

Efficacy and safety of an oral contraceptive containing ethinylestradiol 20 µg/drospirenone 3 mg (24/4 regimen) in three indications in the People's Republic of China: a comparison with international studies

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Abstract: While combined oral contraceptives are a popular choice in developed Western countries, they are used by only 1% of women who are married or in a relationship in the People's Republic of China. The purpose of this review is to describe the efficacy and safety of the combined oral contraceptive containing ethinylestradiol (EE) 20 µg/drospirenone 3 mg taken in a 24/4 regimen (YAZ[®]; Bayer HealthCare Pharmaceuticals, Berlin, Germany) by Chinese women and to compare these results with those in women assessed in the international studies. Studies of EE 20 µg/drospirenone 3 mg in three different indications (contraception, acne, and premenstrual dysphoric disorder [PMDD]) have been conducted in Chinese women. The results of these three studies indicate that the EE 20 µg/drospirenone 3 mg combined oral contraceptive is a good long-term contraceptive option in Chinese women, providing 99% contraceptive protection over the observed 1-year treatment period, and additionally had a favorable effect on moderate acne vulgaris and relieved the symptoms of PMDD. The contraceptive efficacy, improvement in acne, and relief from PMDD symptoms observed in these studies did not differ from the effects observed in other international studies of EE 20 µg/drospirenone 3 mg, indicating that EE 20 µg/drospirenone 3 mg is as effective in Chinese women as in other ethnicities. Further, EE 20 µg/drospirenone 3 mg demonstrated a similar safety and tolerability profile in women enrolled in the Chinese and international trials, with no unexpected adverse events reported in any of the three Chinese trials. Overall, the efficacy, tolerability, and degree of non-contraceptive benefits with EE 20 µg/drospirenone 3 mg appear similar in Chinese women when compared with those reported in larger studies done at other international centers.

Keywords: acne, People's Republic of China, contraception, ethinylestradiol/drospirenone, premenstrual dysphoric disorder, YAZ[®]

Introduction

While oral contraceptives (OCs) are a popular choice in developed Western countries, the prevalence of their use in the People's Republic of China is only approximately 1% among women who are married or in a relationship.¹ This low uptake of modern OCs might be due to a number of factors, including cultural influences, lack of adequate contraceptive education, negative attitudes toward OCs, and/or a fear that they may be harmful.²⁻⁴

The combined oral contraceptive (COC) containing ethinylestradiol (EE) 20 µg and drospirenone 3 mg (YAZ[®]; Bayer HealthCare Pharmaceuticals, Berlin, Germany)

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was developed to be administered once daily for 24 consecutive days followed by 4 days of hormone-free placebo tablets (24/4 regimen). Unlike traditional 21-day COC regimens, this formulation was developed as a contraceptive regimen with a shortened hormone-free interval. This regimen may decrease the incidence of hormone withdrawal symptoms⁵ and lead to more pronounced ovarian suppression and contraceptive efficacy.^{6–9} Studies in women who desire a COC as their contraceptive method have shown that the 24/4 regimen of EE 20 µg/drospirenone 3 mg is an effective form of contraception,¹⁰ is effective in the treatment of moderate acne,^{11,12} and can alleviate the emotional and physical symptoms associated with premenstrual dysphoric disorder (PMDD).^{13,14} EE 20 µg/drospirenone 3 mg has also been shown to be a highly effective contraceptive in routine clinical use and to have a safety profile similar to that of other available COCs.¹⁵

The majority of the clinical data available for EE 20 µg/drospirenone 3 mg is in women from predominantly developed Western countries, and few studies have investigated whether there are any differences in the efficacy and tolerability of EE 20 µg/drospirenone 3 mg between women of different ethnicities, particularly in women from the People's Republic of China. One study compared the pharmacokinetics of EE 20 µg/drospirenone 3 mg in Caucasian and Japanese women and showed that ethnic origin had no influence on the pharmacokinetics of EE 20 µg/drospirenone 3 mg.¹⁶ The purpose of this narrative review is to describe the efficacy and safety of EE 20 µg/drospirenone 3 mg across three indications (contraception, acne, and PMDD) in Chinese women and to compare these results with those for patients enrolled in international studies.

Efficacy of EE/drospirenone in Chinese women

Three studies have investigated the use of EE 20 µg/drospirenone 3 mg (24/4 regimen) in Chinese women.^{17–19} The first was conducted in healthy women between 2008 and 2011, and investigated the contraceptive efficacy, cycle control, bleeding pattern, and safety of EE 20 µg/drospirenone 3 mg.¹⁸ The second, conducted between 2008 and 2010, evaluated the efficacy and safety of EE 20 µg/drospirenone 3 mg in women with moderate acne vulgaris.¹⁷ The third study, conducted between 2009 and 2011, investigated the ability of EE 20 µg/drospirenone 3 mg to alleviate symptoms associated with PMDD.¹⁹ The studies in Chinese women and the comparator studies undertaken elsewhere are summarized in Table 1.

