent hormonal composition was drospirenone plus ethinyl estradiol. Drospirenone is a progestin of synthetic origin that has, among its properties, a mild antiminellocorticoid profile, contributing to minimize the occurrence of fluid retention, an adverse event associated with certain OHC (Oelkers, 2004). Ethinyl estradiol, in turn, belongs to the class of estrogens, and it is the most common category found in OHCs in the last decades (Burkman, Bell, Serfaty, 2011). This combination can be found in Brazil in numerous dosage forms and strengths, produced by different producers, as brand name, generic, or similar medications.

Several reasons were listed for the choice of the OHC, the prevention of unplanned pregnancy being the most mentioned by the users, as observed by the data presented here and by a study conducted at a university in the southern region of Brazil (Steckert, Nunes, Alano, 2016). It is important that the OHC is indicated by a qualified professional, especially because of the need for a medical prescription to obtain the OHC in Brazil (Moura, Silva, Galvão, 2007; Borges *et al.*, 2016). Although most users reported a medical indication for the use of the medication, other sources of indication were also mentioned, such as friends/family, the internet, and the pharmacist. It is possible that the students who received an indication from these sources did not consult a physician, which may represent a risk, as the general condition of the patient was possibly not assessed before the method was started. It is worth mentioning that although the pharmacist has extensive knowledge about contraceptive methods, they are not able to prescribe medications that require a medical prescription in Brazil, with a few exceptions, according to Resolution No. 586/2013 of the Federal Pharmacy Council (CFF, 2013).

The assessment of a woman's general health status is extremely important to check if there are elements, such as comorbidities and personal and family history, which may constitute a contraindication to the use of the OHC. Among comorbidities, migraine was the most common among users, similar to other findings in the literature (Steckert, Nunes, Alano, 2016). Migraine is known to be a risk factor for the development of stroke and other vascular events, and the association between migraine with aura and the increased risk of ischemic stroke is better established than the association between this adverse event and migraine without aura, for which there are still controversies (Nappi *et al.*, 2013; Sacco *et al.*, 2017). Thus, the use of OHC is contraindicated in women with migraine and aura (WHO, 2015).

In this study, a significant association was noted between the presence of migraine and the occurrence of adverse events associated with OHC, although no respondent indicated stroke as an experienced event. No data were found in the literature to indicate that women with a history of migraine may be more predisposed to the development of adverse events with the use of OHC, compared to women without the condition, except stroke. However, there is a clear need for a cautious and individual risk-benefit assessment for these women before making the decision to use OHC, considering the possibility of using contraceptive methods other than hormonal ones (Nappi *et al.*, 2013).

The findings showed that 42.2% of users of OHC experienced adverse events that they considered to be associated with this method, which suggests a high prevalence of undesirable events. Such data corroborate a study conducted with Brazilian women, in which it was observed that 68.75% of users of OHC reported having already experienced some adverse events (Siqueira, Sato,

Santiago, 2017). In the present study, the most reported adverse event by users of the OHC was headache, as seen in previous studies (Loder, Buse, Golub, 2005; Bahamondes *et al*., 2011; Siqueira, Sato, Santiago, 2017). Evidence suggests that there is variation in the prevalence of this event over the period of use of the method, with a decrease from 6.7% among women in the first cycle of OHC, to 3.1% after twenty-four months of use (Loder, Buse, Golub, 2005). Regarding the predisposition to this event, women appear to be at greater risk of worsening of pre-existing headache or even new-onset headache attributable to OHC use if there is a strong family or personal history of troublesome headache, particularly migraine (Loder, Buse, Golub, 2005).

The second most reported adverse event was nausea, which is commonly associated with this method (Sulak *et al*., 2000; Dragoman, 2014). Similar to headache, there is evidence that this event may have its occurrence altered according to the time use of OHC. A study pointed out that there was an increase in the prevalence of nausea among new users, with 54% of these women experiencing nausea or vomiting in the first cycle, while only 32% of older users manifested such symptoms (Sulak *et al*., 2000). Weight gain was also cited as an adverse event experienced, as was the case in other studies conducted using this method (Rosenberg, Waugh, 1998; Steckert, Nunes, Alano, 2016). However, to date, there is no evidence of a causal relationship between OHC and the event, as pointed out in the literature data (Gallo *et al*., 2014).

Regarding the assessment of adverse events, many data come from studies conducted with combined OHCs, such as those mentioned above. However, it is known that for reversible contraceptive methods, many changes have been made to increase the benefits and reduce the risks, such as reducing the concentration of estrogens and changing the progestogens used (Moreau *et al*., 2007; Sacco *et al*., 2017). For OHC containing only progestogens and mini pills, data on adverse events are less robust, but there is evidence that this method does not increase the risk of cardiovascular events and may cause less headache and nausea in women with a history of such symptoms using the combined method (de Melo, 2010).

Most women who reported having experienced an adverse event with the use of OHC reported that the event lasted less than a month, that she consulted the physician because of the event and that she did not discontinue the use of the medication. Evidence suggests that adverse events related to OHC, especially the most common ones, are self-limiting and tend to reduce with time of use (Loder, Buse, Golub, 2005; Barr, 2010; Dragoman, 2014). Among the students who discontinued OHC due to an adverse event, most did it on their own, which may reflect the users' fear regarding the possible risks linked to the use of OHC. These data are in line with a study that included women who were initiating or altering the OHC, which identified that the occurrence of adverse events was the main reason for discontinuing the use of the method, with OHC users reporting "concern about the use of hormones" (Rosenberg, Waugh, 1998).

The following is understood as a limitation of this study: non-detailed questioning about the history of headache, since it was questioned only about the personal history of migraine, and not the personal and family history of other types of headaches. In addition, there was no question as to whether migraine is accompanied by an aura or not, and no specific analysis was performed to evaluate whether there is an association between migraine comorbidity and the report of headache as an adverse event resulting from the use of OHC. However, in view of the high reporting of both, it is believed that it is possible to have a relationship, and part of the headache events may be associated with a worsening of the symptoms of those users with a previous report of migraine.

Other limitations are related to the fact that the information was obtained through self-reporting, which makes possible the existence of memory bias. The possibility of an imprecise calculation of the sample size has been performed, since the value of 50% for the prevalence of use of OHC was considered; conducting the study in a single pharmacy faculty, which makes it difficult to extrapolate the data to the general population; and the application of a survey in the midst of the COVID-19 pandemic, which changed the routine of several Brazilian women and may have impacted the use of contraceptive methods due to social isolation.

CONCLUSION

The results reinforce the high incidence of adverse events among users of OHC and the low rate of discontinuation due to them, which may be an indication that these are tolerable and reduce with time of use. In addition, the most frequently reported are frequent and indicated in the medication package inserts. It is worth noting that even in the presence of comorbidities relevant to OHC, such as migraine, women continue to use the method, which may have been a joint decision between patient and physician after risk-benefit assessment, or it may be a lack of knowledge of users about the risks attributed to it.

It is evident that these users need to be provided with more information about the OHC method, including its risks and contraindications, so that conscious and safe decisions are made about their own health, and in the future, as pharmacists they can share updated and reliable information on the topic. Moreover, it is important to encourage the reporting of events to pharmacy industries, to create this habit among them as patients and future health professionals, in order to contribute to the guarantee of product safety..

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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CONTRIBUTORS

Tozetto HCM and Aguiar PM participated in the design of the project, analysis, interpretation of data, writing, and critical review of intellectual content. Tiguman GMB participated in the analysis, interpretation of data, and critical review of manuscript. Nicoletti MA participated in the design of the project, writing, and critical review of the manuscript.

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