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COMPARISON OF ADVERSE DRUG REACTIONS OF SECOND- AND THIRD-GENERATION ORAL CONTRACEPTIVES

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ABSTRACT

Objective: Oral contraceptives are the second-most widely used contraceptives in Indonesia; however, a high percentage rate of withdrawal is seen owing to adverse drug reactions (ADRs). Only a small proportion of users have been provided information about other oral contraceptives such as newer generation progestin as an alternative option to minimize ADR. This study aimed to compare the prevalence of ADR between combined oral contraceptives containing levonorgestrel (LNG) (second generation) and desogestrel (DSG) (third generation), which was expected to have less side effects.

Methods: The study has a cross-sectional comparative design with random sampling from users in six villages in Depok City, Indonesia. Data were collected through interviews. The sample includes 60 users of LNG and 40 users of DSG.

Results: ADR complaints include intermenstrual bleeding (16.7% vs. 5%), headache (16.7% vs. 5%), nausea/vomiting (25% vs. 0%), breast tenderness (13.3% vs. 0%), impaired sexual intercourse (23.3% vs. 7.5%), weight gain (35% vs. 22.5%), acne (3.3% vs. 7.5%), and face spots/chloasma (28.3% vs. 5%). The LNG group showed significantly higher impaired sexual intercourse (odds ratio (OR): 3.75, 95% confidence interval (CI): 1.003-14.050, p=0.039) and chloasma (OR 7.51, 95% CI: 1.629-34.647, p=0.004).

Conclusion: Users' low knowledge of ADR and how to treat it could be a reason for drug withdrawal. Pharmacies must make efforts to provide counseling in this regard.

Keywords: Oral contraceptive, Levonorgestrel, Desogestrel, Adverse drug reaction.

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INTRODUCTION

Hormonal contraception poses a risk of adverse drug reactions (ADRs); this may result in reduced patient compliance and, in turn, reduced effectiveness of contraception [1]. Combined oral contraceptives are the second most frequently used hormonal contraception method (13.6%) in Indonesia after injections (32%) [2]. Oral contraception methods are short-term in nature. Their effectiveness strongly depends on patient compliance and the continuity of the acceptor [3]. However, evaluations have shown that withdrawal from the use of oral contraceptives due owing to ADR is quite high (13.2% in the 1st year and 14.9% in the 5th year). ADR is the second most frequent cause of contraception withdrawal after the desire to have another child [2].

Studies have shown that the use of second-generation combined oral contraceptives has a higher withdrawal rate than that of third-generation ones because of their side effect such as menstruation cycle disturbance [4]. Second-generation combined oral contraceptives available in Indonesia include pills containing progestin levonorgestrel (LNG), and third-generation contraceptives include pills containing drospirenone, gestodene, and desogestrel (DSG). Other studies have shown that third-generation combined oral contraceptive users (24%) tend to complain more about headaches compared to second-generation users (5.8%) [5]. ADR manifestations are influenced by many factors including race, dosage, duration of drug use, medical history, and patient lifestyle [1]. The differences in the effects of DSG and LNG may be caused by differences in substance affinity with hormone receptors and different androgenic effects [6]. DSG is a third-generation combined oral contraceptive that has a smaller androgenic effect compared to LNG. Therefore, ADR complaints caused by androgenic effects such as acne and lipid level increase are expected to be smaller with DSG than with LNG [7].

Relatively, few users are informed of ADR and steps to take when ADR occurs (27.8% and 23.9%, respectively). In most cases (68.2%), Indonesia users of oral contraceptives obtain them from private sector providers such as midwives, pharmacies, and clinics; however, they do not have adequate information on ADR. This lack of knowledge influences their decision to prematurely withdraw from pills [2]. Data from the national population and family planning commission shows that Depok city has a high number of oral contraceptive users. Thus, the researcher chose Sukmajaya, a location in Depok city, as the research location. This research compares the use of ethinyl estradiol (EE)-LNG and (EE-DSG), difference in ADR between both groups, and contribution of contraceptive use to ADR. The study results will hopefully increase contraception services and support preventative and treatment programs for contraceptive-related ADR. In addition, the study is expected to be useful for the development of tracking methods of ADR incidence, especially the contraceptive-related ones.