Table 1 Baseline characteristics of subjects enrolled in studies of ethinylestradiol 20 µg/drospirenone 3 mg administered in a 24/4 treatment regimen conducted in the People's Republic of China, Europe, Latin America, and the USA

| Indication | Contraception | | | Acne | | | PMDD | | |
|------------------------|--|--|--|---|----------------------------------|-----------------------------------|--|-----------------------------------|--------------------------------------|
| Study (country) | Caiyan et al ¹⁸ (People's Republic of China) ^a | Bachmann et al ¹⁰ (Austria, Argentina, Brazil, Poland, USA) | Hernádi et al ²⁰ (Czech Republic, Italy, Hungary, Slovak Republic, Latvia, Belgium) | Zhang et al ¹⁷ (People's Republic of China) ^a | Koltun et al ¹¹ (USA) | Maloney et al ¹² (USA) | Fu et al ¹⁹ (People's Republic of China) ^a | Yonkers et al ¹⁴ (USA) | Pearlstein et al ¹³ (USA) |
| n | 675 | 1,027 | 1,101 | 173 | 534 | 538 | 187 | 450 | 64 |
| Age, years | 32±5 | 24.7±4.4 | 24.7±4.7 | 23.7±5.6 | 25.3 | 25.1 | 29.0±7.0 | 31.5 | 31.8±5.5 |
| BMI, kg/m ² | 21.4±2.6 | 22.4±3.3 | 21.7±2.8 | 20.1±2.2 | 24.6 | 23.8 | 20.7±2.2 | 25.6 | 26.3±5.1 |
| Ethnicity, n (%) | | | | | | | | | |
| Caucasian | 0 | 902 (87.8) | NR | 0 | 360 (67.4) | 369 (68.6) | 0 | 345 (77.1) | 48 (75.0) |
| Hispanic | 0 | 47 (4.6) | NR | 0 | 60 (11.2) | NR | 0 | 43 (9.6) | 5 (7.8) |
| Black | 0 | 44 (4.3) | NR | 0 | 81 (15.2) | NR | 0 | 45 (10.0) | 7 (10.9) |
| Asian | 675 (100) | 12 (1.2) | NR | (100) | 13 (2.4) | NR | 187 (100) | 5 (1.1) | 1 (1.6) |
| Other | 0 | 22 (2.1) | NR | 0 | 20 (3.7) | NR | 0 | 10 (2.2) | 3 (4.7) |
| Current smoker, n (%) | 4 (0.6) | 263 (25.6) | NR | 5 (2.9) | 92 (17.2) | 60 (11.2) | 2 (1.1) | NR | NR |

Notes: All values are presented as mean ± standard deviation unless otherwise specified; ^aincludes some unpublished data.

Abbreviations: BMI, body mass index; NR, not reported; PMDD, premenstrual dysphoric disorder.

Contraception

The Chinese contraceptive efficacy study was a multicenter, open-label, Phase III, single-arm trial (ClinicalTrials.gov identifier NCT00819312) investigating the efficacy of EE 20 µg/drospirenone 3 mg administered in the 24/4 regimen to 675 healthy females (mean age 31.9 years; mean body mass index 21.4 kg/m²).¹⁸ Women aged 18–45 years who requested contraceptive protection and had a normal cervical smear test were included and received 13 cycles of EE 20 µg/drospirenone 3 mg. Pregnant or lactating women, those with menstrual disorders indicating ovarian failure, and women with any disease or condition that could worsen under hormonal treatment or compromise body function were excluded. The results of this study showed that EE 20 µg/drospirenone 3 mg was a highly effective contraception in Chinese women.¹⁸ During this study, four pregnancies were reported in over 603.78 women-years of EE 20 µg/drospirenone 3 mg exposure, resulting in an unadjusted Pearl Index of 0.7. Three of these pregnancies were considered to be due to method failure, resulting in an adjusted Pearl Index of 0.6. The 1-year cumulative pregnancy rate was 0.66%. Over the 13 cycles, the mean number of bleeding/spotting days was reduced from 26.3±12.4 days in the first 90-day reference period to 15.4±5.5 days by the fourth reference period. Withdrawal bleeding occurred in 94.2%–96.8% of women, and the mean duration of scheduled bleeding decreased from 5.9±3.2 days in cycle 1 to 5.0±1.6 days in cycle 12.¹⁸

Two studies with a trial design similar to that of the Chinese study have previously been conducted in 1,027 women in Europe, Latin America, and the USA (between 2000 and 2003),¹⁰ and in 1,101 women in Europe (between 2004 and 2006).²⁰ Women aged 17–36 years¹⁰ or 18–35 years²⁰ (mean age 24.7 years in both studies) seeking contraception were included. The results of these studies indicated no differences in contraceptive efficacy of EE 20 µg/drospirenone 3 mg between women from the People's Republic of China and those from Europe, USA, and Latin America, with comparable Pearl Index scores observed in all three studies (Figure 1).

