

Safety, efficacy, actions, and patient acceptability of drospirenone/ethinyl estradiol contraceptive pills in the treatment of premenstrual dysphoric disorder

Lesley L Breech
Paula K Braverman

Division of Adolescent Medicine,
Department of Pediatrics, Cincinnati
Children's Hospital Medical Center,
University of Cincinnati College
of Medicine, Cincinnati, OH, USA

Abstract: Premenstrual dysphoric disorder (PMDD) is estimated to affect 3%–8% of reproductive age women. Multiple therapeutic modalities have been evaluated with varying efficacy for the associated somatic and mood symptoms. The majority of older studies had shown that oral contraceptive pills (OCs) were most effective for the physical symptoms. However, newer OCs containing a novel progestin, drospirenone, have shown promise in alleviating both the somatic and affective/behavioral symptoms. This progestin, which is a derivative of spironolactone, has both antimineralocorticoid and antiandrogenic activity. A 24/4 formulation containing 20 µg of ethinyl estradiol has been found effective in randomized double-blind placebo-controlled trials utilizing established scales documenting symptoms associated with PMDD. Multiple studies have shown that drospirenone-containing OCs are safe without evidence of clinically adverse effects on carbohydrate metabolism, lipids, blood pressure, weight, serum potassium or increased thrombotic events compared to other low dose OCs. In addition, significant improvements have been demonstrated in acne, hirsutism, and fluid retention symptoms. Several open label studies demonstrated good patient compliance and reported satisfaction with the method. Because of the significant placebo effect demonstrated in the blinded placebo-controlled trials, additional large randomized placebo-controlled trials are needed to confirm the efficacy of the drospirenone OCs in the treatment of PMDD. However, this OC formulation appears to be a promising therapeutic modality.

Keywords: drospirenone, premenstrual dysphoric disorder, premenstrual syndrome, oral contraceptive pill

Introduction

Many studies have been conducted to evaluate potential treatment modalities for premenstrual dysphoric disorder (PMDD) and premenstrual syndrome (PMS). Recently, new oral contraceptive pills (OCs) containing drospirenone have shown promising results with respect to both the physical and mood symptoms associated with these clinical entities. This paper will provide a nonsystematic review of the literature on the use of drospirenone-containing OCs for the treatment of PMDD/PMS.

Definition

Premenstrual syndrome (PMS) is the term used to describe an array of predictable physical, cognitive, affective, and behavioral symptoms that occur cyclically during the luteal phase of the menstrual cycle and resolve quickly within a few days of onset of menstruation.¹ Some of the common physical symptoms include breast tenderness, abdominal bloating, headache, swelling of extremities, fatigue, acne,

Correspondence: Paula K Braverman
Cincinnati Children's Hospital Medical
Center, 3333 Burnet Avenue, ML 4000,
Cincinnati, OH 45229, USA
Tel +1 513 636 2070
Fax +1 513 636 1129
Email paula.braverman@cchmc.org

and food cravings/increased appetite. Common affective symptoms are irritability, anxiety/tension, labile mood, crying, depression, expressed anger, confusion, forgetfulness, sleep disturbance, and social isolation/withdrawal.^{1–5} It is estimated that 70%–90% of menstruating women have some degree of these symptoms before menses with 20%–40% describing them bothersome enough to impair daily functioning and classified as PMS.² A subset of women experiencing premenstrual symptoms includes the 3%–8% who have very severe symptoms and functional impairment which adversely affects their quality of life. These women are classified as having premenstrual dysphoric disorder (PMDD).²

Research criteria for PMDD are listed in the *Diagnostic and Statistical Manual of Mental Health Disorders*, 4th edition text revision (DSM IV TR) from the American Psychiatric Association.⁵ Although PMDD symptoms are focused more on mood, there is overlap between the criteria for PMS listed in the American College of Obstetricians and Gynecologists (ACOG) practice bulletin published in 2000¹ and the DSM IV TR criteria for PMDD.⁵ Studies in the gynecologic literature do not always draw a clear distinction between the two. Johnson⁶ and Speroff and Fritz⁷ both conclude that it may not be useful to try to differentiate between these entities. PMDD may represent severe PMS with impairment. Halbriech⁸ further discusses that there may be a number of women, up to 13%–18% of reproductive age women, who would benefit from treatment because of symptom severity that is clinically relevant even though they do not meet the minimum number of symptoms required in the DSM IV TR to meet the classification for PMDD.

