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ORIGINAL RESEARCH

Analysis of Adverse Events and Medical Errors in Long-Term Hormone Treatments for Endometriosis: A Study Based on the US Food and Drug Administration Event Reporting System

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Purpose: To investigate adverse events and medical errors, as well as their possible risk factors, of combined oral contraceptives and progestins used in patients with endometriosis.

Patients and Methods: Reports between January 1, 2014 and September 30, 2021 about patients with endometriosis in US Food and Drug Administration Adverse Event Reporting System were analyzed. Disproportional analysis was performed with the Gamma-Poisson Shrinker model to detect overreported drug-event pairs. Logistic regression analysis was utilized to explore potential risk factors.

Results: There were 823 reports on long-term hormone treatments and 6247 reports on other drugs after removing duplicates, most of which were reported by consumers and were from the United States. Procedural complications and product issues were common among long-term hormone treatment users, while some other new adverse events emerged in subgroup analysis of different dosage forms of progestin. Polytherapy was negatively associated with off label use (adjusted OR = 0.47, 95% CI 0.22–0.94) and product use in unapproved indication (adjusted OR = 0.36, 95% CI 0.15–0.76) for combined oral contraceptive users. Combined oral contraceptive users aged greater than or equal to 30 were less likely to have product use issue (adjusted OR = 0.33, 95% CI 0.12–0.82) but were at higher risk of pulmonary embolism (adjusted OR = 4.04, 95% CI 1.35–17.43).

Conclusion: Long-term hormone treatment products in this study are generally safe for endometriosis, while newly detected signals need to be validated by further exploration. Patients' tolerance and fertility desire should be considered when preparing treatment plans.

Keywords: adverse side effect, endometriosis, hormone therapy, pharmacovigilance

Introduction

As a hormone-dependent disease, endometriosis is observed in nearly 10% of women at reproductive age.[1] Combined oral contraceptives (COCs) and progestins may be implemented as an alternative to surgery or a prevention of postoperative recurrence.[2] They can be used alone or be recommended as add-back hormone therapies for patients using gonadotropin-releasing hormone (GnRH) analogues.[3–5] Given that the efficacy of COCs and progestins have been widely acknowledged, they are suggested to be the reference comparator for randomized controlled trials on new endometriosis drugs.[6]

As suppressive solutions to endometriosis, COCs and progestins have similar efficacy in relieving pain and other symptoms,[5] leaving them as the safest long-term treatment for endometriosis.[7–9] However, patients' tolerance could be highly personalized,[10,11] not to mention that women with endometriosis have a higher rate of allergies on medication.[12] In addition to painful symptoms, side effects may increase patients' suffering.[13,14] Patient compliance may be affected due to side effects, especially for the long courses of these hormone drugs,[6] which could be detrimental to the management of the disease. There have been some real-world studies focusing on specific drugs for endometriosis,

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but they either produced negative result or concentrated on drug efficacy.[15–17] Pharmacovigilance evidence determining adverse reactions of long-term hormone drugs for endometriosis are still inadequate.

Post-marketing adverse events reports of drugs and therapeutic biologic products that were submitted to US Food and Drug Administration (FDA) are stored in the FDA Adverse Event Reporting System (FAERS), providing materials for drug safety surveillance. Adverse events and medication errors in FAERS are recorded using Preferred Terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA) terminology.[18,19] This study portrayed reports about long-term hormone therapies for endometriosis in FAERS and performed a disproportional analysis, aimed at investigating drug-type-specific adverse events and exploring their possible risk factors.

Materials and Methods

Data Processing

FAERS reports from patients with endometriosis between Jan 1, 2014 and Sep 30, 2021 were retrieved (date of access: Mar 5, 2022). After removing duplicates, reports were filtered to select those whose diagnosis was coded as endometriosis or endometriosis ablation. Medications of interest in this study included COC, oral progestin, progestin-eluting intrauterine device (IUD), depot progestin, and progestin implant. Cases about these drugs and devices were extracted and were classified as the long-term hormone treatment group by filtering drug names and product active ingredients of the records. Cases whose indication were endometriosis but were treated without any of the drugs mentioned above were classified as the control group.