In a multicenter study conducted across Europe, Latin America, and the USA, eleven pregnancies occurred in over 11,140 EE 20 µg/drospirenone 3 mg treatment cycles (857 woman-years of exposure), resulting in an unadjusted Pearl Index of 1.29.¹⁰ However, six of the pregnancies occurred after missed or irregular tablet intake and other patient compliance issues. Taking this into account, women in this study had an adjusted Pearl Index of 0.72, similar to that observed in the Chinese study. The 1-year cumulative pregnancy rate

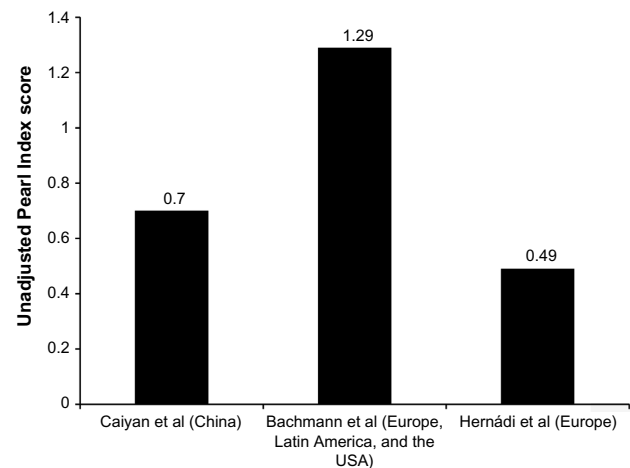


Figure 1 Comparison of unadjusted Pearl Index scores in women after treatment over 1 year with the ethinylestradiol 20 µg/drospirenone 3 mg combined oral contraceptive (YAZ®) in three international studies conducted in the People's Republic of China (Caiyan et al¹⁸), Europe, Latin America, and the USA (Bachmann et al¹⁰), and Europe (Hernádi et al²⁰).

was 1.26%. Further, the mean number of bleeding/spotting days was reduced from 23 days in the first 90-day reference period to 15 days by the fourth reference period,¹⁰ which was similar to that reported in the Chinese study.

In a European study, five pregnancies occurred over 13,248 cycles (1,019 woman-years of exposure) of EE 20 µg/drospirenone 3 mg, resulting in an unadjusted Pearl Index of 0.49.²⁰ Three of these pregnancies occurred after missed or irregular tablet intake and other patient compliance issues, resulting in an adjusted Pearl Index of 0.22. The 1-year cumulative pregnancy rate was 0.5%.²⁰

Other than ethnicity, there were a few differences between the women enrolled in the study conducted in the People's Republic of China and the international studies (Table 1).^{10,18,20} Fewer subjects were enrolled in the study conducted in the People's Republic of China (675 versus 1,027 and 1,101, respectively). In general, women enrolled in the Chinese study were older (mean age 31.9 years versus 24.7 and 24.7 years), had given birth more often (mean number of births 0.84 versus 0.46 and 0.38), and had had more abortions than women in the international studies. However, more women in the international studies were smokers (25.6% and 21.2% versus 0.6% in the Chinese study).^{10,18,20} Of note, the Pearl indices (both unadjusted and adjusted) in the Chinese study lie between the respective values reported in the two international studies.

Acne

Acne is often caused by an overproduction of androgen or a hypersensitivity of the sebaceous glands to androgen,

which leads to increased production of sebum.^{21–24} Hormonal therapy, including COCs, has been used by dermatologists for decades as a treatment for acne. COCs are particularly beneficial; use of low-dose estrogen has been shown to reduce serum androgen levels by increasing sex hormone binding globulin levels and thereby reducing androgen bioavailability,^{25,26} while progestins with antiandrogenic activity competitively inhibit the receptor binding of androgens, leading to dual action antagonism on the effects of endogenous androgens.