Etiology

Although the exact etiology of PMS/PMDD is not known, the current literature suggests that the symptomatology is probably the result of an interaction between sex steroids and central neurotransmitters.⁹ Endorphins, γ -aminobutyric acid (GABA), and serotonin have been implicated.^{6,10–13} Studies have demonstrated reduced GABA receptor sensitivity and reduced plasma GABA in the luteal phase as well as possible serotonergic dysregulation with reduced serotonergic function in the luteal phase. Some of the physical symptoms may be related to the renin–angiotensin–aldosterone system (RAAS).¹³ Gonadal hormones influence the RAAS such that estrogen increases water retention and bloating through mineralocorticoid activity and induction of synthesis of angiotensinogen. Progesterone counteracts these effects through antimineralocorticoid activity. Although the

levels of sex steroids such as estrogen, progesterone, and testosterone are normal, studies have suggested that women with PMS/PMDD may be more sensitive to normal cyclical hormonal fluctuations and have an abnormal response to normal hormone changes. One study supporting this theory¹⁴ demonstrated a recurrence of symptoms in a group of women who were suppressed with the gonadotropin-releasing hormone agonist when given estrogen and progesterone. Some authors have suggested that this vulnerability may be in part related to serotonin.¹⁰

Impact on quality of life

PMS and PMDD have significant impact on quality of life. Studies have shown that individuals with moderate/severe PMS/PMDD are more likely to experience health- and work-related problems.^{15–17} Women with premenstrual symptoms have significantly higher rates of absenteeism from work and poorer productivity. Statistically significant increases in direct medical costs related to outpatient visits, laboratory tests, and radiology services have been demonstrated in addition to the costs related to work attendance and decreased productivity.

The consequences of PMS/PMDD have been demonstrated in studies in many parts of the world. Hylan¹⁸ studied 1,045 subjects from the United States, United Kingdom, and France of whom 23%–31% were classified as having severe premenstrual symptomatology. Interference with home, work, school and social life increased with severity of reported symptoms. There were similarities across the three countries with the most commonly reported symptoms being irritability/anger, fatigue, physical swelling/bloating, and weight gain.

In another recent study, Yang¹⁹ demonstrated a significant quality of life burden from PMDD in relation to both physical and mental health issues. Mental/emotional health issues were most prominent, with PMDD having a greater impact on body pain and mental health scales than chronic back pain. Finally, a study conducted by Robinson²⁰ addressed interpersonal relationships in more detail demonstrating that individuals who had symptomatology classified as moderate to severe PMS/PMDD, through a DSM-IV adapted classification of severity, reported impact on significant interpersonal relationships. Ninety-two percent of these women had one affected social- or work-related domain, with 61.5% having impact at work or school, 59.3% with household activities, 83% in the relationship with their husband, 77.6% in the relationship with their children, and 68.5% in their social life.

Treatment modalities

There is no single treatment modality that has been universally effective, and most studies have found conflicting results. Furthermore, many studies have not involved controlled clinical trials. Treatment interventions have included pharmacologic and nonpharmacologic modalities such as lifestyle change, stress management, and cognitive behavioral therapy, as well as minerals, vitamins, herbal preparations, and dietary manipulations. There is insufficient evidence to date to definitively recommend any of these non-pharmacologic modalities.^{21,22} Pharmacologic interventions have included hormonal therapies and psychotropic medications.²² OCs and GnRH agonists have been utilized to suppress ovulation, cyclic changes, and endogenous sex hormone variability.^{1,6,7,23–25} Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), as well as anxiolytics and other antidepressants, have been used to address somatic and/or affective symptoms.^{12,26–36} Some of the somatic and negative mood symptoms such as breast tenderness, bloating, and weight gain from fluid retention, irritability, and depression have also been demonstrated to improve with use of the diuretic spironolactone.^{37,38}

With respect to pharmacologic options, SSRIs have been considered the drugs of choice for severe PMS/PMDD.²⁶ Placebo-controlled studies have shown improvement in both physical and mood symptoms³⁹ and a recently published meta-analysis confirmed SSRI efficacy.⁴⁰ SSRIs are usually well tolerated and can be used in low doses. However, SSRIs are not without side effects which include insomnia, gastrointestinal disturbance, fatigue, dizziness, sweating, and sexual function disturbance.³⁹ Overall, studies of OCs have shown mixed effectiveness and in some cases worsening of symptoms. In general, OCs appear to have more impact on the physical symptoms rather than mood-related symptoms.^{1,6,23,41} However, a newer OC containing the progestin drospirenone, which is a derivative of spironolactone, has been shown to relieve both physical and mood symptoms. The remainder of this article will address use of OCs containing drospirenone in the management of PMS/PMDD.

