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Original Research

Clinical application and economics of five short-acting combined oral contraceptives over five years of obstetrics and gynecology practice in China based on real-world study

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Summary

Objective: We aimed to better understand the clinical application and economics of five commonly used combined oral short-acting contraceptives (COCs) by analyzing big data collected from an obstetrics and gynecology hospital in China. The COCs studied included desogestrel ethinyl estradiol tablets (DSE), which was administered at a dose of 20 or 30 μg ethinyl estradiol, ethinyl estradiol cyproterone tablets (ECP), drospirenone ethinyl estradiol tablets (DRE; 21 pills/box), and drospirenone ethinyl estradiol tablets (II; 28 pills/box). *Methods:* This retrospective study included patients who were prescribed COCs from 2014-2018 in our obstetrics and gynecology hospital, which is affiliated with Fudan University. We analyzed patient characteristics, clinical indications, drug costs, and types of drugs often prescribed with COCs to identify factors influencing medication choice and use. *Results:* Data from 127,183 patients using COCs was analyzed. The most commonly prescribed COCs was ECP, accounting for 64.16% of all COCs use, while DRE was the second most commonly prescribed (23.13%). Most patients were 21- to 30-year-old (56.82%). ECP, DSE (30 μg), and DRE were most commonly used in the treatment of menstrual disorders, while DRE (II) was more frequently used for contraception. The second most common indication for DSE (30 μg) use was endometriosis, while it was polycystic ovary syndrome (PCOS) for ECP and DRE. DSE (20 μg) was used by only two patients in our study. The per capita cost of either dose of DSE was low: 34.95 $\pm$ 5.34 RMB for the 30 μg dose and 62.56 $\pm$ 0.00 RMB for the 20 μg dose. ECP was the second most affordable at a cost of 82.81 $\pm$ 10.63 RMB, while DRE and DRE (II) were considerably more expensive at 186.88 $\pm$ 23.88 and 265.98 $\pm$ 22.12 RMB, respectively. The rank of the total cost of therapeutic drugs per capita was similar to that of COCs per capita. Either dose of DSE was cheapest, followed ECP. Again, DRE and DRE (II) were the most expensive. Metformin hydrochloride was the mostly commonly drug prescribed in conjunction with ECP; 39.89% of patients took both medications. Spironolactone tablets, other hormonal agents, and various Chinese patent medicines were also commonly prescribed with a COC. *Conclusion:* The main clinical indication for the prescription of COCs in our hospital has not been contraception, rather menstrual disorders and conditions characterized by excess androgen (e.g. PCOS). ECP entered the market the earliest in China, it is approved for the greatest number clinical indications, and it appears in the medical insurance catalogue of China. Thus, it is the most widely used COCs in China. In addition to contraception, it is also widely used to treat polycystic ovary syndrome and endometriosis. However, the 30 μg dose of DSE is the most affordable in regards to total list price, and it is used for menstrual disorders, endometriosis, and contraception.

Key Messages

COCs are widely used in obstetrics and gynecology hospitals. They are not only a reliable method of contraception, but in China they are even more widely used to treat or manage a variety of other conditions. A total of five COCs are commonly used; each has advantages and disadvantages in regards to cost, when they were introduced in China, their presence in the medical insurance catalog, and the conditions they are commonly used to treat. At present, there are few published studies focusing on the clinical applications and economics of COCs in actual practice. In this study, we used "big" clinical data to explore the indications for use and drug economy of these key COCs. We thereby aimed to understand the decision-making process that occurs between doctor and patient to provide a theoretical basis for optimal treatment and resource allocation, while reducing the economic burden.

Based on this data, we determined that compared to the available alternatives, ECP is the most commonly prescribed form of COC, which is most familiar to frontline Gynecologists and Obstetricians while possessing the widest range of approved clinical indications. Although the 30 μg dose of DSE is the most affordable, ECP runs a close second. Combined with its other attributes, it is not surprising ECP is widely prescribed.

Key words: Medication; Compound short-acting oral contraceptives; Obstetrics and gynecology; Big data.