Statistical Analysis

We calculated counts and rates of major baseline characteristics in the long-term hormone treatment group and the control group separately. Gamma–Poisson Shrinker (GPS) model was used for disproportional analysis and to detect overreported drug-event pairs.[20,21] This model represented relative reporting ratios by Empirical Bayes Geometric Mean (EBGM) scores after Bayesian shrinkage. EBGM score, 5th percentile (EB05), and 95% percentile (EB95), i.e. lower and upper limit of 90% confidence interval (CI), were calculated with R (version 4.0.4; The R Foundation for Statistical Computing, Vienna, Austria) and R package openEBGM (version 0.8.3). EB05 $\geq$ 2 was considered signal detected.[22] According to MedDRA hierarchy,[23] PTs whose signals were detected by disproportional analysis were presented in groups according to their primary System Organ Class (SOCs).

Considering the wide age distribution of the cases and that GnRH-analogue/antagonists, aromatase inhibitors, and analgesics are commonly co-administered, logistic regression analysis was performed to explore potential risk factors of the signals detected above. According to 10 events per variable recommendation on sample size for developing a clinical prediction model,[24] events whose drug-event pair counts were greater than 20 were selected for logistic regression analysis. Logistic regression analysis was performed with R (version 4.0.4; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Descriptive Analysis

Between January 1, 2014 and September 30, 2021, there were 1823 reports on long-term hormone treatment and 6247 reports on other drugs applied for endometriosis. Long-term hormone treatment accounted for 501 (27.5%) reports on COCs, 924 (50.7%) reports on oral progestin, 102 (5.6%) reports on depot progestin, 255 (14.0%) reports on progestin-eluting IUD, and 41 (2.2%) reports on progestin implant.

Clinical features of reports are presented in Table 1. The majority of women included were at their reproductive age. In the long-term hormone treatment group, most of the cases were reported from the United States (75.0%), followed by other countries (9.7%) and France (3.2%). While in the control group, most of the cases were reported from the United States (84.5%), followed by Canada (6.0%) and other countries (4.7%). Apart from the category of Other serious event, the most common outcome of both groups was hospitalization (17.2% in long-term hormone treatment group and 9.8% in the control group), and disability came in second (3.6% and 2.6%, respectively).

Table 1 Baseline Characteristics of Patients with Endometriosis

	Long-Term Hormone Treatments n = 1823	**Other Drugs n = 6247**
Age (years)		
<18	45 (2.5%)	92 (1.5%)
≥18, <50	1200 (65.8%)	3432 (54.9%)
≥50	34 (1.9%)	128 (2.0%)
Not specified	544 (29.8%)	2595 (41.5%)
Received Year		
2014	286 (15.7%)	1364 (21.8%)
2015	509 (27.9%)	1346 (21.5%)
2016	182 (10.0%)	711 (11.4%)
2017	154 (8.4%)	450 (7.2%)
2018	168 (9.2%)	364 (5.8%)
2019	171 (9.4%)	912 (14.6%)
2020	210 (11.5%)	735 (11.8%)
2021	143 (7.8%)	365 (5.8%)
Country		
United States	1368 (75.0%)	5278 (84.5%)
France	59 (3.2%)	53 (0.8%)
Brazil	55 (3.0%)	22 (0.4%)
Japan	50 (2.7%)	39 (0.6%)
United Kingdom	41 (2.2%)	68 (1.1%)
Canada	32 (1.8%)	372 (6.0%)
Other countries	177 (9.7%)	293 (4.7%)
Missing	41 (2.2%)	122 (2.0%)
Reporter		
Consumer	1179 (64.7%)	4395 (70.4%)
Health professional	582 (31.9%)	1738 (27.8%)
Lawyer	17 (0.9%)	18 (0.3%)
Missing	45 (2.5%)	96 (1.5%)
Outcome		
Hospitalization	314 (17.2%)	614 (9.8%)
Disability	66 (3.6%)	160 (2.6%)
Life-threatening	44 (2.4%)	59 (0.9%)
Death	13 (0.7%)	32 (0.5%)

(*Continued*)

Table 1 (Continued).