The efficacy of six cycles of EE 20 µg/drospirenone 3 mg in the treatment of moderate acne vulgaris in Chinese women was investigated in a multicenter, double-blind, randomized, Phase III, placebo-controlled study.¹⁷ Moderate acne was defined as a minimum of 40 lesions with at least 20 inflammatory lesions (including papules, pustules and nodules) and 20 non-inflammatory lesions (including open and closed comedones). This study, conducted in 173 women aged 14–45 (mean 23.7) years, demonstrated that EE 20 µg/drospirenone 3 mg reduced the mean total acne lesion count (the primary endpoint of the study) from baseline to endpoint (defined as cycle 6 with last observation carried forward for dropouts) by 66.8% (from 80.8 to 25.4) compared with the 37.7% reduction observed with placebo (from 78.3 to 46.3). After six cycles, EE 20 µg/drospirenone 3 mg also reduced inflammatory and non-inflammatory lesion counts from baseline (by 75.5% and 69.3%, respectively) to a greater extent than placebo (by 60.9% and 50.2%, respectively).¹⁷ These results suggest that EE 20 µg/drospirenone 3 mg is effective for the treatment of moderate acne vulgaris in Chinese women; however, it is important to note that the number of study participants in this study was driven solely by regulatory requirements at the time (Chinese regulatory requirement of 60 evaluable patients in each study group) and not by biostatistical sample size calculations. The fact that no statistical testing was done should be considered when interpreting the results.

Two placebo-controlled studies with a trial design similar to that of the Chinese study have been conducted in 534¹¹ and 538¹² women in the USA (both conducted between 2003 and 2004). Like the Chinese study, both of these studies included healthy females aged 14–45 years (mean 25.3 and 25.1 years, respectively) with facial acne of at least moderate severity and a minimum of 20 inflammatory papules and/or pustules and 20 non-inflammatory lesions. Similar to the Chinese study, the two USA studies showed that EE 20 µg/drospirenone 3 mg was associated with a greater reduction in the number of total lesions from baseline to endpoint

compared with placebo.^{11,12} Further, according to a pooled analysis of the two USA studies, EE 20 µg/drospirenone 3 mg significantly ($P<0.0001$) reduced the number of inflammatory (50% versus 33% reduction) and non-inflammatory (40% versus 21% reduction) lesions compared with placebo at endpoint.²⁷ Interestingly, compared with the two studies conducted in the USA, EE 20 µg/drospirenone 3 mg was associated with a greater percentage reduction in mean total acne lesion count in Chinese women (Figure 2).^{11,12,17}

The small variances in the effect of EE 20 µg/drospirenone 3 mg observed between the study conducted in the People's Republic of China and the international studies could, in part, be explained by differences in the patient populations enrolled in the three studies. While the inclusion criteria for all three studies were similar, there were a few differences in baseline characteristics other than ethnicity between the participants enrolled in the study conducted in the People's Republic of China and the other studies (Table 1). In particular, Chinese subjects had a lower body mass index. In addition, women in the Chinese study had a lower screening failure and dropout rate than women in the US studies, and fewer women were enrolled in the Chinese study. However, despite the small differences in data observed in the studies conducted in the People's Republic of China¹⁷ and the other studies,^{11,12} the efficacy of EE 20 µg/drospirenone 3 mg in the treatment of moderate acne in Chinese women appears consistent with studies undertaken elsewhere.

A Cochrane review of COCs in the treatment of acne concluded that they are effective in reducing inflammatory and non-inflammatory facial acne lesions, with few important

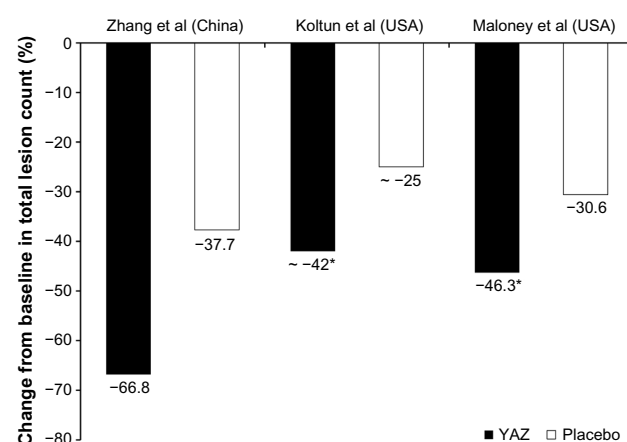


Figure 2 Percentage change from baseline to endpoint (defined as cycle 6 with last observation carried forward for dropouts) in mean total acne lesion count in women with moderate acne treated with ethinylestradiol 20 µg/drospirenone 3 mg combined oral contraceptive (YAZ®) or placebo in the studies conducted in the People's Republic of China (Zhang et al¹⁷) and the USA (Koltun et al¹¹ and Maloney et al¹²). Values for the Koltun et al study are approximate as they were estimated from the graph presented in their publication. * $P<0.001$ versus placebo.

differences in effectiveness between the different types of COC.²⁸ However, the limited available data for COCs containing progestins with no intrinsic androgenic activity (such as cyproterone acetate, chlormadinone acetate, and drospirenone) suggest that these progestins may be more effective than those with residual androgenic activity (such as levonorgestrel and norgestimate).