Introduction

Since Pincus first used a combination of estrogen and progesterone as a compound oral contraceptive in 1958, combined short-acting oral contraceptives (COCs) have become one of the most commonly used forms of contraception worldwide. Complex steroid hormone preparations containing low doses of estrogen and progesterone are used most often clinically. Estrogen is usually provided as ethinyl estradiol, while the progesterone component can

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Table 1. — *Basic information for routinely used COCs.*

Name	Specification	Medical insurance	Listing year	Manufacturer
DSE (30 μg)	21 tablets/box	self-expenditure	1993	Organon
DSE (20 μg)	21 tablets/box	self-expenditure	2009, 2015 renamed	Organon
ECP	21 tablets/box	Medical insurance (Type B, 20%)	1991	Bayer
DRE	21 tablets/box	self-expenditure	2009	Bayer
DRE(II)	28 tablets/box	self-expenditure	2015	Bayer

Note: (1) The National Drug Catalog of Basic Medical Insurance in China divides medicines into three categories as follows: 1) category A, which is fully covered by medical insurance reimbursement, 2) category B, which requires the patient pays a specified portion of the drug cost, and 3) category C, which must be covered entirely by the patient. (2) "Category A" drugs are necessary for clinical treatment. They are widely used, have curative effects, and have lower prices among similar drugs; they are formulated by the state and cannot be adjusted. The expenses incurred for the use of "Category A drugs" are based on basic medical insurance payment. (3) "Category B" drugs are available for clinical treatment and have good efficacy. The prices of similar drugs are slightly higher than "Category A" drugs. "Category B drugs" are formulated by the state, and provinces, cities, and districts set the price based on economic levels and medical needs. It should be adjusted appropriately, but should not exceed the formulate "Category B drugs" formulated by the state. (4) Among the COCs discussed in this article, only **ECP** is covered by medical insurance as a Category B drug. The patient pays 20%, and the remaining 80% is paid by the state.

Table 2. — *Numberof COCs prescribed by year from 2014 to 2018.*

Name	2014	2015	2016	2017	2018	Sum	Percentage
ECP	14446	15084	17591	17065	17417	81603	64.16%
DRE	5062	4926	6236	5844	7350	29418	23.13%
DSE (30 μg)	5459	5182	1664	1882	0	14187	11.15%
DRE (II)	0	0	0	42	1931	1973	1.55%
DSE (20 μg)	1	1	0	0	0	2	0.00%
Sum	24968	25193	25491	24833	26698	127183	100.00%

vary, hence the variety of COCs available. However, exogenous hormone use has some negative effects, especially as first introduced. Over the past 30 years, the concentrations of estrogen and progesterone have been reduced, and the formula has been improved, which has reduced the occurrence of side effects and cardiovascular complications [1, 2].

The COCs in our existing catalogue include the following: 30 μg desogestrel ethinyl estradiol (DSE) tablets containing 30 μg ethynyl estradiol and 150 μg desogestrel, 20 μg DSE tablets containing 20 μg ethynyl estradiol and 150 μg desogestrel, ethinyl estradiol cyproterone (ECP) tablets containing 35 μg ethynyl estradiol and 2000 μg cyproterone, drospirenone ethinyl estradiol (DSE) tablets containing 30 μg ethynyl estradioland 3000 μg drospirenone, and DSE tablets (II) containing 20 μg ethynyl estradiol and 3000 μg drospirenone. All of the COCs in this study came in packages with 21 pieces/box, except DRE (II), which was provided as 28 pieces/box. With routine and correct use, COCs can reach as high as 99% effectiveness in preventing pregnancy. According to the WHO, the main reason for contraception failure is irregular use (e.g. taking a different times during the day) and missed doses. COCs are not only a reliable method of contraception, but they have numerous other indicated uses [2, 3]. Among the commonly prescribed COCs, several factors can vary, such as drug composition, when the drug was introduced in China, cost, presence in the medical insurance catalog, and clinical reason(s) for use. There is a lack of studies on both the use and economics of COCs in China. Here, we examined outpatient electronic medical record data from the Obstetrics and Gynecology Hospital of Fudan University from January 2014 to December 2018. We examined "big" clinical data to better elucidate the typical reason for prescription and the economic burden associated with each COC. This information should provide a theoretical basis to optimize treatment effectiveness and resource allocation, while reducing the overall economic burden experienced by patients.

Materials and Methods

General information

Using the electronic medical record system of the Obstetrics and Gynecology Hospital affiliated with Fudan University, we identified and enrolled patients in our study who used COCs from January 2014 to December 2018.The study was conducted in accordance with the ethical stan-

dards of the Helsinki Declaration, and the Ethics committee of Obstetrics and Gynecology Hospital affiliated with Fudan University approved this study design, the number was kyy2019-96.

Inclusion criteria

We included patients meeting the following criteria: 1) outpatients who were treated in our hospital, 2) patients prescribed DSE (30 μg), DSE (20 μg), ECP, DRE, or DRE (II), and 3) patients with sex hormone test records.

Exclusion criteria

We excluded the following: 1) breastfeeding mothers, 2) patients with a history of cardiovascular disease, 3) patients with neurological diseases, such as migraine, 4) patients with rheumatic diseases, such as antiphospholipid antibody positive or unexplained systemic lupus erythematosus (SLE), 5) patients with breast cancer, and 6) patients with a history of diabetes lasting greater than 20 years or combined with renal disease or other vascular lesions [2]. The data were collected from the hospital's electronic medical record system, which included patient data (e.g. age, clinical diagnosis, medication status, other medication use) and cost information. The patients were divided into five groups according to the COC used.

