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Signal detection of drospirenone-containing oral contraceptives: a disproportionality analysis using the Korea Adverse Event Reporting System Database, 2008–2017

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ABSTRACT

Objectives To detect the signals for drospirenone-containing oral contraceptives (DCOCs) and describe the reporting pattern of adverse events (AEs) caused by DCOCs compared with levonorgestrel/desogestrel/gestodene-containing (second/third generation) oral contraceptives.

Design A descriptive analysis of claims data.

Setting The Korea Institute of Drug Safety & Risk Management-Korea Adverse Event Reporting System Database from 1 February 2008 to 31 December 2017.

Outcome measures Signals for DCOCs were identified using three data mining indices. The characteristics, death cases, and the annual pattern of AE reports were compared between DCOCs and second/third generation oral contraceptives.

Results Of the 242 DCOC-related AEs, 54 signals were detected and 10 were identified as new signals that were not included in Korea, US and UK label. The newly detected signals include deep vein thrombophlebitis and frequent urination. Serious AEs were more likely to be reported with DCOCs (7.85%) than with second/third generation oral contraceptives (2.92%). Five deaths after use of DCOCs were reported with vascular AEs, such as pulmonary embolism and thrombosis, whereas one death after use of second/third generation oral contraceptives was reported with the cardiac arrest.

Conclusions We identified 10 new signals related to DCOCs that were not included in the current label. Additionally, we found higher reports of the deaths and vascular AEs associated with DCOCs than with second/third generation oral contraceptives, which warrants careful monitoring to ensure the safe use of DCOCs.

Strengths and limitations of this study

- We analysed signals of drospirenone-containing oral contraceptives (DCOCs) through the large spontaneous report data in Korea to provide additional safety information on using the DCOCs.
- The proportional reporting ratio, adjusted reporting OR from a multivariate model and the information component were used as data mining algorithm to detect signals.
- Due to the nature of spontaneous adverse event reporting system, it is limited in that the adverse events are under-reported and the data quality is inconsistent.
- As our study design is descriptive epidemiological study, further analytical studies will be needed to confirm a causal relationship between DCOCs and signals.

INTRODUCTION

Oral contraceptives were developed to help with healthy timing of pregnancies and prevent unintended pregnancies. Enovid, the first hormonal pill, was approved by the US Food and Drug Administration (FDA) in 1960, and in the subsequent years, oral contraceptives have evolved with regard to their composition.[1] Nowadays, combined oral contraceptives are predominantly used, comprising oestrogen and progestin, which inhibit the secretion of follicle stimulating hormone and luteinising hormone, respectively.[2] Although some common adverse drug reactions (ADRs), such as nausea (32.9%), menstrual disorder (14.3%) and dizziness (12.7%), occur after the use of oral contraceptives, they are used widely to control the menstruation cycle (60.8%), as contraception (47.1%) and to cure disease (5.8%).[3] Currently, more than 100 million women worldwide use oral contraceptives.

Since the FDA approved drospirenone-containing oral contraceptives (DCOCs), which were the latest developed oral contraceptives, safety concerns related to blood clots and venous thromboembolism have been raised. Owing to these safety concerns, the FDA conducted a post-marketing surveillance study and in 2012, labelled the

DCOCs with a higher risk of thrombosis than with other contraceptives.[4] South Korea also included these results of the post-marketing surveillance to label DCOCs; cardiovascular diseases such as pulmonary embolism (PE) and venous thromboembolism (VTE) were listed as cautions.[5] Accordingly, a recent meta-analysis reported an increased risk of DCOCs compared with the use of levonorgestrel-containing oral contraceptives.[6] However, given the focus on risk of blood clots in previous studies,[6 7] it is necessary to detect an overall signal for DCOCs that have not yet been investigated for the safe use of DCOCs.

Signal detection for drug adverse events (AEs) is a data mining technique to complement the traditional expert review of the spontaneous ADR reports and to analyse the large volume of data rapidly.[8] This technique is used to explore spontaneous report databases for hidden associations between drugs and reported ADRs that cannot be identified by manual case assessment. To our knowledge, no studies have reported the detection of signals associated with DCOCs using the Korean spontaneous AE reporting system database. Additionally, comparison of reported AEs and demographic characteristics between DCOCs and second/third generation oral contraceptives has not been studied.

Therefore, the purpose of our study was to detect unknown signals of DCOCs and analyse the patterns of reported AEs compared with those of second/third generation oral contraceptive drugs. We aimed to compare the detected signals with the drug labels used in Korea, the USA and the UK.