OC formulations

Before addressing the specific OCs containing drospirenone, it is important to understand some key points about OC formulations. Combination oral contraceptive pills (COCs) contain both an estrogen and a progestin. There are essentially three variables to consider in OC formulations. The first

variable is the dose of estrogen. All available COCs contain ethinyl estradiol (EE) in varying amounts, with the lowest available dose being 15 µg EE and the highest 50 µg EE. The EE component is primarily responsible for the fluid retention side effects of the COCs. Lowering the dose of EE has decreased many side effects; however, it has also been associated with a higher incidence of intermenstrual bleeding than the original formulations, which all contained greater than 50 µg EE.⁴² In addition, although the half-life of EE is constant, with the lower estrogen doses used in the more recent formulations, EE is cleared from the circulation within only 2–3 days after the last active pill. This rapid clearance may allow FSH levels to rise and follicular development to occur within several days of the hormone-free interval in the OC pack.⁴³

The second variable is the type and dose of the progestin. There are three classes of progestins (synthetic progesterone-like compounds) in COCs: progesterone (17 α -acetoprogesterone) derivatives, testosterone (19-nortestosterone) derivatives, and spironolactone (17 α -spironolactone) derivatives. The 17 α -acetoprogesterone derivatives, referred to as pregnanes, are similar to the structure of progesterone itself. The testosterone derivatives are the most commonly used and fall into two major categories: estranes (norethindrone, norethindrone acetate, and ethynodiol acetate) and gonanes (norgestrel, levonorgestrel, norgestimate, desogestrel, and gestodene). By chemically altering testosterone, most of the androgenic properties are removed or substantially decreased, but all retain at least some degree of androgenicity. The only spironolactone-derived compound is drospirenone making this progestin the only progestin not derived from a sex steroid.

The effects of progestins are related to the compound's interactions with a number of receptors, including the receptor for progesterone, androgens, estrogen, glucocorticoids, and mineralocorticoids. The ability to either stimulate or block native interaction with such receptors mediates both the desirable and the undesirable side effects of some of the available progestins. Of note, acne and weight gain are commonly cited side effects of COCs which could be mediated by the progestin effect on the androgen and the glucocorticoid receptors respectively. Despite the efficacy of first and second generation progestins in preventing pregnancy, significant undesirable side effects, such as acne, water retention, and bloating limit the use for other indications. Third generation alternatives, such as norgestimate or desogestrel, have some advantages but still possess some androgenic activity. Unlike the other progestins, drospirenone has antimineralocorticoid

(aldosterone antagonist) and antiandrogenic properties⁴⁴ and is pharmacologically similar to endogenous progesterone.⁴⁵ The lack of antimineralocorticoid activity in other progestins may account for the sodium and water retention, minor elevations in blood pressure, and “pill hypertension” seen in some individuals.⁴⁶ The antimineralocorticoid effect of drospirenone has the potential to counteract the influence of estrogen-induced fluid retention that can affect some women who use low-dose COCs and reduce the incidence and severity of side effects related to fluid retention, such as swelling of the extremities, breast tension, and body weight. The antiandrogenic effects have the potential to positively impact dermatologic conditions such as acne and hirsutism.

With the unique characteristics of drospirenone, a COC containing EE and this novel progestin was believed to show promise in areas where other OCs have fallen short. In cohort studies of women with premenstrual symptoms comparing drospirenone and other progestins, there were beneficial trends when compared to other formulations. Foidart demonstrated these trends when comparing drospirenone to desogestrel.⁴⁷ Sangthawan found that the prevalence of water retention, in addition to other potentially negative effects (weight gain, irritability, anxiety) was reduced by half in the EE/drospirenone group while remaining unchanged in an EE/levonorgestrel group.⁴⁸

The third variable is the dosing pattern. The majority of COCs are administered in a standard 21/7 regimen, such that the EE and the progestin are given on days 1–21, followed by placebo pills on days 22–28, constituting the hormone-free interval. As with the estrogenic component, the lower doses of the progestins in the newer COCs are also cleared from the circulation within a few days after stopping the steroid-containing pills, allowing luteinizing hormone (LH) levels to rise. Therefore, ovulation may occur if the new cycle of active pills is not started exactly seven days after the last active pill was taken. In one randomized trial with a 20 µg EE formulation, when the hormone-free interval was five days, in lieu of the historical seven days, there was greater suppression of ovarian follicular size and endogenous estradiol levels.⁴⁹ Use of a 3–4 day hormone-free interval appears to provide a sufficient level of both EE and progestin in the circulation to suppress both gonadotropins until the new cycle of active pills is begun. Newer formulations of COCs (24/4) have decreased the hormone-free interval to four days by providing active medication on days 1–24 and placebo pills on days 25–28. The decrease in the number of days without steroid ingestion should result in constant