Data collection

Medical record numbers, age, medical information, clinical diagnosis, COC usage and dosage, other medication usage, and medication costs were recorded and analyzed.

Observation indicators

Patients were typically prescribed COCs based on clinical diagnoses. To facilitate analysis, diagnostic information was standardized. Economic considerations included the cost of using COCs and the total cost of treatment.

Statistical analysis

We used SPSS 18.0 software to analyze the data. Count data was used for descriptive purposes. A two-sample *t*-test was used for comparison between groups. Count data are presented as a percentage table, and Fisher's exact test was used for comparison between groups. $p < 0.05$ was considered statistically significant. Excel 2007 was used for plotting figures.

Results

Basic information

Four of the COCs in this study were supplied as 21 pieces/box, with the exception of DRE (II), which was supplied as 28 pieces/box. When using a COC supplied as 21 days of pills, a 7-day interval should be observed before starting another 21-day supply, while COCs supplied as 28 pieces/box are to be taken continuously without a pill-free interval. The first COC to be introduced in China was ECP in 1993. DRE (II), on the other hand, was the most recently introduced COC of the five studied here. Of the five COCs, only ECP is listed in the medical insurance catalog. The other four were used at the patient's expense with no medical insurance reimbursement or coverage (see Table 1).

Use of COCs

A total of five COCs were used in our study population. ECP was the most frequently used, followed by DRE and DSE (30 μg). DRE (II) and DSE (20 μg) were even less frequently used, especially DSE (20 μg). The details of usage are summarized in Table 2.

Table 3. — *Age distributions of COC users from 2014 to 2018.*

Age	Count	Percentage
≤ 10	25	0.02%
11-20	11117	8.74%
21-30	72262	56.82%
31-40	33913	26.66%
41-50	8963	7.05%
51-60	877	0.69%
61-70	23	0.02%
71-90	3	0.00%
Sum	127183	100.00%

Characteristics of the study population

Patient ages largely ranged from 11- to 40-years-old (92.22%), while most patients were 21 to 30-years-old (56.82%). The most commonly prescribed single age in this age bracket was 27-years-old (7.47%). The second most common age range included patients that were 31 to 40-years-old (26.66%). The percentage of patients between 11- and 20-year-old was 8.74% (Table 3).

Clinical indications analysis

The most common clinical indication for the use of ECP, DSE (30 μg), or DRE was menstrual disorders. The second most common condition treated by DSE (30 μg) was endometriosis, while PCOS was the second most common condition for which ECP or DRE were prescribed. DSE (20 μg) was used in only 2 patients. DRE (II) was used for contraception, menstrual disorders, and endometriosis. Details on clinical diagnoses can be found in Table 4.

Analysis of treatment costs

Over the five years studied, combined drug use increased each year, and the total cost of the medication also increased. Using other drugs in combination with COCs affects the total cost per capita. Table 5 shows the per capita COC cost for outpatients in the whole hospital from 2014 to 2018, while Table 6 shows a summary of the total drug cost per capita, which reflects costs when a combination of drugs is used. The total cost of either DSE dosage was lowest, followed by ECP, DRE, and DRE (II) (Tables 5 and 6).