METHODS

This study used an observational cross-sectional approach. It was conducted in all subdistricts of Sukmajaya, Depok city, namely, Mekar jaya, Sukmajaya, Abadi Jaya, Bakti Jaya, Cisalak, and Tirta Jaya. The necessary permission was obtained from the district and sub district officials. Data were obtained with the help of family planning field officers in each sub district. A random sample was obtained from these records. The study purpose was explained to these subjects, and informed consent was obtained from them for participating in the study. The subjects were divided into two groups: EE-LNG and EE-DSG oral contraceptive users. Subjects in the EE-LNG group used a contraceptive containing 30 μg of EE and 150 μg of LNG. Subjects in the EE-DSG group used a contraceptive containing 30 μg of EE and 150 μg

of DSG. Up to 10 subjects/group/sub district were randomly selected from each population group. However, each district generally had <10 EE-DSG users, so total sampling was performed to satisfy the minimum sample size (39 people). A total sample of 100 subjects participated in this study, with 60 and 40 subjects in the EE-LNG and EE-DSG groups, respectively.

The ADRs evaluated in this study include intermenstrual bleeding, headaches, breast tenderness, nausea/vomiting, weight gain, impaired sexual intercourse, and acne. The researcher classified headache, breast tenderness, nausea/vomiting, impaired sexual intercourse, and acne as ADR if there was an increase in their frequency after the use of contraceptives. Weight gain was reported as a subjective assumption by users because of the lack of monitoring data of users before they started using contraceptives. Data are obtained through an by interview base on using a questionnaire written by the author. The questionnaire was tested for validity and reliability by 30 lay women who were not part of the study sample. The questionnaire consisted of 41 questions, of which 29 were related to ADR complaints. The validity tests showed that the first five questions related to ADR had r<0.361. This error is related to a structural error, and the author altered the diction used so that it can be interpreted easily; furthermore, the author altered the order of the answers to avoid errors in the codes given by the subjects. Ultimately, all questions were valid with Cronbach's α>0.7. Univariate and bivariate data analysis were conducted using a statistical software. The bivariate analysis included Chi-square and Fisher exact tests, odds ratio (OR), and correlation analysis. The confidence interval (CI) used was 95% with a test power of 80%.

RESULTS

The data from contraceptive users in Sukmajaya indicated that oral contraceptives were the second most frequently used contraception method (29.38%) after injection method (33.27%) (Table 1). Both groups showed similar sociodemographic characteristics. Most respondent were ≥35 years old (76%), unemployed (91%), married for 5-20 years (55%), had <3 children (70%), and educated until high school/similar level (74%). In terms of body mass index (BMI), respondents were mostly normal (51%) or overweight (41%). In terms of duration of contraceptive use, 83% of respondents used oral contraceptives for >6 months; 12%, for 3-6 months; and 5%, for <3 months. Respondents mainly chose oral contraceptives because of their practicality (26%), safety (13%), and ease of returning to a fertile state (3%). Five subjects from the EE-LNG group claimed economic reasons. Some subjects preferred it for regular menstruation (20%) because most of them previously used a 3-month depot medroxyprogesterone acetate (DMPA) injection that may cause amenorrhea [1]. Suggestions from midwives/relatives were claimed as reasons by 20% of respondents.

Both groups claimed that they obtained their oral contraceptives from a pharmacy (78%) or midwive private practices (18%). Two subjects in the EE-LNG group obtained oral contraceptives from the community health center and 2 others, from a doctor's practice. Of all respondents, 31% said that they did not receive any information when purchasing oral contraceptives; the remaining 69% who received information said that they were only told of how to use the contraceptives. Only 6 subjects in the EE-LNG group received information on the possibility of ADR. Furthermore, 83% of EE-LNG respondents and all EE-DSG respondents could correctly explain how to use oral contraceptives. Moreover, 43% of all respondents claimed to not know any side effects of the oral contraceptive they were currently using, whereas most respondents could name at least one side effect. Respondents mainly complained of side effects such as headache (32%), nausea (26%), and face spots (24%).

Of all respondents, 90% had used contraception methods other than combined oral contraception. The 3-month DMPA injection method was used most frequently before oral contraceptives (37.5%). Respondents' reasons for switching methods included side effects (42%) and the desire to have another child (2.5%). In the EE-DSG group, 90% of respondents did not have any restrictions for use (Category 1). In the EE-LNG group, 15% of respondents theoretically had a higher risk than benefit (Category 3), mainly because of hyperlipidemia or hypertension.