METHODS

Database

We used the AE data related to DCOCs and second/third generation oral contraceptives from the Korea Institute of Drug Safety & Risk Management-Korea Adverse Event Reporting System Database (KIDS-KD). We collected the data from February 2008 to December 2017, considering the approval date of DCOCs in Korea. The KIDS-KD includes information on patient demographics, the suspected drug, AEs, serious AEs (SAEs), the reporter, a causality assessment and medical history.[9] In this study, all information was integrated using the randomised report number. A randomised report number is a new number given to individual patients when building the KIDS-KD from the Korea Adverse Events Reporting System Database (KAERS). As the original report number from KAERS is randomised, individual patients cannot be distinguished.

Study drug and data extraction

We selected our study drugs as DCOCs and the comparator drugs as second/third generation oral contraceptives that contained levonorgestrel, desogestrel or gestodene as progestin. From the initial data, all duplicates were removed and only the potential drug cases and initial reports were included. In addition, among the report types of spontaneous, research, article or other, we included the spontaneous and research report type formats only. The final data included 2013 case reports for DCOCs and 4350 case reports for second/third generation oral contraceptives (figure 1). By using one-to-one correspondence between the drug and the AEs in each report, 3463 and 7926 drug–AE pairs were created for

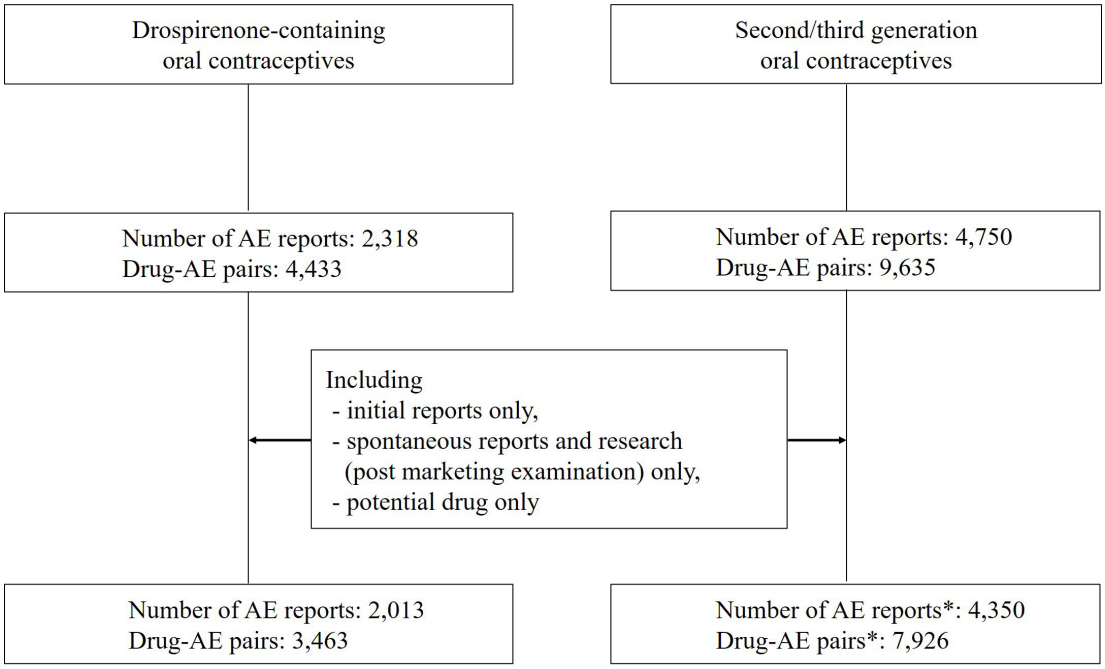

Figure 1 Study flow diagram describing the extraction of research data. *The number of reports for levonorgestrel-containing oral contraceptives (second generation) was 330 and the number of drug–AE pairs was 578. AE, adverse event.

DCOCs and second/third generation oral contraceptives, respectively.

The reported AEs were coded by the preferred term (PT), one of the four components of WHO Adverse Reaction Terminology, which has been developed by the WHO Uppsala Monitoring Centre. The causality of drug–AE pairs was evaluated using the WHO-causality assessment programme and we only included 'certain,' 'probable' and 'possible' drug–AE pairs in our analysis.

Characterisation of cases of death among SAEs

The cases of death caused after DCOCs and second/third generation oral contraceptives were characterised by the date on which the AE was recognised to have occurred, the age, if hospitalisation occurred, the PT of the AE and a causality assessment.

Statistical analysis

The proportion and frequency of DCOC AE reports were analysed by age, period of use, SAEs and reporters. Age was categorised into four groups: 1–19, 20–29, 30–39 and over 40 years of age. The following groups were analysed for period of use: 0–1, 1–3, 3–5 and over 5 months, and the AE reporters were doctors, pharmacists, nurses, consumers and others. The AE reports of DCOCs were compared with second/third generation oral contraceptives using the X^2 test. PT descriptions were used to investigate the type and frequency of AEs.