	Long-Term Hormone Treatments n = 1823	Other Drugs n = 6247
Required intervention	3 (0.2%)	6 (0.1%)
Congenital anomaly	2 (0.1%)	9 (0.1%)
Other serious events	678 (37.2%)	1873 (30.0%)
Missing	703 (38.6%)	3494 (55.9%)

Disproportional Analysis

In both COC and progestin groups, the most prevalent PT was off label use (N = 130 in the COC group, and N = 119 in progestin group), followed by product use in unapproved indication (N = 102 in the COC group, and N = 55 in progestin group). However, these 2 PTs were not overreported in progestin users (EB05 were 1.6 and 1.3, respectively). Overreported PTs among COC users were more diverse, while PTs among progestin users were mainly under the SOCs of injury, poisoning and procedural complications and product issues. Signals of some uncommon adverse events including eye disorders and nervous system disorders were detected, too (Table 2).

Disproportional analysis was also performed in different dosage forms of progestin (Table 3). All signals detected in overall progestin users were specified in subgroups, and signals of some new adverse events such as cardiac disorders, gastrointestinal disorders, metabolism and nutrition disorders, and musculoskeletal disorders emerged in subgroup

Table 2 Preferred Terms of Overreported Adverse Events and Medical Errors of Endometriosis Patients Receiving Long-Term Hormone Treatment

SOC	PT	Combined Oral Contraceptive		Progestin	
		No.	EBGM (EB05, EB95)	No.	EBGM (EB05, EB95)
Eye disorders	Atopic keratoconjunctivitis	5	12.7 (2.5, 28. 8)*	0	/
Injury, poisoning and procedural complications	Device use issue	0	/	32	6.0 (4.4, 8.0)*
	Injury	11	6.1 (2.5, 10.8)*	3	0.8 (0.4, 1.4)
	Off label use	130	5.4 (4.6, 6.2)*	119	1.8 (1.6, 2.1)
	Off label use of device	0	/	42	6.0 (4.6, 7.7)*
	Procedural pain	0	/	33	3.7 (2.5, 5.3)*
	Product use in unapproved indication	102	8.1 (6.8, 9.5)*	55	1.6 (1.3, 1.9)
	Product use issue	32	5.2 (3.7, 7.0)*	42	2.3 (1.8, 3.0)
Nervous system disorders	Hemiplegia	5	12.7 (2.5, 28.8)*	0	/
	Uhthoff's phenomenon	5	12.7 (2.5, 28.8)*	0	/
Product issues	Device dislocation	0	/	22	5.5 (3.5, 8.0)*
	Product quality issue	21	8.7 (6.0, 12.3)*	4	0.7 (0.4, 1.2)
	Product substitution issue	19	11.5 (7.7, 16.5)*	1	0.5 (0.2, 1.0)
Psychiatric disorders	Libido increased	7	8.4 (2.3, 17.0)*	0	/

(*Continued*)

Table 2 (Continued).

SOC	PT	Combined Oral Contraceptive		Progestin	
		No.	EBGM (EB05, EB95)	No.	EBGM (EB05, EB95)
Reproductive system and breast disorders	Genital haemorrhage	2	0.8 (0.4, 1.6)	34	5.5 (4.0, 7.3)*
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	49	10.3 (8.0, 13.0)*	10	0.8 (0.5, 1.2)
Vascular disorders	Deep vein thrombosis	36	10.8 (8.1, 14.1)*	6	0.7 (0.4, 1.2)

Note: *EB05 ≥ 2.