suppression of LH and follicle-stimulating hormone (FSH) levels and prevent follicular growth during the hormone-free interval. Constant inhibition of follicular development and endogenous estradiol synthesis throughout each month of oral contraceptive use should decrease the incidence of unscheduled bleeding as well as the incidence of escape ovulation and pregnancy that occurs with typical oral contraceptive use. In addition, the shortening of the hormone-free interval should decrease several of the adverse hormonal withdrawal symptoms experienced during the seven day hormone-free interval in the standard COC regimens.

OC formulations containing drospirenone

Two OCs are available which contain the progestin drospirenone. One is a standard 21/7 formulation containing 30 µg of ethinyl estradiol and the other is a 24/4 formulation containing 20 µg of ethinyl estradiol. Drospirenone has properties that are similar to its analog, spironolactone – an aldosterone antagonist, with antimineralocorticoid activity resulting in naturietic and antihypertensive qualities. The antimineralocorticoid effect of the 3 mg dose of drospirenone, contained in the commercially available OCs, is equivalent to 25 mg of spironolactone. The 24/4 formulation which contains a lower dose of EE (20 µg) with 3 mg of drospirenone and shorter hormone-free interval is proposed to minimize hormone withdrawal effects and have less fluid retention and stimulation of the renin–angiotensin–aldosterone system. Use of drospirenone with its long half life and antialdosterone and antiandrogenic qualities appears to be an excellent choice for a 24/4 OC regimen, particularly with respect to physical side effects and mood symptoms.

Impact of drospirenone-containing OCs on PMS and PMDD

There are a number of studies evaluating the impact of OCs containing drospirenone on PMS and PMDD. However, only a few were conducted as randomized placebo-controlled studies. This is especially important because of the potential for strong placebo effects in open trials.

The first double-blind placebo-controlled study was published by Freeman and colleagues⁵⁰ in 2001 and included 82 women who fit the diagnosis of PMDD per the DSM IV manual criteria. The subjects were evaluated after random assignment to drospirenone 3 mg/EE 30 µg (Yasmin) or placebo for three cycles. Symptoms were evaluated by the Calendar of Premenstrual Experiences (COPE) scale, Beck Depression Inventory (BDI), and Profile

of Mood States (POMS). Subjects' ratings were compared to their baseline scores. Although there was more numerical improvement in total COPE scores, BDI, and POMS when comparing the drospirenone OC to placebo, the only items that demonstrated statistical significance were factor 3 of the COPE scale which included acne, increased appetite, and food cravings. This study was limited by not having adequate power but was suggestive of positive effects of drospirenone 3 mg/EE 30 µg on PMDD symptoms.

In a second multicenter double-blind placebo-controlled crossover study by Pearlstein and colleagues,⁵¹ 64 subjects meeting DSM IV criteria for PMDD were given the either placebo or a 24/4 regimen of 20 µg of EE and 3 mg of drospirenone. After three cycles, they had a washout period and were then switched to the other regimen for another three cycles. Potential subjects were excluded if they had another concurrent mental health disorder including depression, anxiety, eating disorder, bipolar, psychosis, somatoform, dysthymic, or drug/alcohol problems in the previous two years. Symptoms were measured by the Daily Record of Severity of Problems Scale (DRSP), the Endicott Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), the Clinical Global Impressions-Improvement (CGI-I), and the Premenstrual Tension Scales (PMTS). There was statistically significant improvement on the total DRSP score comparing the drospirenone group to the placebo group with significant changes in the individual items including mood symptoms, irritability, anxiousness, difficulty concentrating, fatigue, appetite, and breast symptoms. In addition, there was significant improvement in functional impairment items such as productivity, social activities, and social relationships. Statistical significance was also found in the PMTS scores comparing the treatment to placebo group and in the Q-LES-Q showing significant changes in all items including overall life satisfaction except for the medication satisfaction rating. Statistically significant differences were also found in the CGI-I scale with 62% of women on the drospirenone preparation versus 32% on placebo showing positive responses. There was no significant difference in the total DRSP score comparing pill pack days 21–24 to 25–28 in the drospirenone group suggesting that the subjects did not experience hormone withdrawal symptoms and supporting the effectiveness of the 24/4 regimen.

A third study by Yonkers and colleagues⁵² involved a multicenter, double-blind randomized placebo-controlled trial with 450 women assigned to the 24/4 regimen of 20 µg EE and 3 mg of drospirenone (Yaz) or placebo and included two run-in cycles followed by three treatment cycles.