PMDD

PMDD is characterized by moderate-to-severe behavioral, mood, and physical symptoms that significantly affect the quality of life of the woman on a monthly basis.²⁹ PMDD has been classified as having a burden-of-illness category similar to that of chronic depression and other common medical disorders.³⁰ Currently, the exact biological processes of PMDD are unknown; however, one hypothesis is that PMDD symptoms are due to fluctuations of the gonadal hormones during the menstrual cycle,^{30,31} given that symptoms are reduced when ovarian activity is suppressed.^{32,33} As COCs generally limit hormonal fluctuations through suppression of ovarian activity, they are often used to reduce the symptoms of PMDD.³⁴

One study investigating EE 20 µg/drospirenone 3 mg in the treatment of PMDD was conducted in Chinese women.¹⁹ This multicenter, double-blind, randomized, placebo-controlled, parallel-group trial investigated the reduction of symptoms of PMDD (diagnosed using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] criteria) in 187 women aged 18–45 (mean 29) years who received EE 20 µg/drospirenone 3 mg.¹⁹ The primary endpoint was change from baseline score on the Daily Record of Severity of Problems (DRSP) scale, which provides reliable and valid measures of premenstrual symptoms in both the original English version³⁵ and in the Chinese version.³⁶ In addition, the Clinical Global Impressions (CGI) global improvement scale, a single-item measure (1, very much improved; 7, very much worse), which was used to define response (a score of 1 or 2, corresponding to very much or much improved) was also completed at treatment cycles 2 and 3. After three cycles of treatment, women who received EE 20 µg/drospirenone 3 mg had a reduction from baseline in DRSP score of -29.1 ± 16.9 , which was greater than the reduction observed with placebo (-24.9 ± 19.4). The mean self-rated CGI global improvement score for the EE 20 µg/drospirenone 3 mg group decreased from 2.70 ± 0.90 at cycle 2 to a mean of 2.10 ± 1.00 at the final examination, compared with a decrease from 2.90 ± 0.80 to 2.30 ± 1.00 in the placebo group. These results suggest that EE 20 µg/

drospirenone 3 mg is effective for the treatment of PMDD in Chinese women; however, as with the acne study, it is important to note that the number of participants recruited for this study was driven by regulatory requirements and not by biostatistical sample size calculations, so no statistical testing was done.¹⁹

Two randomized, double-blind, placebo-controlled, multicenter studies in women with PMDD have been conducted in the USA, one with a parallel-trial design similar to the Chinese study ($n=449$) conducted between 2001 and 2004 and the other with a crossover design ($n=64$) conducted between 2002 and 2003.^{13,14} Both of these studies enrolled women aged 18–40 years with PMDD (diagnosed using DSM-IV criteria), regular menstrual cycles, and no other relevant psychiatric disorders.

Similar to the Chinese study, the two USA studies showed that patients receiving EE 20 µg/drospirenone 3 mg had greater reductions in DRSP scores than patients who received placebo. In the parallel-group trial, EE 20 µg/drospirenone 3 mg improved the behavioral, mood, and physical symptoms of PMDD (change from baseline in DRSP subscale scores -7.7 , -19.2 , and -10.7 , respectively).¹⁴ These improvements resulted in an overall reduction in DRSP score of -37.49 , and were significantly greater ($P \leq 0.001$) than the reductions observed with placebo, despite a substantial placebo effect (-6.2 , -15.3 , and -8.6 , for behavioral, mood and physical symptoms, respectively; change in total DRSP score -29.99).¹⁴ Similarly, self-rated CGI global improvement was greater in the EE 20 µg/drospirenone 3 mg group than in the placebo group (2.3 versus 2.5, adjusted mean

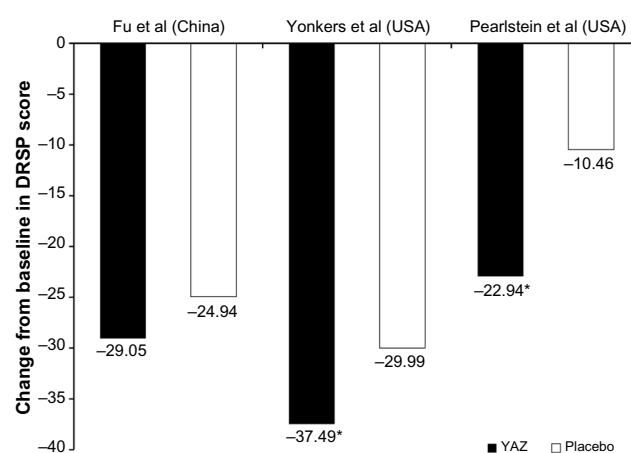


Figure 3 Change from baseline in DRSP scale scores after three cycles of treatment in women with premenstrual dysphoric disorder in ethinylestradiol 20 µg/drospirenone 3 mg combined oral contraceptive (YAZ®) placebo-controlled studies conducted in the People's Republic of China (Fu et al¹⁹) and the USA (Yonkers et al¹⁴ and Pearlstein et al¹³). * $P < 0.001$ versus placebo.