Table 4. — *Clinical diagnoses.*

ECP			DSE (30 μg)			DRE			DRE (II)			DSE (20 μg)		
Diagnosis	Count	Percentage (%)	Diagnosis	Count	Percentage (%)	Diagnosis	Count	Percentage (%)	Diagnosis	Count	Percentage (%)	Diagnosis	Count	Percentage (%)
Menstrual disorder	46962	36.92	Menstrual disorder	8180	6.43	Menstrual disorder	8180	6.43	Contraception	468	0.37	Adenomyosisl of uterus		0
polycystic ovarian syndrome	22644	17.8	Endometriosis	1352	1.06	Polycystic ovarian syndrome	5085	4.00	Menstrual disorder	461	0.36	Contraceptionl		0
Female infertility	3103	2.44	Female infertility	898	0.71	Contraception	5028	3.95	Endometriosis	265	0.21			
Endometrial hyper-plasia	1162	0.91	Adenomyosis of uterus	568	0.45	Endometriosis	4178	3.29	polycystic ovarian syndrom	167	0.13			
Endometriosis	983	0.77	Polycystic ovarian syndrome	514	0.4	Other post-operative status	2428	1.91	Other post-operative status	131	0.10			
Ovarianandrogen overproduction	866	0.68	Other post-operative status	432	0.34	Adenomyosis of uterus	1207	0.95	Adenomyosis of uterus	92	0.07			
Adenomyosis of uterus	492	0.39	Adenomyosis of uterus	305	0.24	Endometrial hyperplasia	577	0.45	Pregnancy	49	0.04			
Irregular vaginal bleeding	446	0.35	Endometrial hyperplasia	295	0.23	Female infertility	532	0.42	Uterine diverticulum	47	0.04			
Menstruation is rare	439	0.35	Contraception	185	0.15	Uterine di-verticulum	295	0.23	Abnormal uterine bleeding	33	0.03			
Abnormal uterine bleeding	424	0.33	dysmenorrhea	164	0.13	Abnormal uterine bleeding	279	0.22	Female infertility	26	0.02			
Contraception	401	0.32	Dysfunctional uterine bleeding	132	0.10	Dysmenorrhea	180	0.14	Gynecological examination	16	0.01			
Hyperinsulinemia	370	0.29	Irregular vaginal bleeding	90	0.07	Hypofunction of ovary	132	0.10	insulin resistance	16	0.01			
Other post-operative status	306	0.24	Hypofunction of ovary	78	0.06	Adenomyosis	120	0.09	Endometrial hyperplasia	15	0.01			
Excessive androgen secretion	239	0.19	Fibroid	66	0.05	Fibroid	95	0.07	Hypofunction of ovary	15	0.01			

Table 5. — *Cost of COCuse per person each year from 2014 to 2018.*

Name	Cost of COCs per capita (RMB)					
	2014	2015	2016	2017	2018	2014-2018
ECP	88.06	92.65	87.89	79.77	65.7	82.81 ± 10.63
DSE(30 μg)	32.10	33.01	31.77	42.92	0	34.95 ± 5.34
DRE	213.87	206.55	185.02	173.41	155.56	186.88 ± 23.88
DRE(II)	0	0	0	281.62	250.34	265.98 ± 22.12
DSE(20 μg)	62.56	62.56	0	0	0	62.56 ± 0.00

Table 6. — *Total drug cost of COCs per capita each year from 2014 to 2018.*

Name	Total cost of the COCs per capita (RMB)					
	2014	2015	2016	2017	2018	2014-2018
ECP	126.97	136.82	140.68	141.56	141.17	137.44 ± 6.15
DSE (30 μg)	76.29	71.11	65.33	79.95	0	73.17 ± 6.36
DRE	228.45	220.98	200.76	202.6	220.47	214.65 ± 12.27
DRE (II)	0	0	0	294	315.05	304.53 ± 14.89
DSE (20 μg)	62.56	62.56	0	0	0	62.56 ± 0.00

Table 7. — *Number using drug combinations each year per from 2014 to 2018.*

Name	Number of combined drugs per capita					
	2014	2015	2016	2017	2018	2014-2018
ECP	0.4441	0.5023	0.5487	0.6660	0.6975	0.57 ± 0.11
DSE (30 μg)	0.4378	0.3682	0.3828	0.3783	0.0000	0.31 ± 0.18
DRE	0.1766	0.1693	0.1916	0.2907	0.6001	0.29 ± 0.18
DRE (II)	0.0000	0.0000	0.0000	0.1905	0.6007	0.16 ± 0.26
DSE (20 μg)	1.0000	1.0000	0.0000	0.0000	0.0000	0.40 ± 0.55

Combined drug analysis

Of the five COCs, ECP was most likely to be used in combination with another drug. Over time, DRE (II) use, in combination with other drugs, increased. Various drugs were used in combination with COCs, but metformin hydrochloride was one of the most commonly used, typically which ECP. This combination accounted for 39.89% of all combined drug use. ECP was also frequently combined with spironolactone, sex hormones, and a variety of patent Chinese medicines. DSE (20 μg) was only combined with another drug in two cases, so it was not included in the summary in Tables 7 and 8. To more intuitively observe the spectrum of drugs frequently combined with the remaining four COCs, radar charts were used (Figure 1).

Discussion

Variety selection

The main approved indication for COC use is contraception. DRE (II) has also been approved for moderate acne in addition to contraception. ECP is also approved for androgen-dependent diseases, such as PCOS. This may explain why ECP was the most frequently used drug in this study, as it has a greater number of clinical indications and is often combined with other drugs. Both doses of DSE have been out of stock since 2016, which at least in part explains their less frequent use. In general, lower doses of DSE have been used; the 20 μg ethinyl estradiol tablets had no advantage in regards to price. DRE (II) was eventually included in the catalogue for our hospital and belongs to a 24-day combined 4-day use program. Compared to COCs with a 21-day active hormone period, reductions in the concentration of estrogen and progesterone induced monthly withdrawal bleeding, which can better inhibit ovulation and reduce fluctuations in hormone levels. These features confer certain advantages in facilitating patient compliance. Additional doses require further observation [4].