Both groups complained of 6 out of 8 ADRs that were analyzed. The EE-DSG group did not report nausea and breast tenderness. In both groups, only impaired sexual intercourse and face spots showed statistically significant (p<0.05) results. Table 2 summarizes the respondents' proportions of ADR.

DISCUSSION

The respondent profiles obtained in this study are in accordance with those of oral contraceptive users in Indonesia. A survey of the national population and family planning federation commission in 2012 showed that oral contraceptive users in Indonesia are commonly from rural areas and ≥35 years old (53.7%) and that they obtain their contraceptives from a pharmacy (39.4%). Only 0.2% of users obtained their oral contraceptives from a community health center. Most users had more than three children [2].

Of all EE-DSG respondents, 27.5% claimed to choose the contraceptive because of advice from their midwife or relative, whereas most EE-LNG respondents claimed these reasons. This shows that advice from midwives and relatives plays an important role in respondents' decisions to choose contraception methods. Most users obtained oral contraceptives from the pharmacy (78%), whereas only a small proportion (18%) obtained them from a midwife. EE-DSG pills were more expensive (Rp. 56,815) compared to EE-LNG ones (Rp. 8,000-10,000) (MIMS, 2015). None of the EE-DSG respondents chose cost as a reason for their choice, whereas 8.3% of EE-LNG respondents did. This is why there were lesser EE-DSG respondents in Sukmajaya than EE-LNG ones. Of all EE-LNG respondents, 50 (83%) could correctly explain how to use the contraceptive another 7 said that it should be taken in the morning, although it is suggested to take it at night [8]. Finally,

Table 1: Respondents' eligibility category for using combined oral contraceptives

Category	Quantity (%)	Annotation
EE-LVG group		
1 (no restrictions for use)	45 (75)	
2 (benefit is higher than risk)	5 (8.3)	4 subjects were breastfeeding (6.7%), 1 subject was obese (1.7%)
3 (theoretically, risk is higher than benefit)	10 (15)	2 subjects had controlled hypertension (3.3%), 4 subjects had hyperlipidemia (6.7%), 1 subject had controlled hypertension and hyperlipidemia (1.7%), 1 subject was obese and had hyperlipidemia (1.7%), 1 subject was obese and had controlled hypertension (1.7%)
EE-DSG group		
1 (no restrictions in use)	36 (90)	
2 (benefit is higher than risk)	1 (2.5)	Obesity
3 (theoretically, risk is higher than benefit)	3 (7.5)	Controlled hypertension

LNG: Levonorgestrel, EE: Ethinyl estradiol, DSG: Desogestrel

Table 2: Respondents' proportion of ADR with combined oral contraceptives in EE-LNG and EE-DSG groups, Sukmajaya District, Depok city, 2015

ADR	n (%)		OR (95% CI) (LNG/DSG)	Significance
	EE-LNG	EE-DSG		
Menstruation disturbance	10 (16.7)	2 (5)	3.8 (0.786-18.369)	0.117
Headache	10 (16.7)	2 (5)	3.8 (0.786-18.369)	0.117
Breast tenderness	8 (13.3)	0	-	-
Nausea/vomiting	15 (25)	0	-	-
Weight gain	21 (35)	9 (22.5)	1.855 (0.745-4.618)	0.181
Impaired sexual intercourse	14 (23.3)	3 (7.5)	3.754 (1.003-14.050)	0.039
Acne	2 (3.3)	3 (7.5)	0.425 (0.068-2.667)	0.386
Face spots	17 (28.3)	2 (5)	7.512 (1.629-34.647)	0.004

LNG: Levonorgestrel, EE: Ethinyl estradiol, DSG: Desogestrel, ADR: Adverse drug reaction, OR: Odds ratio, CI: Confidence interval

10 said that it need not be taken when menstruating. This is considered imprecise understanding because the contraceptives should be taken even when menstruating [8]. During menstruation, users commonly take a placebo pill, but they should continue to consume their pills during menstruation every month [9]. All EE-DSG respondents could correctly explain how to use the oral contraceptives. They noted that the pills were to be taken daily at night. Furthermore, they knew that if a pill was not taken on time, it should be taken as soon as possible; alternatively, two pills should be taken the next day [10]. This is owing to the information given to them by health caregivers. Information on ADR was given to only 10% of EE-LNG respondents and none of the EE-DSG respondents. This shows that information on contraception is not focused on risks. As with other hormonal contraception methods, oral contraceptives pose ADR risks that users must be aware of [3]. If adequate information about ADR and how to treat it is not given to users, it may lead to drug withdrawal or noncompliance [2].