Drug–AE pairs and the number of AE reports were separately analysed to fulfil different purposes. Drug–AE pairs were analysed to investigate the frequency and type of AEs reported for DCOCs and second/third generation oral contraceptives. Based on the number of AE reports, the annual proportion of SAEs of the total number of AEs reported for DCOCs and second/third generation oral contraceptives was calculated from 2008 to 2017.

Data mining techniques were used in this study. Quantitative signal detection is widely used to analyse the spontaneous reports and aims to find true signals and avoid false positives.[10] The measurement of disproportionality is one method for quantitative signal detection and there are several measures. To identify signals, we calculated disproportionality using the proportional reporting ratios (PRRs),[11] reporting OR (ROR)[12] and Bayesian confidence propagation neural networks of information components with the lower limit for 95% CI (IC025).[13] To supplement the uncertainty of any estimates, CIs and X^2 tests are used to determine the threshold.[14] A 2×2 contingency table with the DCOCs and second/third generation oral contraceptives as the rows and specific AE and all other AEs as the columns was designed and used for the calculation. The PRR was defined as the ratio of the reporting rate of a certain AE among all the AEs for a DCOC to the reporting rates for a second/third generation oral contraceptive. The criteria for signals were PRR ≥2, ≥4 and the number of AEs ≥3.[11] The ROR is the odds of the reporting rate for one specific AE when exposed to a DCOC compared with the reporting rate for a specific AE after exposure to a second/third generation oral contraceptive. We calculated crude ROR using 2×2 contingency table and adjusted ROR by logistic regression analysis. Patient's age group, whether SAE or not, and the type of AE reporter were used as covariate for adjustment. To be classified as a signal, the criteria were adjusted ROR ≥2, ≥4 and the number of AEs ≥3.[15 16] When the number of AE of interest with second/third generation oral contraceptives is 0, the PRR and ROR cannot be computed; thus, we set the values at 99.9 arbitrarily to reflect a potential signal.[17] IC is the log of the probability of an AE after use of a drug divided by the product of the probability of AE and the probability of the drug when it is assumed that the drug use and occurrence of AE are independent. When the lower limit of the 95% CI of the IC is greater than zero, it is considered as a signal.[18] In this study, AEs that satisfy at least one of the criteria for three indices (PRR, adjusted ROR and IC025) were detected as a signal.

We compared the detected signals with the drug labels in Korea, the USA and the UK. We obtained the label

Table 1 Characteristics of adverse event reports for drospirenone-containing oral contraceptives and second/third generation oral contraceptives

	Drospirenone-containing oral contraceptives	Second/third generation oral contraceptives	
	N (%)	N (%)	P value
Total	2013 (100)	4350 (100)	–
Age (years)			<0.0001*
1–19	57 (2.83)	50 (1.15)	
20–29	375 (18.63)	517 (11.89)	
30–39	281 (13.96)	185 (4.25)	
≥40	219 (10.88)	99 (2.28)	
Unknown	1081 (53.70)	3499 (80.44)	
Period of use (months)			<0.0001*
0–1	242 (12.02)	300 (6.90)	
1–3	118 (5.86)	40 (0.92)	
3–5	37 (1.84)	14 (0.32)	
>5	87 (4.32)	32 (0.74)	
Unknown	1529 (75.96)	3964 (91.13)	
Serious adverse events			0.2333
Total	158 (7.85)	127 (2.92)	
Death	5 (0.25)	1 (0.02)	
Reporting group by profession			<0.0001*
Doctors	252 (12.52)	18 (0.41)	
Pharmacists	364 (18.08)	362 (8.32)	
Nurses	101 (5.02)	19 (0.44)	
Consumers	925 (45.95)	2844 (65.38)	
Others	199 (9.89)	638 (14.67)	
Unknown	172 (8.54)	469 (10.78)	

*P value of <0.05: significant.

information for Korea at EZDrug (http://ezdrug.mfds.go.kr/), which is collated by Korea Ministry of Food and Drug Safety. For the US FDA labels, we searched DailyMed (http://dailymed.nlm.nih.gov/dailymed/about.cfm). For the UK labels, we mainly used the Electronic Medicines Compendium (EMC) database (http://www.medicines.org.uk/emc/).

All statistical analyses were performed using Microsoft Excel 2010 and SAS V.9.4 (SAS Institute). P values of <0.05 were considered to indicate statistical significance.

Patient and public involvement

Patients and the public were not involved in the design or conduct of our study.

RESULTS

The total numbers of AEs reported for DCOCs and second/third generation oral contraceptives between 2008 and 2017 were 2013 and 4350, which corresponded to 3463 and 7926 drug–AE pairs, respectively. Among 4350 of AE reports for second/third generation oral contraceptives, 330 was reported for second generation oral contraceptives (figure 1). For both DCOCs and second/third generation oral contraceptives, the proportions of reported AEs were highest in the age of 20s, followed by the age of 30s and finally those over 40 years (p<0.0001). For the period of use, the occurrence of AEs after using DCOCs and second/third generation oral contraceptives for 0–1 month was highest, and the proportion attributable to DCOCs was higher in the groups of 1–3 months, 3–5 months and over 5 months than that for the comparator drugs (p<0.0001). In terms of reporting group, higher reporting frequencies for DCOC-related AEs were observed from the pharmacists, nurses and doctors than that for comparator drugs (p<0.001) (table 1).