Abbreviation: DRSP, Daily Record of Severity of Problems.

Table 2 Safety and tolerability of ethinylestradiol 20 µg/drospirenone 3 mg combined oral contraception administered in a 24/4 regimen (YAZ®) in women from the People's Republic of China, Europe, Latin America, and the USA. Adverse events shown are those reported by ≥2% of participants

| Reference (study design, country) | Treatment (number of subjects ^a) | Treatment cycles (n) | Proportion of subjects, n (%) | | | Any SAE | Any study drug-related SAE | Most reported AEs (n [%]) | |
|---|--|----------------------|-------------------------------|---------------------------|-----------------------------------|--------------------|----------------------------|--|--|
| | | | Any AE | Any study drug-related AE | Any AE leading to discontinuation | | | | |
| Indication: oral contraception Caiyan et al ¹⁸ (SA, MC, OL; People's Republic of China) | YAZ ^b (675) | 13 | 272 (40.3) | 89 (13.2) | 38 (5.6) | 4 (0.6) | 0 | Nausea | 23 (3.4) |
| | YAZ ^b (1,027) | 13 | NR | 395 (38.5) | 77 (7.5) | NR | 3 (0.3) | Headache Breast pain Nausea | 67 (6.5) 65 (6.3) 26 (2.5) |
| | YAZ ^b (1,101) | 13 | 526 (47.8) | 233 (21.2) | 69 (6.3) | 22 (2.0) | 0 | Metrorrhagia Amenorrhea Headache | 88 (8.0) 50 (4.5) 32 (2.9) |
| Indication: acne Zhang et al ¹⁷ (R, DB, MC, PC; People's Republic of China) | YAZ ^b (87) Placebo (86) | 6 | 26 (29.9) 10 (11.6) | 22 (25.3) 4 (4.7) | 2 (2.3) 2 (2.3) | 0 0 | 0 0 | YAZ: Menorrhagia Metrorrhagia Placebo: Acne | 7 (8.0) 7 (8.0) 3 (3.5) |
| | YAZ ^b (266) Placebo (268) | 6 | 170 (63.9) 129 (48.1) | NR 4 (1.5) | 17 (6.4) 13 (4.9) | 1 (0.4) 1 (0.4) | 0 0 | YAZ: Upper respiratory infection Metrorrhagia Headache Nausea Sinusitis Pap smear suspicious Placebo: Headache Nausea Emotional lability Depression Metrorrhagia | 35 (13.2) 28 (10.5) 23 (8.6) 17 (6.4) 15 (5.6) 15 (5.6) 10 (3.7) 7 (2.6) 6 (2.2) 5 (1.9) 3 (1.1) |
| | YAZ ^b (270) Placebo (268) | 6 | 149 (55.2) 123 (45.9) | NR 5 (1.9) | 16 (5.9) 9 (3.4) | 1 (0.4) 5 (1.9) | 0 0 | YAZ: Upper respiratory infection Metrorrhagia Papanicolaou smear suspicious Headache Placebo: Upper respiratory infection Headache | 25 (9.3) 25 (9.3) 15 (5.6) 14 (5.2) 10 (3.7) 31 (11.6) 14 (5.2) |