Table 3 Preferred Terms of Overreported Adverse Events and Medical Errors of Endometriosis Patients Receiving Different Dosage Forms of Progestin

a Preferred terms of overreported adverse events and medical errors of patients receiving oral progestin			
SOC	PT	No.	EBGM (EB05, EB95)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatic adenoma	14	4.8 (2.3, 8.1)*
	Meningioma	11	7.4 (4.0, 12.3)*
Nervous system disorders	Ulnar tunnel syndrome	11	8.2 (4.6, 13.4)*
b Preferred terms of overreported adverse events and medical errors of patients receiving progestin-eluting IUD			
Gastrointestinal disorders	Abdominal pain lower	28	9.3 (6.7, 12.5)*
General disorders and administration site conditions	Complication of device insertion	6	24.1 (11.5, 46.0)*
	Complication of device removal	7	20.2 (10.2, 36.7)*
	Feeling hot	10	5.7 (2.2, 10.4)*
Infections and infestations	Uterine infection	5	22.7 (9.9, 46.5)*
Injury, poisoning and procedural complications	Device use issue	32	30.9 (22.9, 41.1)*
	Off label use	59	4.8 (3.8, 5.9)*
	Off label use of device	42	31.1 (23.9, 39.9)*
	Post procedural haemorrhage	11	20.5 (12.1, 33.1)*
	Procedural pain	30	19.4 (14.2, 26.0)*
Metabolism and nutrition disorders	Abnormal weight gain	7	16.9 (8.5, 30.7)*
Pregnancy, puerperium and perinatal conditions	Pregnancy with contraceptive device	4	16.0 (2.9, 39.1)*
Product issues	Device breakage	5	12.9 (4.0, 28.2)*
	Device dislocation	19	25.2 (17.0, 36.4)*
	Device expulsion	15	20.7 (13.2, 31.2)*
	Embedded device	9	24.0 (13.3, 40.7)*

(*Continued*)

Table 3 (Continued).

Psychiatric disorders	Anhedonia	7	15.6 (7.8, 28.4)*
	Loss of libido	12	12.5 (7.5, 19.8)*
Reproductive system and breast disorders	Galactorrhoea	7	16.9 (8.5, 30.7)*
	Genital haemorrhage	26	21.7 (15.5, 29.7)*
c Preferred terms of overreported adverse events and medical errors of patients receiving depot progestin			
Cardiac disorders	Mitral valve prolapse	4	36.3 (14.0, 80.4)*
Eye disorders	Chromatopsia	3	53.4 (16.9, 136.1)*
	Ocular discomfort	3	32.6 (8.5, 88.0)*
Gastrointestinal disorders	Anal incontinence	3	53.4 (16.9, 136.1)*
	Constipation	10	7.4 (3.7, 12.7)*
General disorders and administration site conditions	Condition aggravated	8	6.9 (2.3, 13.3)*
	Feeling hot	1	0.9 (0.4, 1.9)
Injury, poisoning and procedural complications	Drug dose omission by device	4	41.8 (16.3, 92.4)*
	Face injury	3	53.4 (16.9, 136.1)*
	Incorrect dose administered by device	4	49.3 (19.3, 108.7)*
	Prescribed overdose	4	28.4 (10.8, 63.8)*
	Product administration error	5	46.9 (20.6, 94.8)*
	Product dose omission issue	6	34.6 (16.5, 65.9)*
	Product use in unapproved indication	15	5.3 (2.8, 8.5)*
Investigations	Heart rate irregular	4	17.4 (4.7, 41.8)*
Metabolism and nutrition disorders	Decreased appetite	10	6.3 (2.5, 11.2)*
Musculoskeletal and connective tissue disorders	Bone disorder	6	22.3 (10.6, 42.5)*
	Osteopenia	9	23.6 (13.1, 40.0)*
Nervous system disorders	Autonomic nervous system imbalance	4	41.8 (16.3, 92.4)*
	Judgement impaired	3	53.4 (16.9, 136.1)*
	Motor dysfunction	3	32.6 (8.5, 88.0)*
	Small fibre neuropathy	4	59.9 (23.5, 131.8)*
Product issues	Device occlusion	4	31.9 (12.2, 71.1)*
	Needle issue	7	59.7 (30.2, 108.3)*
	Syringe issue	5	53.9 (23.7, 109.0)*
Psychiatric disorders	Communication disorder	3	53.4 (16.9, 136.1)*
Respiratory, thoracic and mediastinal disorders	Throat tightness	5	22.7 (9.9, 46.5)*

(*Continued*)

Table 3 (Continued).