The number of SAEs from the total number of AEs was 158 out of 2013 (7.85%) for DCOCs and 127 out of 4350 (2.92%) for second/third generation oral contraceptives; however, this difference was not statistically significant (p=0.2333). Among the SAEs, five cases of death were reported for DCOCs and one case was reported for second/third generation oral contraceptives (table 1). All these cases of death occurred in the age group of 20s and 30s. For the deaths observed after use of DCOCs, vascular diseases such as PE, hypoesthesia, thrombosis, atherosclerosis and thromboembolism were reported as AEs. Of the five cases, two cases were rated with 'possible' causality and one case accompanied hospitalisation. For the death observed after use of second/third generation oral contraceptives, the reported AE was cardiac arrest (table 2).

The proportion of SAEs among the total AEs reported after DCOCs unexpectedly increased in 2011, at 25.79%, which was higher than the value with the second/third generation oral contraceptives, 6.41% (figure 2). The number of AEs and SAEs for DCOCs and second/third generation oral contraceptives and the number of AEs reported for all drugs through KIDS-KD from 2008 to 2017 are presented in online supplemental table 1.

The type and frequency of AE after use of oral contraceptives analysed by WHO-PT classification are shown in online supplemental table 2. Of the 3463 AE reports for DCOCs, 242 types of AE were reported, and the most common AEs were menstrual disorder (11.78%), nausea (8.55%), vaginal haemorrhage (7.83%), vomit (3.93%) and headache (3.81%). Of the 7926 AE reports for second/third generation oral contraceptives, inappropriate administration schedule was most common (17.04%), followed by menstrual disorder (10.65%), vaginal haemorrhage (10.56%) and medication error (9.17%).

The detected signals of DCOCs are listed together with the value of PRR, adjusted ROR and IC025 in table 3. Crude and adjusted RORs with 95% CIs are presented in online

Table 2 Characterisation of death cases of the serious adverse events (SAEs) after oral contraceptive drugs

Drug	No	Date*	Age	SAE	Death	Hospitalisation	Adverse event (PT)	Causality assessment
Drospirenone-containing oral contraceptives	1	15 May 2012	28	Yes	Yes	No	Pulmonary embolism	—†
	2	19 Nov 2012	26	Yes	Yes	No	Hypoesthesia, pulmonary embolism, medication error	—†
	3	02 July 2014	—†	Yes	Yes	No	Pulmonary embolism	—†
	4	30 Mar 2016	—†	Yes	Yes	Yes	Thrombosis, atherosclerosis	Possible
	5	07 Apr 2016	35	Yes	Yes	No	Thromboembolism	Possible
Second/third generation oral contraceptives	1	18 Jan 2016	32	Yes	Yes	No	Cardiac arrest	Possible

*Date on which recognising adverse event occurrence.
†— refers to missing data.
PT, preferred term.

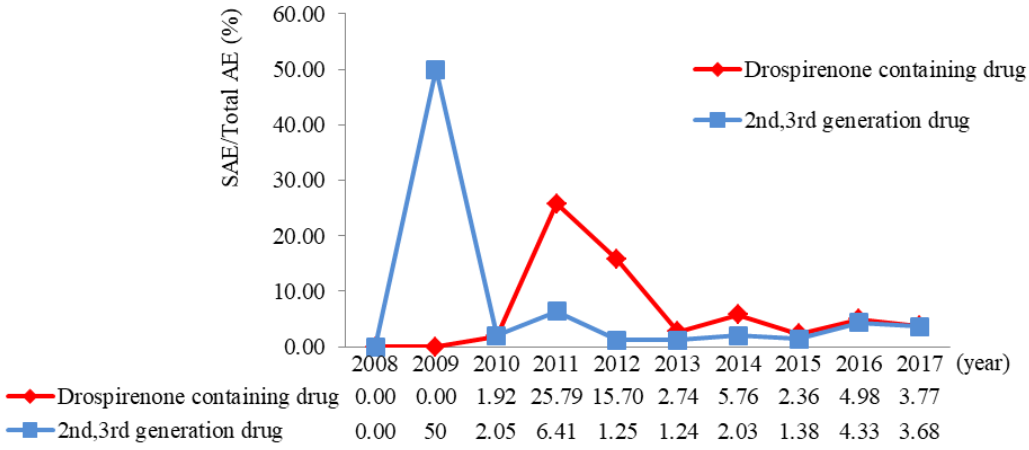

Figure 2 Annual proportion of serious adverse events (SAEs) among total adverse events (AEs) after drospirenone-containing oral contraceptives and second/third generation oral contraceptives, 2008–2017.