| Indication: PMDD | | | | | | | | | |
|--|---|---|------------------------|-------------------------|----------------------|--------|--------------|-----------------------------|-----------|
| Fu et al ¹⁹ (R, DB, MC, PC; People's Republic of China) | YAZ [®] (93) Placebo (94) | 3 | 41 (44.1) 29 (30.9) | 35 (37.6) 20 (21.3) | 5 (5.4) 1 (1.1) | 0 0 | 0 0 | Flu syndrome | 12 (4.5) |
| | | | | | | | | Metrorrhagia | 6 (2.2) |
| | | | | | | | | Nausea | 7 (2.6) |
| | | | | | | | | YAZ: | |
| | | | | | | | | Metrorrhagia | 12 (12.9) |
| | | | | | | | | Menorrhagia | 8 (8.6) |
| | | | | | | | | Nausea | 5 (5.4) |
| | | | | | | | | Hypomenorrhea | 4 (4.3) |
| | | | | | | | | Headache | 3 (3.2) |
| | | | | | | | | Weight increased | 3 (3.2) |
| Yonkers et al ¹⁴ (R, DB, MC, PC; USA) | YAZ [®] (232) Placebo (218) | 3 | NR | 118 (51.1) 66 (30.3) | 35 (15.1) 9 (4.1) | NR | 1 (0.4) 0 | Placebo: | |
| | | | | | | | | Hypomenorrhea | 5 (5.3) |
| | | | | | | | | Nausea | 4 (4.3) |
| | | | | | | | | Metrorrhagia | 3 (3.2) |
| | | | | | | | | Dizziness | 3 (3.2) |
| | | | | | | | | YAZ: | |
| | | | | | | | | Metrorrhagia | 58 (25.1) |
| | | | | | | | | Headache | 45 (19.5) |
| | | | | | | | | Nausea | 43 (18.6) |
| | | | | | | | | Breast pain | 31 (13.4) |
| Pearlstein et al ¹³ (R, DB, MC, CO; USA) | YAZ [®] (34) Placebo (30) | 3 | NR | 26 (48.2) 14 (28.6) | 4 (11.8) 3 (10.0) | NR | NR | Upper respiratory infection | 23 (10.0) |
| | | | | | | | | Asthenia | 19 (8.2) |
| | | | | | | | | Abdominal pain | 12 (5.2) |
| | | | | | | | | Sinusitis | 9 (3.9) |
| | | | | | | | | Placebo: | |
| | | | | | | | | Metrorrhagia | 10 (4.6) |
| | | | | | | | | Headache | 44 (20.2) |
| | | | | | | | | Nausea | 11 (5.0) |
| | | | | | | | | Breast pain | 11 (5.0) |
| | | | | | | | | Upper respiratory infection | 24 (11.0) |
| Pearlstein et al ¹³ (R, DB, MC, CO; USA) | YAZ [®] (34) Placebo (30) | 3 | NR | 26 (48.2) 14 (28.6) | 4 (11.8) 3 (10.0) | NR | NR | Asthenia | 8 (3.7) |
| | | | | | | | | Abdominal pain | 6 (2.8) |
| | | | | | | | | Sinusitis | 11 (5.0) |
| | | | | | | | | YAZ: | |
| | | | | | | | | Nausea | 10 (18.5) |
| | | | | | | | | Upper respiratory infection | 9 (16.7) |
| | | | | | | | | Headache | 8 (14.8) |
| | | | | | | | | Intermenstrual bleeding | 8 (14.8) |
| | | | | | | | | Breast pain | 6 (11.1) |
| | | | | | | | | Nervousness | 5 (9.3) |
| Asthenia | 4 (7.4) | | | | | | | | |

(Continued)

(Continued)

Table 2 (Continued)

| Reference (study design, country) | Treatment (number of subjects ^a) | Treatment cycles (n) | Proportion of subjects, n (%) | | | Any SAE | Any study drug-related SAE | Most reported AEs (n [%]) |
|-----------------------------------|--|----------------------|-------------------------------|---------------------------|-----------------------------------|---------|----------------------------|--|
| | | | Any AE | Any study drug-related AE | Any AE leading to discontinuation | | | |
| | | | | | | | | Placebo: Nausea 5 (10.2) Upper respiratory infection 3 (6.1) Headache 7 (14.3) Asthenia 4 (8.2) Tooth disorder 4 (8.2) Accidental injury 4 (8.2) |

Notes: ^aNumber of subjects in the full analysis set of each study; ^boral contraceptive containing 20 µg ethinylestradiol and 3 mg drospirenone administered once daily for 24 consecutive days followed by a 4-day hormone-free interval. **Abbreviations:** AE, adverse event; CO, crossover; DB, double-blind; MC, multicenter; NR, not reported; OL, open-label; PC, placebo-controlled; PMDD, premenstrual dysphoric disorder; R, randomized; SA, single-arm; SAE, serious adverse event.

difference −0.26, 95% confidence interval −0.53 to 0.008; *P*=0.014 by rank analysis of covariance). In the crossover trial, the mean total DRSP scores were also significantly reduced with EE 20 µg/drospirenone 3 mg compared with placebo (−22.94 versus −10.46; *P*<0.001).¹³ Overall, 29 (61.7%) subjects responded (ie, CGI global improvement score of 1 or 2) while using EE 20 µg/drospirenone 3 mg compared with 14 (31.8%) while using placebo (*P*=0.009).

Compared with the parallel-group designed trial in the USA, the treatment effect with EE 20 µg/drospirenone 3 mg was less pronounced in Chinese women (Figure 3). However, lower baseline DRSP scores in women enrolled in the study in the People’s Republic of China may explain why the treatment effect was less pronounced. Further, the Chinese study was not powered to show a significant difference, which could explain why this difference between the Chinese and US study was observed. Although the Chinese version of the DRSP scale has been shown to provide reliable and valid measures of PMDD symptoms,³⁶ there may be some unknown transcultural differences between the scales, which could affect outcomes. Finally, other than ethnicity, there were a few differences between the subjects enrolled in the study conducted in the People’s Republic of China and the studies in the USA (Table 1). In particular, Chinese subjects had a lower body mass index than subjects enrolled in the USA studies.