Subjects were evaluated with the DRSP, Q-LES-Q, the CGI-I, and PMTS. Similar to the Pearlstein study,⁵¹ there were statistically significant improvements in the CGI-I and PMTS comparing the treatment group to placebo. Statistically significant improvements in the DRSP scores were seen in the group with the active preparation compared to placebo in all of the physical and mood symptoms items on the DRSP questionnaire, as well as the functional impairment items including productivity, social activities, and quality of relationships. Similar to the Pearlstein study, there were also statistically significant differences in the Q-LES-Q for the first fourteen items. However, overall life satisfaction as well as medication satisfaction was not significant. As in the Pearlstein study, comparison of DRSP scores in the active group between days 21–24 and 25–28 of the pack did not show statistically significant differences supporting the absence of withdrawal symptoms with the 24/4 formulation.

In a published abstract from a poster presentation at the May 2008 ACOG meeting, Yonkers⁵³ reported on a further analysis by symptom category in which the DRSP items were grouped into the three categories of interpersonal relationships, food, or water retention. The scores were evaluated for the three treatment cycles and OC users were compared to the placebo group. Interpersonal relationships demonstrated the largest percent change followed by food and then water-retention symptoms. Statistically significant improvements were seen in all three cycles starting with the first active cycle. Since this is only a published abstract and the related full article is not available, it is not possible to completely evaluate the data; however, the results from the published abstract are promising.

Strengths and limitations of studies

The greatest strength of the referenced literature is the randomized nature of these three studies and the use of a double blind placebo controlled design. The Yonkers⁵² and Pearlstein⁵¹ studies also used similar evaluation tools which allows for easier comparison of results. However, there are limitations that should be considered. Two of the studies had small sample sizes (82 and 64 subjects) and the Freeman study⁵⁰ did not have enough power to effectively evaluate the study question. All of the studies had follow-up which was limited to only three cycles thereby limiting evaluation of long term efficacy. None of the studies compared the drospirenone OC to another OC so it is not possible to evaluate whether the drospirenone OC is superior to others on the market. Heterogeneity

is also an important consideration since completers in each study may have differed from non-completers, thus negatively impacting the generalizability of the results. Loss to follow-up was significant in all of the three studies. In Freeman, although there was no statistically significant difference in discontinuation rates between the drospirenone OC and placebo groups, 50% of the treatment group and 30% of the placebo group discontinued the study. In Pearlstein, total losses were 64%, including 58% for the group that received drospirenone first and 70% in the group randomized to use of placebo first. In the group that took the OC first, the noncompleters had a higher baseline mean for the DRSP than the completers, indicating more severe baseline symptoms. In terms of clinical relevance, those subjects actually may be ones most likely to benefit, but data is not available because they did not complete the study. Yonkers and colleagues also had subject attrition although that study had fewer losses than Pearlstein with a total of 27% including 31% for the drospirenone group and 23% for placebo.

Another limitation of all of these studies is the existence of the placebo effect as indicated by the fact that the placebo groups had high response rates. For example, in Freeman's paper, a 43% placebo response was reported. In Yonker's paper, 36% of participants given the placebo met criteria for "responders" in contrast to 48% of the women given the drospirenone OC. The number of individuals who need to be treated to see an actual benefit attributed to the therapy is larger as the placebo effect increases. As discussed in the recent Cochrane review,⁵⁴ depending on the size of the placebo effect, it could be less expensive and less risky to treat PMDD with a placebo rather than a COC. Although the Pearlstein and Yonkers' studies strongly suggest that drospirenone with 20 µg EE in a 24/4 formulation may help treat premenstrual symptoms in women with PMDD, the strong placebo effect makes evaluation of the clinical significance of the difference more difficult to interpret. More randomized placebo controlled studies are needed to further evaluate this issue.

Results of other studies

Several studies have been conducted to evaluate the effects of an OC containing drospirenone on quality of life. These additional studies include Borenstein,⁵⁵ Endrikat,⁵⁶ Taneepanichskul,⁵⁷ Sangthawan,⁴⁸ Apter,⁵⁸ Borges,⁵⁹ Brown,⁶⁰ and Parsey.⁶¹ These studies used standardized questionnaires such as the Menstrual Distress Questionnaire (MDQ), Medical Outcomes Short Form (SF-12), Women's Health Assessment Questionnaire, and the Psychological General

Well Being Index and compared ratings on physical and emotional/mood symptoms over several cycles ranging from 2–13. The various studies demonstrated statistically significant improvements in premenstrual symptomatology, including water retention, abdominal bloating, breast tension/tenderness, weight gain, swelling, skin disorders including undesirable hair change, and food cravings, as well as improvement in negative affect including crying, loneliness, anxiety, restlessness, irritability, mood swings, depression, and tension. Among these various studies, there was also a statistically significant improvement shown in reported ability to perform usual activities, general sense of well being, self control, and vitality.