Social circumstances	Mental disability	3	53.4 (16.9, 136.1)*
d Preferred terms of overreported adverse events and medical errors of patients receiving progestin implant			
General disorders and administration site conditions	Complication associated with device	3	56.4 (18.0, 143.4)*
	Implant site pain	4	122.2 (47.9, 268.4)*
	Implant site paraesthesia	2	69.7 (7.9, 251.4)*
Injury, poisoning and procedural complications	Incorrect product administration duration	5	92.2 (40.5, 186.4)*
	Product use in unapproved indication	11	10.1 (5.9, 16.4)*
	Product use issue	6	10.4 (3.4, 21.2)*
	Neuralgia	5	36.3 (15.9, 73.4)*
Product issues	Device dislocation	3	14.5 (1.3, 49.2)

Note:*EB05 ≥ 2.

analysis. Among oral progestin users, only PTs of hepatic adenoma (N = 14, EB05 = 2.3), meningioma (N = 11, EB05 = 4.0), and ulnar tunnel syndrome (N = 11, EB05 = 4.6) were overreported. PTs belonging to injury, poisoning and procedural complications and product issues were mainly reported among progestin-eluting IUD users and depot progestin users. Besides, plenty of nervous system disorders occurred in the depot progestin subgroup. Most over-reported PTs in the progestin implant subgroup were under the SOC of general disorders and administration site conditions.

Risk Factors for Overreported Events

Logistic regression analysis indicated that among adverse events or medical errors that happened over 20 times, polytherapy was negatively associated with off label use (adjusted OR = 0.47, 95% CI 0.22−0.94) and product use in unapproved indication (adjusted OR = 0.36, 95% CI 0.15−0.76) for COC users. COC users aged greater than or equal to 30 were less likely to have product use issue (adjusted OR = 0.33, 95% CI 0.12−0.82) but were at higher risk of pulmonary embolism (adjusted OR = 4.04, 95% CI 1.35−17.43). Meanwhile, age greater than or equal to 30 and polytherapy seemed to have no statistical association with adverse events or medical errors in progestin-eluting IUD users. Detailed data are presented in Table 4.

Table 4 Logistic Analysis of Patients with Common Adverse Events and Medical Errors

Event	AEs of Interest	Other AEs	Crude OR (95% CI)	Adjusted OR (95% CI)
Combined oral contraceptive				
Deep vein thrombosis				
Age ≥ 30	15	197	2.89 (0.93, 12.68)	2.82 (0.90, 12.36)
Age <30	3	114		
Polytherapy	3	103	0.32 (0.08, 0.91)	0.51 (0.12, 1.61)
Monotherapy	33	362		

(*Continued*)

Table 4 (Continued).

Event	AEs of Interest	Other AEs	Crude OR (95% CI)	Adjusted OR (95% CI)
Off label use				
Age ≥ 30	38	174	1.06 (0.59, 1.95)	1.02 (0.57, 1.89)
Age <30	20	97		
Polytherapy	14	92	0.37 (0.19, 0.65)	0.47 (0.22, 0.94)
Monotherapy	116	279		
Product quality issue				
Age ≥ 30	8	204	0.73 (0.25, 2.25)	0.71 (0.24, 2.21)
Age < 30	6	111		
Polytherapy	3	103	0.61 (0.14, 1.85)	0.67 (0.15, 2.20)
Monotherapy	18	377		
Product use in unapproved indication				
Age ≥ 30	33	179	0.75 (0.42, 1.37)	0.72 (0.40, 1.31)
Age < 30	23	94		
Polytherapy	10	96	0.34 (0.16, 0.66)	0.36 (0.15, 0.76)
Monotherapy	92	303		
Product use issue				
Age ≥ 30	8	204	0.34 (0.13, 0.86)	0.33 (0.12, 0.82)
Age < 30	12	105		
Polytherapy	3	103	0.37 (0.09, 1.06)	0.40 (0.09, 1.23)
Monotherapy	29	366		
Pulmonary embolism				
Age ≥ 30	21	191	4.18 (1.40, 17.97)	4.04 (1.35, 17.43)
Age < 30	3	114		
Polytherapy	4	102	0.31 (0.09, 0.77)	0.36 (0.08, 1.08)
Monotherapy	45	350		
Progestin-eluting IUD				
Abdominal pain lower				
Age ≥ 30	14	112	0.85 (0.35, 2.14)	0.90 (0.37, 2.29)
Age < 30	9	61		
Polytherapy	0	13	0	0
Monotherapy	28	214		
Device use issue				
Age ≥ 30	15	111	0.92 (0.38, 2.30)	0.90 (0.37, 2.29)