Age groups

Patients using COCs were most commonly prescribed in the 21- to 30-year-old age group, which represents more than half the total. This finding is expected and consistent with the approved indications for use, namely contraception.

Clinical diagnosis

The percentage of patients using COCs exclusively for contraception was small. Across China, the frequency of COC use in women of gestational age tends to be low [5]. The reasons for this include a fear of hormonal drugs, insufficient understanding of how COCs work and their side effects, and prejudice. Furthermore, many physicians do not completely understand the benefits and risks of COCs. In turn, they are less likely to prescribe them for their patients.

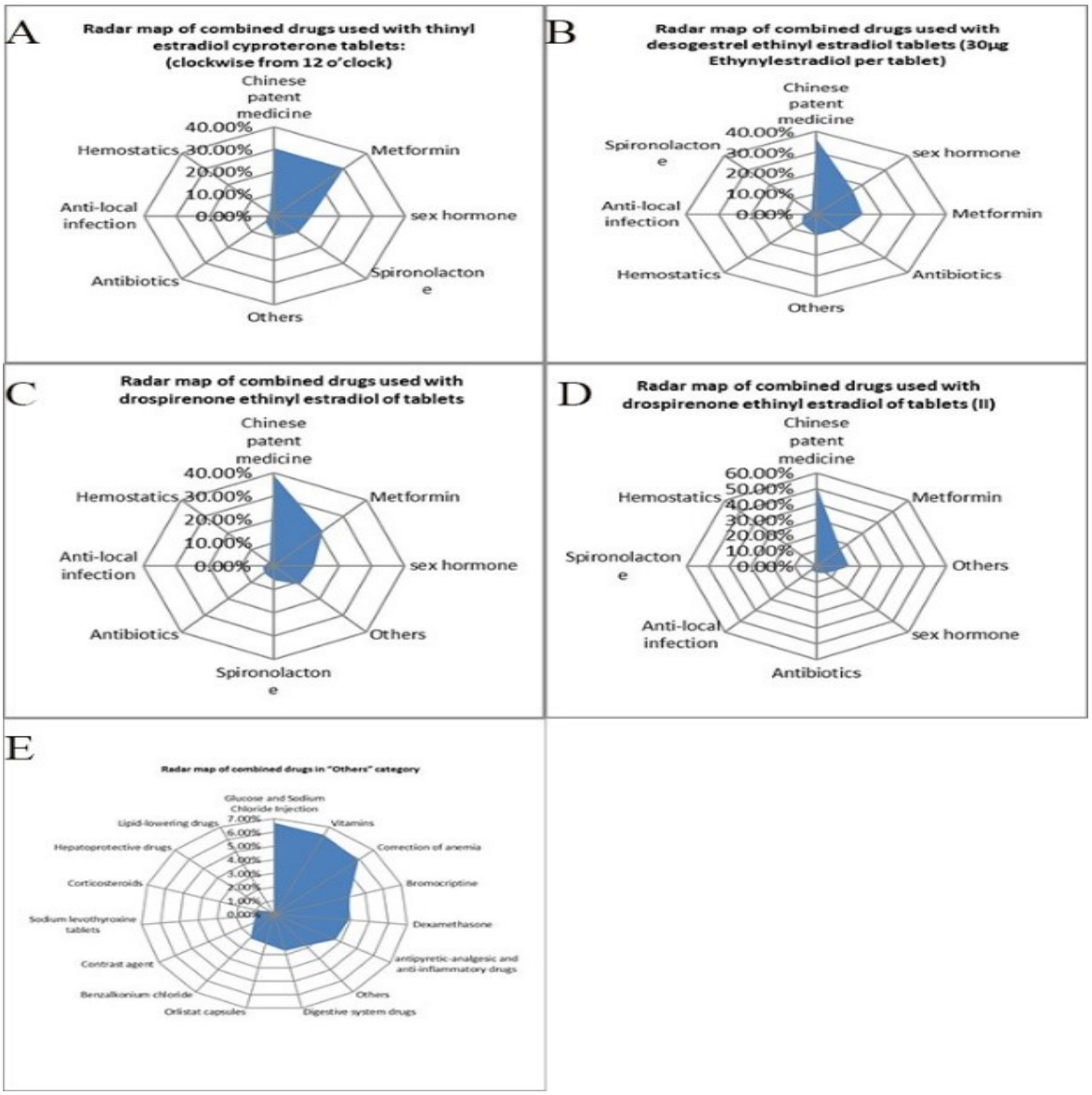

Figure 1. — Radar maps of combined drug use. (A) Proportion of combined drugs used with ECP were Chinese patent medicine (30.42%), metformin (30.24%), sex hormone (11.54%), spironolactone (10.45%), others (8.81%), antibiotics (3.9%), anti-local infection (2.5%) and hemostatics (2.13%), Chinese patent medicine metformin and sex hormone were mostly used in combination with ECP. (B) Proportion of combined drugs used with DSE (30 μg) were Chinese patent medicine (36.64%), sex hormone (15.97%), metformin (14.34%), antibiotics (10.50%), others (10.15%), hemostatics (6.20%), anti-local infection (4.06%) and spironolacton (2.14%), Chinese patent medicine sex hormone and metformin were mostly used in combination with DSE (30 μg). (C) Proportion of combined drugs used with DRE were Chinese patent medicine (39.11%), metformin (21.01%), sex hormone (12.34%), others (11.48%), spironolacton (6.13%), antibiotics (4.34%), anti-local infection (3.44%) and hemostatics (2.14%), Chinese patent medicine, metformin and sex hormone were mostly used in combination with DRE. (D) Proportion of combined drugs used with DRE(II) were Chinese patent medicine (51.11%), metformin (15.92%), others (15.33%), sex hormone (6.42%), antibiotics (4.20%), anti-local infection (3.51%), spironolacton (2.05%) and hemostatics (1.46%), Chinese patent medicine, metformin and sex hormone were mostly used in combination with DRE(II). (E) Proportion of combined drugs used with DRE(II) were glucose and sodium chloride injection (6.70%), vitamins (6.35%), correction of anemia (5.93%), bromocriptine (4.16%), dexamethasone (3.91%), antipyretic-analgesic and anti-inflammatory drugs (3.69%), others (2.82%), digestive system drugs (2.72%), orlistat (2.19%), benzaloonium chloride (2.15%) and contrast agent (1.24%) principally, glucose and sodium chloride injection, vitamins and correction of anemia were mostly used. Note: (1) The figure provided the radar maps of combined drug use of the DSE (30 μg), DSE (20 μg), ECP, DREandDRE (II) (2) The percentages in the figure showed the proportion of a combination drug. (3) Chinese patent medicine, metformin, sex hormone, spironolactone, antibiotics and others were mostly used in combination with COCs.