supplemental table 3. There were 22 signals that satisfied the three criteria and the signals included xerophthalmia, endometriosis, thrombosis and varicose vein. Of the 22 signals, intrauterine device complication, dyspnoea, chest pain, and fatigue were unlabelled in Korea, the USA and the UK. There were 25 signals that met two criteria, PRR and ROR or IC025; these signals included hypertrichosis and urinary incontinence. Among them, the AEs of pneumothorax, osteoporosis, pallor, deep vein thrombophlebitis, tinnitus, and frequent urination were unlabelled in Korea, the USA and the UK. The AEs that satisfied only one criterion included myalgia, insomnia, oedema generalised, vaginitis and candidiasis genital. Among them, myalgia and insomnia were unlabelled AEs in Korea and the USA.

DISCUSSION

This study described the AE characteristics and signal after use of DCOCs compared with second/third generation oral contraceptives between February 2008 and December 2017. AEs after use of DCOCs were reported from older group compared with second/third generation oral contraceptives; moreover, they used the drugs for longer period, thus, increasing the chance of a thrombotic event. Five cases of death were reported after the use of DCOCs through KIDS-KD and were all reported with vascular diseases, which are SAEs. We detected 54 signals associated with DCOCs; these signals included xerophthalmia, endometriosis, thrombosis and varicose vein. Of the 54 signals, 10, including dyspnoea, chest pain and frequent urination, were unlabelled in Korea, the USA and the UK.

For both DCOCs and second/third generation oral contraceptives, the AE reports were highest in the group with 0–1 months of drug use. Previous research has indicated that the risk of venous thrombosis was highest during the first 3 months of oral contraceptive use.[19] The frequency of AE reported by professionals was higher for DCOCs than for second/third generation oral contraceptives. This might be due to the fact that DCOCs are prescription drugs and second/third generation oral contraceptives are over-the-counter drugs in Korea. The AEs and SAEs for DCOCs were first reported in 2010. The proportion of SAEs from the total number of AEs was highest in 2011 and in the following year, the FDA issued a safety alert on thrombosis and VTE.[4] After the FDA alert, the proportions of SAEs among total AEs for DCOCs have decreased. The proportion of SAEs among total AEs for second/third generation oral contraceptives was 50% in 2009. However, the reported numbers of SAEs and AEs were 1 and 2, respectively; therefore, it should be interpreted with caution.

Our results are similar to case reports in Japan, where three deaths after taking DCOCs were reported, all caused by vascular diseases such as intracranial venous sinus thrombosis, PE and deep vein thrombosis.[20] In a previous study that aimed to analyse the AEs induced by DCOCs using the FDA Adverse Event Reporting System, the signal related to 'venous thrombotic,' first appeared in 2002 and persisted until 2015, at the time when the IC05 for DCOCs was five times higher than that for levonorgestrel-containing oral contraceptives.[7] Our study also suggested the risk of AE associated with 'venous thrombotic', such as thrombosis, varicose vein, PE, cerebral infarction and thromboembolism. Hence, among the newly detected signals, which were unlabelled in Korea, the USA and the UK, deep vein thrombophlebitis was identified, which might be in line with the risk of thrombosis.

The risk of VTE after the use of DCOCs has been an issue in many countries, including Korea. However, there has much been controversy regarding the effects of oral contraceptives on thrombosis. One study has confirmed that during the use of oral contraceptives, the level of coagulant factors and prothrombin increases,[21] which is

Table 3 Detected signals for drospirenone-containing oral contraceptives by WHO-ART code PT and labelling