Overall these studies have limitations. Although some were large multicenter studies, others had small sample sizes. Further, although some compared the effects of an OC with drospirenone to an OC with another progestin, many were open-label noncomparative studies and subject to difficulty in interpretation because of potential substantial placebo effects. The studies also used a variety of different instruments which make comparison between them more difficult. Despite these limitations, the results do show common trends in improvement in PMS/PMDD symptoms and strongly suggest the need for further evaluation and confirmation of the results with more rigorously designed clinical trials. They also provide some longer term follow up than the three randomized double blind placebo controlled studies discussed above.

Side effects of drospirenone-containing OCs

Many studies have evaluated the side effects of drospirenone-containing OCs. Although some of these studies were not placebo-controlled or double-blinded, some of the outcomes were related to laboratory tests and clinical measurements such as blood pressure, weight, and serum potassium levels, which are objectively measured by an instrument and therefore raise less concern about the placebo effect seen in subjective behavioral outcome measures. These side effects include both negative and potentially beneficial side effects. Beneficial side effects of an OC containing drospirenone would be anticipated because of the antiandrogenic and antimineralocorticoid activity of this progestin.

Skin

Acne

Studies of OC preparations containing drospirenone have shown improvement in acne in terms of severity and

lesion count.^{62–65} One open label randomized multicenter study⁶² followed 2,069 women over 13 treatment cycles and found a reduction in the incidence of acne from 21.5% to 7.8% by the end of the study. In a double-blind study,⁶³ an OC containing drospirenone showed improvement which reached statistical significance when compared to an OC containing norgestimate. A multicenter randomized placebo-controlled double-blind study⁶⁴ of 538 14–45-year-old women with moderate acne who were evaluated after six cycles demonstrated improvement in acne severity and lesion count compared to placebo. This study utilized the Investigator Static Global Assessment Scale, and demonstrated a statistically significant reduction in total lesions (46%) in the treatment group compared to placebo (31%) as well as an increase in the number of subjects rated as clear or almost clear in the treatment group. Finally, a randomized double-blind placebo-controlled trial⁶⁵ included 534 women of reproductive age and showed improvement in both lesion counts and a statistically significant improvement in both the investigator's and the subject's self rating of improvement in acne. Compared to the placebo group, those in the drospirenone OC group had a fourfold greater chance of being rated as clear or almost clear at the end of study.

Hirsutism

Two small studies^{66,67} demonstrated improvement in hirsutism. The first⁶⁶ was an open prospective study of 20 women demonstrating a statistically significant improvement in the Ferriman–Gallwey score⁶⁸ after six cycles of a drospirenone containing OC. The second⁶⁷ was a prospective open controlled clinical trial with 50 women that showed a statistically significant improvement in Ferriman–Gallwey scores at both six and 12 months of therapy with a reduction of 67% in the score at six months and 78% at 12 months compared to baseline.

Cycle control

Multiple studies have demonstrated good cycle control with drospirenone-containing OCs.^{47,58,59,61,62,69} Similar to other OCs, intermenstrual bleeding is highest during the first cycle and remits during subsequent cycles. Two studies^{47,62} which compared users of a drospirenone-containing OC to desogestrel found no significant differences in intermenstrual bleeding between these two formulations over 13 months and 26 months, respectively. In the double-blind, randomized, placebo-controlled study by Yonkers,⁵² 25.1% of treatment subjects compared to 4.6% of placebo

subjects had intermenstrual bleeding. This difference was statistically significant but it is difficult to adequately assess this finding since the study was limited to three cycles when intermenstrual bleeding is most common on all low dose OCs. In the smaller similarly designed study by Pearlstein,⁵¹ there was a trend toward increased intermenstrual bleeding in the drospirenone group compared to placebo but this was not statistically significant ($p = 0.067$).

Weight

One of the most common complaints among COC users is weight gain. Multiple studies have demonstrated stable or lower body weight with the drospirenone-containing OC.^{47,58,59,62,69–72} These studies included comparative studies demonstrating lower body weight with the drospirenone-containing OC than a formulation containing desogestrel.