Table 8. — *Drug used in combination with COCs.*

ECP			DRE			DSE (30 μg)			DRE (II)		
Combined use of drugs	Count	Percentage	Combined use of drugs	Count	Percentage	Combined use of drugs	Count	Percentage	Combined use of drugs	Count	Percentage
Metformin Hydrochloride Tablet	14260	30.24%	Metformin Hydrochloride Tablet	1,898	21.01%	Metformin Hydrochloride Tablet	810	14.34%	Metformin Hydrochloride Tablet	186	15.92%
spironolactone tablets	4930	10.45%	spironolactone tablet	554	6.13%	Lysteda	340	6.02%	NuangongQiwei pill	64	5.48%
QubanTiaojing Capsule	2069	4.39%	Medroxyprogesterone Acetate Tablet	307	3.40%	Ankun Granule	212	3.75%	CongrongYishen Granule	48	4.11%
NuangongQiwei pill	1776	3.77%	Estradiol valerate tablet	293	3.24%	Baibai Capsule	205	3.63%	Dangui Capsule	48	4.11%
Progesterone Capsule	1676	3.55%	BazhenYimu Capsule	293	3.24%	Sanjie Analgesic Capsule	188	3.33%	Baibai Capsule	48	4.11%
Dydrogesterone Tablet	1578	3.35%	NuangongQiwei pill	255	2.82%	Cefixime Dispersible Tablet	166	2.94%	FukeZaizao Capsule	44	3.77%
CongrongYishen Granule	1059	2.25%	Dangui Capsule	255	2.82%	Cefaclor Capsule	151	2.67%	Baogui Capsule	32	2.74%
Lysteda	981	2.08%	Baibai Capsule	252	2.79%	Medroxyprogesterone Acetate Tablet	146	2.59%	Atropine sulfate injection	31	2.65%
Dangui Capsule	734	1.56%	Lysteda	189	2.09%	Estradiol valerate tablet	145	2.57%	Sanjie Analgesic Capsule	28	2.40%
Estradiol valerate tablet	731	1.55%	BaoguiCapsul	183	2.03%	Progesterone Capsule	140	2.48%	BazhenYimu Capsule	27	2.31%
FukeZaizao Capsule	711	1.51%	Dydrogesterone Tablet	182	2.01%	Zhitonghuazheng Capsule	134	2.37%	Kunning Oral Liquid	26	2.23%
Medroxyprogesterone Acetate Tablet	706	1.50%	FukeZaizao Capsule	175	1.94%	QubanTiaojing Capsule	133	2.36%	Spironolactone tablet	24	2.05%
Baibai Capsule	702	1.49%	XuefuZhuyucapsule	173	1.92%	Xiaojie'an Capsule	122	2.16%	Ankun Granule	24	2.05%
Baogui Capsule	685	1.45%	Cefaclor Capsule	160	1.77%	spironolactone tablet	121	2.14%	Dydrogesterone Tablet	23	1.97%
50% Glucose Injection	645	1.37%	Yikunning Granule	150	1.66%	Ornidazole Capsule	100	1.77%	Progesterone Capsule	23	1.97%
Vitamin E Soft Capsule	614	1.30%	Progesterone Capsule	149	1.65%	tamoxifen citrate tablet	97	1.72%	JinkuiShenqi Tablet	22	1.88%
Ankun Granule	509	1.08%	Sanjie Analgesic Capsule	135	1.49%	Estradiol Tablets/Estradiol Didrogesterone Tablet	97	1.72%	Lysteda	17	1.46%
Nifuratel Tablet	470	1.00%	CongrongYishen Granule	131	1.45%	Zhitonghuazheng Capsule	84	1.49%	Cefaclor Capsule	17	1.46%
Kunling Pill	457	0.97%	Dexamethasone Acetate Tablet	125	1.38%	Nifuratel nystatin vaginal ointment	81	1.43%	Fresh Leonurus Capsule	17	1.46%
Cefaclor Capsule	454	0.96%	Vitamin E Soft Capsule	122	1.35%	Dydrogesterone Tablet	81	1.43%	Zhitonghuazheng Capsule	16	1.37%