No	Adverse event (PT)	The number of AE	PRR*	ROR*	IC025	χ^2	Label		
							Korea	USA	UK
Satisfying three criteria									
1	Xerophthalmia	6	99.90†	99.9†	0.17†	13.74	N	N	Y
2	Endometriosis	11	99.90†	99.9†	0.54†	25.20	Y	N	N
3	Thrombosis	6	99.90†	99.9†	0.17†	13.74	Y	Y	Y
4	Varicose vein	6	99.90†	99.9†	0.17†	13.74	Y	Y	Y
5	IUD complication	5	99.90†	99.9†	0.05†	11.45	N	N	N
6	Weight decrease	10	22.89†	28.69†	0.39†	19.05	Y	Y	Y
7	Pulmonary embolism	10	11.44†	2.40†	0.29†	15.90	Y	Y	Y
8	Anxiety	19	10.87†	18.25†	0.58†	29.68	Y	Y	N
9	Uterine haemorrhage	23	10.53†	7.22†	0.65†	35.50	Y	Y	Y
10	Chloasma	14	4.58†	6.57†	0.20†	13.07	Y	Y	Y
11	Alopecia	20	4.16†	4.18†	0.30†	17.09	Y	Y	Y
12	Dyspnoea	22	3.87†	4.02†	0.30†	17.47	N	N	N
13	Depression	36	3.43†	3.17†	0.39†	24.96	Y	Y	Y
14	Appetite increased	17	3.24†	3.12†	0.12†	10.94	Y	Y	Y
15	Chest pain	27	2.94†	3.26†	0.23†	15.21	N	N	N
16	Temperature changed sensation	18	2.94†	3.02†	0.09†	10.13	N	N	Y
17	Migraine	20	2.69†	3.58†	0.08†	9.81	Y	Y	Y
18	Breast pain	21	2.53†	2.91†	0.35†	27.98	Y	Y	Y
19	Somnolence	20	2.41†	3.75†	0.01†	8.06	Y	N	Y
20	Pruritus	41	2.41†	2.60†	0.22†	16.54	Y	Y	Y
21	Fatigue	21	2.40†	2.53†	0.02†	8.42	N	N	N
22	Headache	132	2.34†	2.13†	0.43†	51.35	Y	Y	Y
Satisfying two criteria									
23	Hypertrichosis	3	99.9†	99.9†	−0.32	6.87	Y	Y	Y
24	Urinary incontinence	3	99.9†	99.9†	−0.32	6.87	Y	N	N
25	Skin exfoliation	3	99.9†	99.9†	−0.32	6.87	Y	N	Y
26	Pneumothorax	4	99.9†	99.9†	−0.11	9.16	N	N	N
27	Cerebral infarction	4	99.9†	99.9†	−0.11	9.16	Y	Y	Y
28	Thromboembolism	3	99.9†	99.9†	−0.32	6.87	Y	Y	Y
29	Osteoporosis	3	99.9†	99.9†	−0.32	6.87	N	N	N
30	Candidiasis	3	99.9†	99.9†	−0.32	6.87	Y	Y	N
31	Hepatic function abnormal	5	11.44†	7.58†	−0.11	7.95	Y	N	Y
32	Pallor	4	9.16†	99.9†	−0.29	5.81	N	N	N
33	Hyperlipidaemia	4	9.16†	6.10†	−0.29	5.81	Y	Y	N
34	Deep vein thrombophlebitis	4	9.16†	4.06†	−0.29	5.81	N	N	N
35	Tinnitus	6	6.87†	2.74†	−0.10	7.52	N	N	N
36	Frequent urination	8	4.58†	11.35†	−0.06	7.46	N	N	N
37	Cystitis	7	4.01†	2.92†	−0.18	5.75	Y	Y	N
38	Emotional lability	10	2.86†	2.18†	−0.16	5.39	Y	Y	Y
39	Dyspepsia	101	2.60†	1.53	0.46†	47.26	Y	Y	Y
40	Acne	95	2.42†	1.99	0.40†	38.99	Y	Y	Y

Continued

Table 3 Continued

No	Adverse event (PT)	The number of AE	PRR*	ROR*	IC025	X^2	Label		
							Korea	USA	UK
41	Weight increase	62	2.41†	1.43	0.32†	25.08	Y	Y	Y
42	Breast pain female	21	2.40†	0.81	0.02†	8.42	Y	Y	Y
43	Asthenia	17	2.29†	3.41†	−0.08	6.19	Y	Y	Y
44	Pain	18	2.29†	2.56†	−0.06	6.55	Y	Y	Y
45	Paresthesia	13	2.29†	2.11†	−0.18	4.73	N	N	Y
46	Urticaria	49	2.29†	1.77	0.23†	17.93	Y	Y	N
47	Nausea	296	2.16†	1.82	0.47†	100.69	Y	Y	Y
Satisfying one criterion									
48	Myalgia	10	2.54†	1.03	−0.23	4.44	N	N	Y
49	Insomnia	21	2.18†	1.95	−0.04	6.93	N	N	Y
50	Oedema generalised	15	2.02†	1.36	−0.21	4.11	Y	Y	Y
51	Vaginitis	15	2.45†	1.46	−0.08	6.24	Y	Y	Y
52	Candidiasis genital	5	5.72†	1.38	−0.26	5.57	Y	Y	Y
53	Dizziness	82	1.90	1.47	0.20†	19.29	Y	Y	Y
54	Vomiting	136	1.55	1.51	0.12†	16.25	Y	Y	Y

PRR: PRR ≥2, χ^2 ≥4 and number of AE ≥3. ROR: ROR ≥2, χ^2 ≥4 and number of AE ≥3. IC: underlimit of 95% CI ≥0.
*If the number of AE of interest with all other drugs is 0, the PRR and ROR were set at 99.9 arbitrarily since the values cannot be computed.
†Satisfies the criteria.
AE, adverse event; IC, information component; IUD, intrauterine device; PRR, proportional reporting ratio; PT, preferred term; ROR, reporting OR; WHO-ART, WHO Adverse Reaction Terminology.

associated with the increased risk of venous thrombosis. Nevertheless, individual susceptibilities and external risk factors should also be considered when interpreting the data.[22] Moreover, oral contraceptives contain doses of 20 or 30 µg of oestrogen and 21 or 24 tablets per month, which indicates the heterogeneity of formulations. A recent study found a cardiovascular safety profile for oestrogen-free contraceptive containing 4 mg of drospirenone;[23] therefore, further study is required to explore whether the risk of thrombosis is different among formulations of oral contraceptives.