Intermenstrual bleeding

Intermenstrual bleeding usually occurs in respondents who are ≥35 years, have at most two children, and have normal BMI. This complaint is usually found in respondents who have used oral contraceptives for >6 months. Intermenstrual bleeding in combined oral contraceptive users may be influenced by the EE dosage; progestin preparate used EE:progestin ratio, user compliance, and history of cervical or pelvic diseases [11]. If users take the oral contraceptive regularly, interim bleeding usually only occurs in the first 3 months of use. However, if users are not compliant in taking the pills, they may experience intermenstrual bleeding after 3 months [12].

Of all respondents, 16.7% (10) in the EE-LNG group and 5% (2) in the EE-DSG group complained of intermenstrual bleeding. Theoretically, when used correctly, oral contraceptives do not cause intermenstrual bleeding. However, hormone fluctuations caused by user noncompliance may cause intermenstrual bleeding [13]. Smoking may also cause menstrual disturbances as it induces ethinyl estradiol metabolism [3]. None of the patients admitted to smoking; however, the bias of social judgement in admitting to smoking cannot be ignored. Oral contraceptives may also reduce the intensity of menstrual bleeding as well as the incidence and severity of dysmenorrhea. This is because EE influences the stability of the endometrial lining [14]. Data show that a decrease in menstrual bleeding intensity and/or duration occurs in 33.3% of EE-LNG respondents and 22.5% of EE-DSG respondents.

There are no statistically significant differences (p=0.117) in intermenstrual bleeding between both groups. The incidence of intermenstrual bleeding is higher in the EE-LNG group than in the EE-DSG group. These findings agree with Maitra *et al.*'s literature review [5]. Intermenstrual bleeding occurred in 43% of LNG users compared to 19.8% of DSG users [5]. It is concluded that both oral contraceptive pills pose intermenstrual bleeding risks, with a higher incidence rate in LNG users. Compliance in taking the oral contraceptives may mitigate this risk [13].

Headache

Complaints of headache in oral contraceptive users may be influenced by many mechanisms. One mechanism is a decrease in estrogen. Headaches are caused by low estrogen when users consume placebo pills during menstruation. Another mechanism is an increase in estrogen; this produces headaches when the contraceptives are taken. The incidence of such headaches decreases after multiple uses of the oral contraceptive [15]. Headaches were reported by 10 (16.7%) EE-LNG respondents and 2 (5%) EE-DSG respondents; this difference was not statistically significant. Of all respondents, 33.3% experienced headaches when approaching menstruation and 41.67% experienced headaches moments after taking the pill. In the EE-DSG group, complaints of headaches only occurred when approaching menstruation, indicating that they were caused by a decrease in EE. In the EE-LNG group, headaches were caused more often after taking the pill (50%) rather than when approaching menstruation (20%). These differences are influenced by the respondents' sensitivity to EE and the risk of LNG causing headaches [16]. This study shows that headaches occur more commonly in respondents ≥35 years; this findings are supported by Grossman Barr study [1]. Respondents complaining of headaches in this study had mostly been taking oral contraceptives for over 6 months (66.7%); it is hoped that the incidence would decrease after 6 months of use [17]. The low incidence of headaches in the EE-DSG group was caused by DSG, which has a positive effect on headache frequency. Merki-Feld *et al.*'s study showed that 60% of participants experienced decreased headache incidence, frequency and intensity and need of medication when using pills containing only DSG [18]. This contradicts the findings of another study that showed that combined DSG pills have a higher headache incidence rate compared to LNG pills (24% vs. 5.8%) [4]. This may be caused by the difference in assessment methods and subject bias. In this study, the headache intensity was assessed using the Wong-Baker FACES pain rating scale. In general, both groups categorized their headaches as mild pain (60% of EE-LNG group vs. 100% of EE-DSG group). The questionnaire did not contain any questions about comparing headaches before and after contraceptive use, so whether contraceptive use causes more severe headaches remains unknown. Oral contraceptives are safe to use for users with headache complaints. Use should be avoided if users have stroke risk factors. When the headache intensity or frequency increases, other nonhormonal contraception methods should be considered. Users who experience headaches when approaching menstruation can instead use oral contraceptives with a shorter hormone-free interval [16].