In China, COCs are most commonly used to treat menstrual disorders, irregular vaginal bleeding, adolescent bleeding, and other indications. Randomized trials have demonstrated that compared with placebo, COCs containing 30-35 μg ethinyl estradiol help regulate menstrual bleeding patterns in women [6, 7]. According to research, COCs can regulate the menstrual cycle, a small dose of estrogen can repair the endometrium, and progesterone can limit the effects of estrogen in promoting endometrial growth to reduce withdrawal bleeding.

The causes of female infertility were diverse, and many of the drugs prescribed are used to treat other pathogeny inherent in female infertility, such as endometriosis and polycystic ovary syndrome. The infertility rate in patients with endometriosis is as high as 30-50%, Many guidelines recommended COCs for the management of endometriosis [8, 9]. Similarly, COCs were commonly prescribed for adults and adolescents with PCOS to ameliorate the clinical symptoms and associated hormonal disturbances. Different combinations of COCs are available with heterogeneous estrogen and progestin preparations with varying pharmacological and clinical properties [10]. COCs can help to treat the underlying causes of infertility, which can improve fertility following a course of treatment.

Drugs commonly used to treat endometrial hyperplasia include progesterone, GnRHa, and aromatase inhibitors. The clinic will formulate individualized treatment plans based on the degree of endometrial hyperplasia, age, and requirements for fertility. Individualized treatment plans usually include COCs. COCs can inhibit the hypothalamic-pituitary-ovarian axis, reduce the size of the ovary, prevent endometrial overgrowth, control the menstrual cycle, and reduce the stimulatory effects of estrogen on the endometrium. COCs can help rescue the atrophic endometrium [11, 15]. Of course, in the traditional sense, exogenous estrogen excessively stimulates the endometrium, which may induce endometrial hyperplasia. However, COCs contain both estrogen and progesterone, which affect the endometrium, effects that are caused by progesterone [16, 17]. At the same time, risk factors for endometrial hyperplasia include obesity and polycystic ovary syndrome. Some patients diagnosed with endometrial hyperplasia also have PCOS, insulin resistance, or other comorbid diseases. Many of these can be treated with COCs. ECP is one such COC that can treat these conditions. It is also commonly used to treat PCOS.

Only 25 were younger than 11-years-old of the 127,183 patients. Most of these very young patients experience dysfunctional uterine bleeding caused by abnormal regulation of the adolescent hypothalamic-pituitary-ovarian axis. The main goal of treatment then is to stop bleeding and adjust the menstrual cycle. Common sex hormone treatment schemes include progesterone for endometrial shedding. The endometrium, which continues to proliferate under the action of hormones is converted into the secretory period to achieve hemostasis. Under the estrogen endometrial repair method, a large amount of estrogen can quickly promote the growth of the endometrium and repair the wound in a short period of time to stop bleeding. COCs treat the atrophic endometrium, which is often effective in treating adolescent anovulatory dysfunctional uterine bleeding [18, 20].