(*Continued*)

Table 4 (Continued).

Event	AEs of Interest	Other AEs	Crude OR (95% CI)	Adjusted OR (95% CI)
Age < 30	9	61		
Polytherapy	1	12	0.57 (0.03, 3.03)	1.25 (0.06, 8.10)
Monotherapy	31	211		
Genital haemorrhage				
Age ≥ 30	11	115	0.86 (0.32, 2.44)	0.92 (0.34, 2.60)
Age < 30	7	63		
Polytherapy	0	13	0	0
Monotherapy	26	216		
Off label use				
Age ≥ 30	27	99	0.92 (0.46, 1.89)	0.99 (0.49, 2.03)
Age < 30	16	54		
Polytherapy	0	13	0	0
Monotherapy	59	183		
Off label use of device				
Age ≥ 30	17	109	0.62 (0.29, 1.37)	0.62 (0.28, 1.38)
Age < 30	14	56		
Polytherapy	1	12	0.41 (0.02, 2.16)	1.07 (0.05, 6.87)
Monotherapy	41	201		
Procedural pain				
Age ≥ 30	17	109	1.21 (0.51, 3.11)	1.29 (0.54, 3.33)
Age < 30	8	62		
Polytherapy	0	13	0	0
Monotherapy	30	212		

Discussion

By reviewing FAERS data, this study comprehensively described reports of endometriosis patients treated with COCs and progestin on adverse event signals overall and in different dosage form subgroups. We also explored the possible effects of age and polytherapy on frequently reported adverse events.

During hormone treatment for endometriosis, change in hormone levels can lead to hormone-related adverse events. Besides, lifestyle and diet may affect symptoms, too.[25] The broad spectrum of PTs detected in this study may result from individual variation in ER-alpha and PR distributions.[26] It is reported that for patients with endometriosis who are intolerant of COC or norethisterone acetate's side effects, shifting one to the other could improve their satisfaction.[27] Since patients suffering from adverse effects of one drug may benefit from another, the regimen they receive should be adjusted in time once intolerable.

Common side effects of COC and progestins include bleeding, mastodynia, psychological disorders, weight gain, constipation, emotional fluctuation, galactorrhoea, thrombosis, decreased bone mineral density, libido changes,

meningioma, hepatocellular adenoma, and some androgenic symptoms.[28–37] In this study, signals of similar PTs as well as their secondary outcomes: genital haemorrhage, mental disability, abnormal weight gain, constipation, pulmonary embolism, deep vein thrombosis, hemiplegia, bone disorder, osteopenia, loss of libido, libido increased, anhedonia, meningioma, and hepatic adenoma were detected by proportional analysis. Since there was no true control in our study, some minor discrepancies lied between this pharmacovigilance research and previous clinical trials.