Among the signals that were unlabelled in Korea, the USA and the UK, frequent urination was detected as a signal. The detection of frequent urination and decrease in weight is attributed to the fact that drospirenone is an analogue of spironolactone, an aldosterone receptor antagonist, which reduces sodium reabsorption and induces the excretion of water in the kidney.[24] Additionally, spironolactone inhibits the action of testosterone and stimulates the synthesis of oestradiol, which leads to AEs such as chest pain, an unlabelled signal.[25] As an increase in the concentration of oestradiol cause nausea,[26] signals such as headache, urticaria and nausea were detected for DCOCs.

This study has several strengths. First, we used the nationwide database from the spontaneous AE reporting system, which is an important tool to detect unknown and rare adverse reactions that occur after market approval.[27] This database includes all spontaneously reported AE which has been collected for more than 1 million patients in Korea. In addition, we compared the labels of DCOCs between Korea, the USA and the UK, and identified the unlisted signals. Second, unlike the previous study, we compared the AEs and demographic characteristics between DCOCs and previous generation oral contraceptives. There was a study on the risks of DCOCs conducted using the spontaneous AE reporting system,[7] but comparisons on the characteristics of AE reports with respect to other oral contraceptives were not made. Third, we conducted data mining using three different statistical indices, PRR, ROR and IC025, to account for inconsistent signal detection results due to their varying levels of specificity in defining AEs and signal score threshold.

However, this study also has some limitations. First, due to the nature of passive spontaneous AE reporting system that we used in this study, the under-reporting of AEs cannot be avoided.[28] Therefore, every AE after drug use cannot be collected by this reporting system. Second, there was no information about the total number of patients who have taken the drug. The prevalence of DCOCs and other generations of oral contraceptives should be examined in future studies. According to a report released by United Nations, the estimated prevalence of oral contraceptive use among women in South Korea was 3.3%, which is relatively lower than that of the USA (13.7%) or the UK (26.1%).[29] Third, information on previous oral contraceptive drug use, which could be an important factor in evaluating their adverse effects, was not available

in the spontaneous AE reporting system. Fourth, when calculating adjusted ROR, the estimates may be biased by residual confounding. We included patient's age group, period of use and the type of AE reporter in the multivariate analysis as covariates, as patients who used DCOCs tended to be older, used drugs for a longer period, and had higher frequencies of reporting from the group of doctors, pharmacists, and nurses. However, there were not enough variables available for the adjustment due to too many missing values. In addition, numerous factors including body mass index and smoking affecting the relationship between the drug and the AE could not be considered due to inherent limitations of pharmacovigilance data. For example, smoking is a risk factor for thrombosis and acts synergistically when administered with oral contraceptives.[30] However, it is hard to know whether the patient is a smoker or a non-smoker through the spontaneous reports. Therefore, higher level evidence-based studies should be conducted to determine whether other factors can affect AEs that were detected as signals. Lastly, KIDS-KD does not represent patients worldwide. Further pharmacoepidemiological studies that include overseas data are required. Although there are some limitations, this study is significant as it is the first study to detect signals of DCOCs using KIDS-KD. As the population of women taking oral contraceptives increases,[31] the detection of signals in advance will be important to prevent unexpected AEs.

CONCLUSIONS

To conclude, statistically significant differences in the patterns of AEs between DCOCs and previous generation oral contraceptives were observed. In addition, deaths and SAEs, including vascular diseases, were more often reported with DCOCs than with second/third generation oral contraceptives. We also detected signals of AE including cardiovascular events (eg, thrombosis, varicose vein, cerebral infarction and thromboembolism) and new signals which were not identified in Korea, US and UK label in relation to DCOCs. Although the evidence from signal detections is not conclusive, it helps to develop new hypotheses of causal relationship. Further analytical studies will be needed to identify the causality between oral contraceptives and AEs.