COCs are also one of the most commonly used drugs for the treatment of PCOS, as they have anti-androgenic effects. PCOS is characterized by hyperandrogenism, which leads to anovulation and alterations to the menstrual cycle, along with infertility. COCs are usually the first-line treatment for adolescent girls with PCOS who experience abnormal menstrual bleeding, skin changes (e.g. acne), excess hair growth (hirsutism), and obesity. The estrogen-progestin combination inhibits the hypothalamic-pituitary-ovarian axis and reduces excess androgen production in the ovaries, establishing a normal menstrual cycle, while reducing anovulatory uterine bleeding, hirsutism, and acne. Progesterone also inhibits endometrial proliferation, preventing endometrial hyperplasia and reducing the risk of endometrial cancer. Cycloprogesterone has the strongest anti-androgenic activity of the COCs and is most commonly prescribed for PCOS, followed by droxone, which exhibitsalt-resistant corticosteroid activity, accelerates water and sodium excretion, adjusts the menstrual cycle, confers contraception, and effectively controls body weight. COCs that show anti-androgenic activity or reduce androgen activity are most advantageous for the treatment of PCOS, as they can rapidly correct menstrual abnormalities and improve hirsutism and acne. Deoxypregnene plays a role through its metabolite, 3-keto-deoxypregnene, which is not ideal for the treatment of PCOS, because it is not anti-androgenic and in fact possesses androgenic effects [21].

In this study, a large percentage of the patients were diagnosed with endometriosis. For these patients, drospirenone ethinyl estradiol tablets and desogestrel ethinyl estradiol were mostly commonly prescribed. COCs are thought to inhibit ovarian function, causing the decidualization of endometrial tissue, which in turn leads to intimal atrophy and reduces the clinical pain of endometriosis. In addition, some studies have shown COCs may slow progression of the disease [22, 23]. Therefore, for most women with endometriosis-associated pain, an estrogen-progestin combined contraceptive is often ideal and can been tolerated for a long period of use. In addition, these drugs are relatively inexpensive and convenient to use, while conferring contraception and reducing the risk of both ovarian and endometrial cancer [24]. Long-term continuous or periodic oral use of COCs after laparoscopic surgery for ovarian endometriosis has been demonstrated to reduce the frequency and severity of endometriosis-related dysmenorrhea [25].

Combined use of drugs

In this study, metformin, spironolactone, and patent Chinese medicines were mostly used in combination with ECP. The most common clinical indications for ECP were PCOS and menstrual disorders. The use of an insulin sensitizer in the treatment of PCOS is also recommended to reduce

blood insulin levels. At the same time, the high levels of androgens in PCOS patients is reduced, and menstruation and ovulation typically improve. In the United States, spironolactone is recommended as a safe and effective antiandrogenic drug that can also alleviate other PCOS symptoms, such as excess hair growth and acne [26]. Traditional Chinese medicines are used under the belief that the cause of PCOS is kidney deficiency and dampness. Under this thinking, it is crucial to replenish the kidney and strengthen the spleen to remove phlegm and dampness. Recent studies reported that some Chinese medicines doinduceovulation in patients with PCOS [27, 28]. Sex hormones, hemostatic agents, and antibacterial agents are most commonly prescribed in addition to COCs. In this study, these were prescribed most frequently for menstrual disorders. During the treatment of menstrual disorders, other sex hormones were used, such as estrogen for endometrial repair, progesterone for intimal shedding, and high-efficiency synthetic progesterone for intimal atrophy. Hemostatic drugs are often used to reduce the amount of bleeding during treatment or are supplemented with iron or folic acid. For patients with long-term bleeding, antibiotics or other drugs to prevent infection are used.

In summary, the data in this study were collected from the electronic medical data of our hospital. The resulting analysis included a large data set consisting of diagnostic and treatment information for 127,183 patients. The sample size is large and the authenticity is high, reflecting the current use of different COCs in Chinese patients. ECP not only entered the market the earliest in China, but it is familiar to frontline physicians. Furthermore, it has been approved for the greatest number of clinical indications and is listed in the medical insurance catalogue of China. In addition to contraception, it is widely to treat PCOS and endometriosis and is generally cost-effective. DSE (30 μg) has the lowest per capita cost and is clinically used to treat menstrual disorders, endometriosis, and contraception. With revised specifications, DRE (II) could be used to foster patient compliance. Although its approved indications include moderate acne, due to late entry into our hospital directory, it is currently only used for contraception. Use for other indications requires further observation. These data provide the basis for the drug administration office to understand the clinical use of these drugs. Our data are also helpful for post-marketing supervision and future application and selection of various COCs. In addition, this information is essential for pharmaceutical companies to examine the characteristics of these drugs in clinical application. Finally, this information is helpful for the development of new drugs, further evaluation of the effectiveness and safety of the existing drugs, and provides information for physicians and patients to ensure proper drug usage.

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Conflict of Interest

The authors declare no conflict of interest.

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