Breast tenderness

Yonkers found a statistically significant difference in breast pain complaints between treatment and placebo subjects (13.4% vs 5%) in a double-blind, randomized placebo-controlled study.⁵² The smaller similarly designed study by Pearlstein,⁵¹ however, did not demonstrate a statistically significant difference between treatment and placebo subjects.

Nausea

Yonkers⁵² found a statistically significant difference in complaints of nausea when comparing the drospirenone group to placebo (18.6% vs 5%). Pearlstein⁵¹ did not find this difference to be statistically significant in a smaller similarly designed study. It is difficult to know if this symptom would have persisted since the Yonkers study only followed subjects for three months and this common complaint frequently improves after a few pill cycles.

Headache

Neither Yonkers⁵² nor Pearlstein⁵¹ found statistically significant differences in complaints of headache when comparing the drospirenone group to the placebo group in their double-blind placebo-controlled randomized trials.

Safety

Hyperkalemia

One of the primary safety concerns with drospirenone is the possibility of hyperkalemia. Because drospirenone shares spironolactone's potassium-sparing characteristic, OCs containing this progestin carry a warning about the

possibility of hyperkalemia in high-risk women.⁷³ Several studies have reported on the incidence of hyperkalemia in women using drospirenone. In the randomized placebo-controlled study by Yonkers,⁵² there were no differences in serum potassium between the placebo and OC group. In the open-labeled study by Bachmann,⁶⁹ only four of 1,027 subjects had a serum potassium between 5.5–5.7 mEq/L, and there were no recorded adverse potassium-related events. Schürmann⁷⁴ conducted an open-label study investigating whether drospirenone alone increased the risk of hyperkalemia in subjects with renal impairment. Twenty-eight women were divided into three groups classified as normal renal function and mild or moderate renal impairment and were given drospirenone 3 mg/day for 14 days. There were no significant changes in the mean serum potassium concentrations during the 14 days of steady state drospirenone treatment. These results included 25% of subjects who continued to use antihypertensive medications that had the potential to elevate their potassium concentration during the study. No statistically significant or clinically meaningful differences in serum potassium concentrations in subjects with renal insufficiency versus subjects with normal renal function were found.⁷⁴ Oelkers⁷⁰ investigated the effects of a drospirenone-containing OC on serum potassium with different doses of EE (30 µg EE, 20 µg EE, 15 µg EE) and compared these to an OC with levonorgestrel and 30 µg EE. Twenty women with normal renal function indices participated in each group. Serum potassium did not change significantly during treatment and was approximately 4.1 mmol/L in all four groups. Finally, one study by Schütt⁷⁵ evaluated the effect of co-administration of estradiol/drospirenone and indomethacin in a randomized open-labeled crossover study in postmenopausal women and did not find significant changes in serum potassium levels. The results of this study would imply that concomitant use of NSAIDs with a drospirenone-containing OC should not be a concern.

The largest evaluation was a multinational, prospective noninterventional cohort study of new users of OCs, including drospirenone, levonorgestrel, and other progestin-containing formulations (European Active Surveillance study [EURAS]).⁷⁶ A total of 58,674 women were followed for 142,475 women-years of observation. In this investigation, 28.2% used a drospirenone-containing OC, 26.3% used a OC containing levonorgestrel, 44.9% used OCs containing another progestin, and 0.6% did not use a combined oral contraceptive. Data regarding the incidence of arrhythmias was used as a surrogate measure of serum potassium levels. None of the

99 confirmed new arrhythmias were suggestive of the types associated with increased serum potassium. However, potassium levels were not directly measured.

Venous thromboembolic events

It is well established that OCs increase the risk of venous thromboembolic events (VTE). An important consideration for any new progestin is the evaluation of the potential VTE risk. The EURAS study is important because it is a prospective multinational study with a large number of subjects.⁷⁶ In this study, the monophasic 30 µg EE/levonorgestrel products represented 53% of the levonorgestrel exposure, which allowed a direct comparison of drospirenone to levonorgestrel for OCs containing a monophasic dosing pattern of 30 µg of EE. The incidence of VTE was 10.2/10,000 women years in the levonorgestrel subcohort and 9.1/10,000 women years in the drospirenone cohort. Cox regression analysis found a crude hazard ratio (HR) for drospirenone of 0.9 (95% confidence interval [CI]: 0.5–1.6) and an HR_{adj} of 0.8 (95% CI: 0.5–1.5) indicating that there was no evidence of a higher risk of VTE in the drospirenone group compared to the levonorgestrel group.