Brest tenderness

As many as 8 (13.3%) EE-LNG respondents complained of breast tenderness after the use of contraceptives. These respondents were generally >35 years old, had normal BMI, and had used oral contraceptives for >6 months. Another 37.5% of respondents complained of breast tenderness when approaching menstruation, and others were not specific. No EE-DSG respondents complained of breast tenderness. This finding differs from that of a previous study that showed that the incidence of breast tenderness with the use of LNG and DSG was 4% and 8%, respectively [4]. As with headaches,

breast tenderness can be associated with estrogen increase before menstruation [16]. Estrogen may cause node swelling in breast milk channels that traps fluid inside the breast and causes tenderness [1]. Breast tenderness may also occur after months of use [1]. Many other factors may contribute to breast tenderness, such as the use of an ill-fitting bra and caffeine consumption [11].

Nausea/vomiting

No EE-DSG respondents experienced nausea after the use of contraceptives, whereas 15% of EE-LNG respondents did. This finding differs from that of previous studies that showed that the DSG group had higher nausea rate than the levonorgestrel group (12% vs. 4%) [4]. Nausea related to the use of oral contraceptives is caused by a decrease in the lower esophageal sphincter pressure or because of the inducing effect of the chemoreceptor trigger zone caused by the binding of the pills with the receptor in the digestive tract. Both effects might be caused by EE and/or its combination with different progestins [19]. High doses of progesterone can reduce the colon motility, resulting in an increase in the stomach clearance time [20]. This increases the risk of nausea/vomiting in oral contraceptive users [21]. The significant difference in both groups is caused by the sensitivity levels of respondents' digestive tracts. Nausea can be reduced by taking the contraceptive at night [14].

Weight gain

There was statistically significant difference (p=0.181) in weight gain between both groups. Some studies also showed no significant difference in weight gain with the use of combined oral contraceptives [1]. Reviews also showed that the incidence rate of weight gain in DSG and LNG groups was similar (2% vs. 2.3%) [4]. Progestin has a large androgenic effect and is associated with appetite increase. Androgenic effects also increase the risk of abdominal obesity. Second-generation LNG is known to have a higher androgenic effect than DSG [22]. In this study, 35% of EE-LNG respondents and 22.5% of EE-DSG respondents experienced weight gain after using oral contraceptives. Weight gain was not accompanied by an increase in eating frequency. Only 26.7% of respondents admitted to increased eating frequency owing to appetite increase (20%) and mood changes (13.3%). The average weight gain in respondents cannot be calculated as there is a lack of data on weight before starting the use of oral contraceptives. Unlike injection contraceptive users who are periodically tested for blood pressure and weight gain, oral contraceptive users are not supervised. It is recommended that weight and BMI be measured periodically in oral contraceptive users [11]. In this study, weight gain incidence was determined based on user complaints. The results showed no difference between the effects of second- and third-generation progestin on weight. Risk factors that may contribute to weight gain are BMI before the use of oral contraceptives and race [23]. This study did not obtain the BMI before the use of oral contraceptives, and all subjects were Asian.

Impaired sexual intercourse

In total, only 17% of respondents experienced impaired sexual intercourse; this included 23.3% (14) of EE-LNG respondents and 7.5% (3) of EE-DSG respondents. This complaint was mainly caused by mood swings (52.9%) and pain/dryness during intercourse (29.4%). These complaints are, respectively, associated with the effect of EE on mood and that of progestin on genital dryness, which causes pain during intercourse [24,25]. Another study found that genital dryness occurs in 12.7% of respondents during the 3 months of EE-LNG use. Reduced sexual appetite occurs in 42.5% of respondents and reduced sexual satisfaction, in 37.2% of respondents. These complaints lessen as the duration of contraceptive use increases, although their incidence remains around 30% (14). One study found that oral contraceptive users who complain of impaired sexual intercourse are usually younger (<29 years), have higher education, and are Caucasians or South Asians. The study found that sexual complaints were related to the difference in each respondent's preferential outcome. Younger women generally had higher expectations with regard to sexual intercourse [24,25]. This study had different findings, where complaints of impaired sexual intercourse were mostly experienced by women ≥35 years and with <3 children. Each respondent's sexual expectation influenced the results. Mood swings that affect sexual intercourse may be caused by multiple factors. Only 5 respondents reported vaginal dryness. The EE-LNG group reported higher incidences of these complaints, and the difference between both groups was statistically significant (p=0.039). This suggests that EE-LNG is more likely to cause mood swings and vaginal dryness compared to EE-DSG. These findings are consistent with those of previous studies that state that third-generation contraceptive pills have better effects on women's mood swings compared to second-generation ones [26].