Safety and tolerability of EE/drospirenone in Chinese women

In all three indications, the proportion of Chinese women who experienced an adverse event while receiving EE 20 µg/drospirenone 3 mg (24/4 regimen) appeared to be lower than the proportion of women in the international studies who experienced adverse events (Table 2). The most common adverse events reported with EE 20 µg/drospirenone 3 mg in Chinese women were metrorrhagia (8.0%–12.9%), menorrhagia (8.0%–8.6%), and nausea (3.4%–5.4%). Four patients reported a serious adverse event (intervertebral disc protrusion, sciatica, gastric cancer, and cervical dysplasia) in the 1-year contraceptive trial;¹⁸ no serious adverse events were reported in the acne or PMDD trials.^{17,19} Over the three Chinese studies, of 1,035 women, 45 withdrew because of adverse events.^{17–19}

In the 1-year Chinese contraceptive trial, the tolerability of EE 20 µg/drospirenone 3 mg was generally good.¹⁸ Study drug-related adverse events were reported in 13.2% of patients; the most common adverse events were nausea (3.4%), increased serum triglycerides (1.3%), breast

tenderness (1.2%), dizziness (1.2%), and vaginal hemorrhage (1.2%). However, as this study lacked a placebo control, the occurrence of these non-specific adverse events may simply reflect the nocebo phenomenon or their background incidence.³⁷ Nonetheless, the adverse events experienced by Chinese women were consistent with the adverse events reported in the two contraceptive studies undertaken elsewhere^{10,20} and the adverse event profile was consistent with that observed with other low-dose COCs when administered in Chinese women.

When six cycles of EE 20 µg/drospirenone 3 mg was administered to Chinese women with moderate acne, study drug-related adverse events were observed in 25.3% of recipients, compared with 4.7% of women who received placebo in the same study.¹⁷ The most common adverse events associated with EE 20 µg/drospirenone 3 mg treatment were menorrhagia (8.0%), metrorrhagia (8.0%), abdominal pain (2.3%), and breast pain (1.1%), whereas acne was the most common adverse event reported with placebo treatment (3.5%) followed by breast pain (1.1%). All of these adverse events were mild or moderate in intensity. Two participants in each treatment group discontinued treatment due to an adverse event. Like the contraceptive study, the adverse events experience by women with acne in this trial are similar to those reported in international studies investigating EE 20 µg/drospirenone 3 mg in women with acne.^{11,12}

Three cycles of EE 20 µg/drospirenone 3 mg were well tolerated by most Chinese women with PMDD.¹⁹ Adverse events were generally similar to those in the international PMDD trials.^{13,14} Adverse events were reported in 44.1% of EE 20 µg/drospirenone 3 mg recipients and 30.9% of placebo recipients in Chinese women with PMDD, of which 37.6% and 21.3%, respectively, were considered treatment-related.¹⁹ Again, like the contraceptive and acne trials, the adverse event profile of EE 20 µg/drospirenone 3 mg in Chinese women with PMDD was similar to that observed in the international trials.^{13,14}

Conclusion

The EE 20 µg/drospirenone 3 mg COC administered in a 24/4 regimen is as effective in Chinese women as elsewhere, with a similar safety and tolerability profile. In Chinese women, EE 20 µg/drospirenone 3 mg provided 99% contraceptive protection over the observed 1-year treatment period and reduced lesion counts over six treatment cycles in women with moderate acne. EE 20 µg/drospirenone 3 mg was also shown to improve, over three treatment cycles, the emotional and physical symptoms associated with PMDD in

Chinese women. EE 20 µg/drospirenone 3 mg was generally well tolerated by Chinese women, with adverse events generally typical of those experienced with other COCs. Although the Chinese studies included in our review have a limited number of subjects based on regulations rather than biostatistical considerations, the efficacy, tolerability, and degree of non-contraceptive benefits appears comparable with larger studies done at other international centers. Our review highlights the need for more cross-cultural and cross-racial contraceptive studies in order to ensure that assumptions made in previous studies are truly generalizable to all women.

Acknowledgment

The authors would like to thank Simone Boniface of inScience Communications, Springer Healthcare, who provided medical writing assistance with the manuscript.

Disclosure

JM and KR are employees of Bayer Pharma AG. ZH, BW, and HZ are principal investigators for the three Chinese YAZ studies, which were funded by Bayer HealthCare China Ltd. Medical writing assistance was funded by Bayer HealthCare Pharmaceuticals. The authors have no other relevant conflicts of interest to report.

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