Some medical therapies for endometriosis aim to create a hypoestrogenic environment to delay disease progression,[26] leading to menopause-like side effects. While GnRH-analogues and aromatase inhibitors are well known for their hypoestrogenic effects,[38,39] the effects of COC and progestins vary in different age groups and dosages.[40,41] Several studies indicated that oral progestin and progestin-eluting IUDs had an unapparent hypoestrogenic effect,[42] except that DMPA users may encounter more menopausal symptoms.[40,43,44] In this study, we detected signals of heart rate irregular, bone disorder, osteopenia, and autonomic nervous system imbalance in depot progestin users. Signals of feeling hot, abnormal weight gain, and loss of libido were detected in progestin-eluting IUD users as well. To determine the effect of different dosage forms of progestin on estrogen level, further researches with larger sample size need to be conducted. Besides, the signal of decreased appetite was detected in depot progestin users in this study. Since progestin metabolites have been reported to modulate GABA-A receptors directly rather than lowering estrogen levels to regulate appetite and mood,[45] exact mechanisms behind the effect of progestins remain to be further investigated.

We detected plenty of signals about procedural complications, product issues, and administration site conditions as well as their potentially secondary PT: abdominal pain lower. But no signal of more serious PTs such as uterine perforation or fat necrosis was detected. Perforation rates of levonorgestrel-releasing intrauterine systems (LNG-IUS) and copper IUDs in the literature were both approximately 1/1000,[46] which is relatively low. And relevant fat necrosis was only reported in a case report.[47] Lactation, atrophic uterus due to long-term administration of depot injectables, and mismatch between uterine cavity size and the size of the IUD could be risk factors for IUD dislocation.[48] As infection remains a considerable cause of withdrawal from IUD use,[49,50] and the reasons for these events are clear, they may be avoided by comprehensively assessing the patient's condition, standardizing procedures, and improving perioperative care.

In this study, we found that the PT spectrum varied in different dosage forms of progestin. Therefore, patients' tolerance should be considered before regimen recommendation. When choosing among these long-term hormone treatments with contraceptive effects, patients' fertility desires should be taken into account, too. The techniques of ovarian stimulation and egg freezing have been quite advanced[51,52] and have been applied in the early stage of malignancy.[53–55] Especially in cases of ovarian endometrioma that requires surgical intervention, fertility-sparing procedures and fertility preservation should be included in the therapy plan.

There were signals of some uncommon adverse effects, too. This study identified increased risk of meningioma with oral progestin treatment. Estrogen receptors (ER) and progesterone receptors (PR) are both expressed in meningioma tissue,[56,57] the association between progestin and meningioma remains to be explored in large-sample clinical trials.

We found that atopic keratoconjunctivitis (AKC) and ocular discomfort cases were elevated in COC users (EB05 = 2.5). As an allergic conjunctival disease, inflammatory cells play an important role in the pathophysiology of AKC.[58] Estrogen and progesterone receptors have been found positive in conjunctival biopsies from vernal keratoconjunctivitis (VKC), which is another subtype of the allergic conjunctival disease, and the majority of positive cells were eosinophils.[59] Therefore, it is possible that the altered sex hormone level of COC users is related to AKC, which should raise concerns in future clinical practice and research.

Other nonspecific PTs, such as Uhthoff's phenomenon, ulnar tunnel syndrome, mitral valve prolapse, chromatopsia, throat tightness, and mental disability were also detected in this study. None of them has reported relationship with sex hormones. A study which included more than 4000 patients with surgically diagnosed endometriosis reported no higher mitral valve prolapse prevalence in endometriosis patients than in general population.[60] These nonspecific signals were detected possibly because of some underlying pathophysiological mechanisms or even entry errors. Though some of them may have already existed before drug administration, they still require proper treatment.

Product use issue in COC users was associated negatively with user's age older than 30, which was observed on similar PTs of off label use and product use issue in unapproved indication. It is estimated that pregnancies caused by

incorrect use of contraceptives are 9 times the rate of pregnancies with perfect use of contraceptives.[61,62] There are over 1 million unintended pregnancies associated with the use, misuse, or discontinuation of oral contraceptives each year in the United States.[63] In a national survey involving almost 2000 women in 2004,[61] almost all oral contraceptive users set a daily reminder about taking the pill, but 38% had missed at least one pill within 3 months before the survey. In different age subgroups, users younger than 24 years old had a higher inconsistent use rate than older participants, too.[61] Another study focusing on college and graduate students demonstrated that stress, long hours of paid employment, and living with a sex partner were associated positively with missed doses.[64] As our study also revealed age-related differences in drug adherence, possible hidden factors behind the age, such as understanding of contraception, work/study pressure, medical insurance status, should be considered in future research.