Acne

Only 3.3% of respondents in the EE-LNG group and 7.5% of respondents in the EE-DSG group experienced acne. The difference between the two groups was not statistically significant (p=0.386). In all respondents, 60% of acne occurred when approaching menstruation and 40% was unspecified. This finding do not prove that DSG has less androgenic effects than LNG. Theoretically, the androgenic effect of DSG is smaller, and it is less likely to cause acne [6]. Previous studies have shown that DSG users experienced up to 70% improvement in acne [1]. Acne can also be influenced by the respondents' sanitary habits [12]. This factor was difficult to evaluate in this study, so a conclusion cannot be made.

Face spots (chloasma)

The EE-LNG group (28.3%) showed a higher occurrence of chloasma than the EE-DSG group (5%), and the difference between the two groups was statistically significant (p=0.004). Chloasma is experienced by respondents ≥35 years and who have used oral contraceptives for >6 months. This finding is similar to that of other studies that showed that chloasma is more common in oral contraceptive users who have used these contraceptives for >10 years [27]. Other studies also support the findings that 25% of chloasma occurs after the use of contraceptives [28]. Chloasma mostly occurred in respondents who did not use sunscreen. Chloasma showed no correlation to the respondents' daily activities (p=0.203) and sunscreen use (p=0.078). Chloasma in oral contraceptive users is caused by the steroid effects of melanogenesis in melanocytes [29]. An increase in EE is known to activate melanocytes and cause hyperpigmentation in the face [30]. The difference in the incidence rate of chloasma is assumed to be caused by the effects of combined progestin and EE. Progestin may inhibit EE induction of melanogenesis in melanocytes [30]. DSG as a third-generation progestin is assumed to have better inhibition effect (antiestrogenic) than LNG.

Analysis of ADR with oral contraceptive type

The results show a statistically significant difference in impaired sexual intercourse and face spots (p<0.05). Although it is proportionally different, breast tenderness could not be statistically analyzed further because its incidence in the EE-DSG group is zero. EE-LNG is 3.75 times more likely to cause impaired sexual intercourse and 7.51 times more likely to cause face spots compared to EE-DSG. In general, this study found that EE-LNG poses a higher risk of ADR than EE-DSG. This proves the hypotheses that third-generation progestin has lower ADR risks [4].

Theoretically, ADR can be influenced by the contraceptive type, duration of use, user age, user BMI, compliance, and other risk factors [14]. This study analyzed the effects of contraceptive type, user age, duration of use, and BMI on ADR. Bivariate analysis showed that age, duration of use, and BMI affected sexual intercourse and face spots without a significant difference between both groups. This study uses retrospective data obtained from an interview, and bias of memory recall may be present. The relations between ADR and user compliance as well as decision to continue using the contraceptive were not clarified. The correlation of ADR with compliance must be determined. Data in Indonesia show that ADR is the second most important reason for withdrawal from the use of contraceptives. Furthermore, enough users are still not given information about ADR [2]. Periodic observance and counseling

are needed to minimize withdrawal from the use of contraceptives. Pharmacies must play a role in this regard because most users obtain contraceptives from pharmacies.

CONCLUSION

The effect of ADR was higher in the EE-LNG group than in the EE-DSG group. The EE-LNG group showed a statistically significant difference for impaired sexual intercourse (OR: 3.75, 95% CI: 1.003-14.050, p=0.039) and chloasma (OR: 7.51, 95% CI: 1.629-34.647, p=0.004). Furthermore, 43% of users were not aware of ADR risks arising from oral contraceptives. Most users had previously withdrawn from the use of injection contraceptives because of ADR. Users' low knowledge of ADR and how to treat it could be the reason for drug withdrawal. Pharmacies must make an effort to provide counseling in this regard.

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