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REFERENCES

1 Christin-Maitre S. History of oral contraceptive drugs and their use worldwide. *Best Pract Res Clin Endocrinol Metab* 2013;27:3–12.
2 Korea Ministry of Food and Drug Safety (MFDS). Online pharmaceutical library contraceptive information. Available: http://drug.mfds.go.kr/html/index.jsp [Accessed 14 Jun 2019].
3 Um H*et al*. A survey of oral contraceptive utilization patterns and adverse event in Korean women aged 20 to 49 years. *Korean Public Health Res* 2015;41:1–11.
4 The Food and Drug Administration (FDA). Drug safety communication: updated information about the risk of blood clots in women taking birth control pills containing drospirenone, 2012. Available: https://www.fda.gov/Drugs/DrugSafety/ucm299305.htm [Accessed 14 Jun 2019].
5 Korea Ministry of Food and Drug Safety (MFDS). Drug safety information 2014:94–100.
6 Dragoman MV, Tepper NK, Fu R, *et al*. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. *Int J Gynaecol Obstet* 2018;141:287–94.
7 Madigan D, Shin J. Drospirenone-containing oral contraceptives and venous thromboembolism: an analysis of the FAERS database. *Open Access J Contracept* 2018;9:29–32.
8 Harpaz R, DuMouchel W, LePendu P, *et al*. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. *Clin Pharmacol Ther* 2013;93:539–46.
9 Korea Institute of Drug Safety & Risk Management. Manual for using Korea institute of drug safety & risk management Korea adverse event reporting system database, 2018. Available: https://open.drugsafe.or.kr/original/guidelines/List.jsp [Accessed 14 Jun 2019].
10 Lindquist M, Ståhl M, Bate A, *et al*. A retrospective evaluation of a data mining approach to aid finding new adverse drug reaction signals in the who international database. *Drug Saf* 2000;23:533–42.
11 Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRS) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf* 2001;10:483–6.
12 Poluzzi E*et al*. Data mining techniques in pharmacovigilance: analysis of the publicly accessible FDA adverse event reporting system (AERS), in data mining applications in engineering and medicine. *IntechOpen* 2012.
13 Gould AL, Lawrence Gould A. Practical pharmacovigilance analysis strategies. *Pharmacoepidemiol Drug Saf* 2003;12:559–74.
14 Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol Drug Saf* 2009;18:427–36.
15 Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf* 2004;13:519–23.

16 Park K, Soukavong M, Kim J, *et al*. Signal detection of imipenem compared to other drugs from Korea adverse event reporting system database. *Yonsei Med J* 2017;58:564–9.
17 Group, E.E.W. *Guideline on the use of statistical signal detection methods in the eudravigilance data analysis system*. London: European Medicines Agency, 2006.
18 van Puijenbroek EP, Bate A, Leufkens HGM, *et al*. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf* 2002;11:3–10.
19 van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, *et al*. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 2009;339:b2921.
20 Pharmaceuticals and Medical Devices Agency (PMDA). YAZ TAB case report details, 2016. Available: https://www.pmda.go.jp/files/000153603.pdf [Accessed 14 Jun 2019].
21 Middeldorp S, Meijers JC, van den Ende AE, *et al*. Effects on coagulation of levonorgestrel- and desogestrel-containing low dose oral contraceptives: a cross-over study. *Thromb Haemost* 2000;84:4–8.
22 Vandenbroucke JP, Rosing J, Bloemenkamp KWM, *et al*. Oral contraceptives and the risk of venous thrombosis. *N Engl J Med Overseas Ed* 2001;344:1527–35.
23 Palacios S, Colli E, Regidor P-A. Efficacy and cardiovascular safety of the new estrogen-free contraceptive pill containing 4 mg drospirenone alone in a 24/4 regime. *BMC Womens Health* 2020;20:1–9.
24 Korea Pharmaceutical Information Center. Spironolactone. Available: http://www.health.kr/searchDrug/search_detail.asp [Accessed 14 Jun 2019].
25 Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. *Contraception* 2000;62:29–38.
26 Goldzieher JW, Moses LE, Averkin E, *et al*. A placebo-controlled double-blind crossover investigation of the side effects attributed to oral contraceptives. *Fertil Steril* 1971;22:609–23.
27 Scott HD, Thacher-Renshaw A, Rosenbaum SE, *et al*. Physician reporting of adverse drug reactions. Results of the Rhode island adverse drug reaction reporting project. *JAMA* 1990;263:1785–8.
28 Alvarez-Requejo A, Carvajal A, Bégaud B, *et al*. Under-reporting of adverse drug reactions. Estimate based on a spontaneous reporting scheme and a sentinel system. *Eur J Clin Pharmacol* 1998;54:483–8.
29 United Nations, Department of Economic and Social Affairs, Population Division. *Contraceptive use by method 2019*. Data Booklet (ST/ESA/SER.A/435), 2019.
30 Pomp ER, Rosendaal FR, Doggen CJM. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. *Am J Hematol* 2008;83:97–102.
31 Rashed AN, Hsia Y, Wilton L, *et al*. Trends and patterns of hormonal contraceptive prescribing for adolescents in primary care in the UK. *J Fam Plann Reprod Health Care* 2015;41:216–22.