We also found that age greater or equal to 30 was associated positively with pulmonary embolism in COC users. Age as a risk factor for thrombosis in COC users has been the consensus of medical professionals.[32,33,65] Unfortunately, our regression analysis failed to demonstrate more associations between drug users' characteristics and adverse events. Much of the age information of cases in our study was missing, resulting in a very limited number of valid data for regression analysis. The numbers of some drug-event pairs were inadequate for regression analysis, too. Due to these sampling errors, the results of regression analysis may not reflect the true situation of all patients with endometriosis in FAERS.

The FAERS provides sufficient reports from multiple countries for pharmacovigilance research. Not only manufacturers but also healthcare practitioners and users can report adverse events and medical errors to the FAERS. The MedDRA terminology helps to standardize the description of adverse events and diagnoses, making it easier for researchers to process and summarize these real-world data in batches. Meanwhile, this FAERS-based pharmacovigilance study has some drawbacks, too. Firstly, some identical events might be reported as similar but different PTs such as off label use and off label use of device according to the reporter's understanding of the MedDRA terminology. Some other events which were different might be coded as the same general PT. For example, "libido decreased" and libido increased could both be coded as libido disorder. These coding inaccuracies could lead to imprecise results of statistical analysis. Secondly, one PT may have multiple different SOCs. MedDRA terminology has assigned a primary SOC for each PT.[66] In this study, we grouped PTs by their primary SOCs. However, primary SOC may only indicate manifestation site rather than aetiology of the PT in some circumstances, which may mislead pathophysiological investigations. For example, the primary SOC of throat tightness is respiratory, thoracic and mediastinal disorders, while its secondary SOC is psychiatric disorders. These two SOCs are quite different. Thirdly, demographic information and detailed clinical records of these reports were limited for regression analysis, and existing variables including age had lots of missing values. Therefore, the regression analysis in our research could only yield preliminary results. Fourthly, information about drug or medical device users who never encounter any adverse event or medical error cannot be accessed from the FAERS, leaving it impossible to calculate the rates of the events. What is more, submitting reports by consumers, patients and health professionals are not mandatory, leaving some events missed by the FAERS. Reporting awareness of consumers, patients and healthcare professionals should be encouraged so that more comprehensive information can be collected.

Conclusion

Both COCs and progestin products are relatively safe for patients with endometriosis. Polytherapy was negatively associated with some medical errors for COC users, while patients older than or equal to 30 had more pulmonary embolisms, but fewer product use issues were reported. Newly detected signals in this pharmacovigilance study should be monitored in clinical practice and need to be validated in future research. When choosing hormone treatment regimens, gynaecologists should consider the patient's satisfaction and fertility desire, and assess efficacy, costs, and side effects comprehensively.

Abbreviations

COC, combined oral contraceptive; GnRH, gonadotropin-releasing hormone; FDA, US Food and Drug Administration; FAERS, the FDA Adverse Event Reporting System; PT, preferred term; MedDRA, Medical Dictionary for Regulatory

Activities; IUD, intrauterine device; GPS, Gamma-Poisson Shrinker; EBGM, Empirical Bayes Geometric Mean; CI, confidence interval; SOC, System Organ Class; DMPA, depot medroxyprogesterone acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; PRL, prolactin; ER, estrogen receptor; PR, progesterone receptor; AKC, atopic kerato-conjunctivitis; VKC, vernal keratoconjunctivitis.

Data Sharing Statement

All raw data used in this study have been released on FAERS website (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files) and are available to the public.

Ethics Approval and Informed Consent

Exemption from the ethical review has been granted by the Ethics Committee of Shanghai First Maternity and Infant Hospital since the FAERS is an anonymized publicly available database.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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