In another large study in the United States, Seeger and colleagues collected data from a database maintained by the health insurer, United Healthcare.⁷⁷ The authors identified EE/drospirenone initiators along with a comparison group of other OC initiators with similar demographic and health care characteristics. There were 22,429 EE/drospirenone initiators and 44,858 initiators of other oral contraceptive initiators who were followed for an average of 7.6 months. Cases of thromboembolism were identified through claims for medical services and only those claims that were confirmed through review of the medical record were considered true cases of VTE. There were eighteen cases of thromboembolism in EE/drospirenone subjects (1.3/10,000 woman-years) compared to 39 cases (1.4/10,000 woman-years) in the other OC initiators. The rate ratio was 0.9 with a confidence interval of 0.5–1.6 demonstrating no difference in risk of thromboembolism between the two groups making the thromboembolism risk of a drospirenone OC similar to other COCs.

Blood pressure

No significant adverse effects on blood pressure (BP) were found in multiple studies,^{47,59,61,62,69–71} and in several comparative studies the BP was slightly lower in the drospirenone group.

Insulin resistance and glucose tolerance

Multiple studies^{70,78,79} have demonstrated a lack of clinically significant changes in glucose tolerance utilizing oral

glucose tolerance tests and measurements of glucose and insulin levels. These results were evaluated in ranges of six to 12 months depending on the study.

Lipids

Overall OCs containing drospirenone show a favorable lipid profile with an increase in high-density lipoprotein and decrease in low-density lipoprotein cholesterol levels.^{61,70,79} Although these studies demonstrated an increase in serum triglycerides, the plasma lipid changes were within the reference range or did not suggest clinically significant atherogenic changes. A study by Klipping⁷⁹ compared two different OCs and did not find significant differences in lipids between the subjects taking an OC with drospirenone and those taking an OC-containing desogestrel.

Other adverse events

When comparing the drospirenone-containing OC cohort to other OC cohorts, the EURAS study did not find any increase in arterial thromboembolism or any of 14 other disease categories, including malignant neoplasms, benign tumors, infection, injury, or in any other organ systems including blood-forming, eye, respiratory, endocrine, central nervous system, skin, genitourinary, cardiovascular, digestive, and musculoskeletal.⁷⁶ The incidence for cancer of the breast, cervix, and uterus were similar or lower when comparing the drospirenone group to the other OC cohorts. In addition, there were no statistically significant differences in fatal outcomes between the drospirenone cohort and the other OC cohorts and no causal relationship found for any deaths in the drospirenone cohort by the Advisory Council.

Patient satisfaction/compliance

Several studies have addressed patient satisfaction. In the open label noncomparative study of 1,018 women by Bachmann⁶⁹ of a 24/4 drospirenone formulation with 20 µg of EE, 86% of subjects reported that they were satisfied or very satisfied with the treatment and 72.7% reported a desire to continue with the study medication. This was associated with over 85% reporting improved or unchanged physical and emotional well being. Subjects demonstrated excellent compliance with 92.6%–95.7% taking 26 or more tablets per cycle. In an open-label study of 326 women by Parsey,⁶¹ utilizing the 21/7 30 µg EE formulation drospirenone OC, 73% did not miss any pills during the study, with 80% compliance among subjects who had used OCs in the past and 65% for those who were new OC users. Borges⁵⁹ found that 84.2% of 241 women given a 21/7 30 µg EE

formulation of a drospirenone OC in an open-label study reported improvement in their premenstrual symptoms and that the treatment was successful. Finally, Apter⁵⁸ studied 336 subjects in an open label uncontrolled study of a 21/7 30 EE µg formulation of a drospirenone OC and found that 86% of the time there was agreement between the investigator and subjects regarding symptom improvement with 85% of the subjects reported being much or very much satisfied at cycle 6 of the treatment protocol.

Conclusions

PMDD/PMS is a significant condition that adversely affects quality of life for a subset of menstruating women. Randomized placebo-controlled double-blind studies have shown that the OCs containing drospirenone, and more specifically the 24/4 formulation, may significantly improve the mood and physical symptoms associated with PMDD and improve quality of life issues. Based on large studies in Europe and the United States, there do not appear to be any increased adverse physiologic or health outcomes related to the drospirenone-containing OC compared to other OCs on the market. Furthermore, OCs containing drospirenone appear to have several beneficial effects including improvement in acne, fluid retention symptoms, and hirsutism without significant weight gain. Although more double-blinded placebo-controlled studies are needed, several open label studies suggest high rates of patient satisfaction and compliance with drospirenone-containing OCs.

Disclosure

The authors report no conflicts of interest in this work.

References

1. American College of Obstetrics and Gynecology. *ACOG Practice Bulletin Number 15: Premenstrual Syndrome*. Washington, D.C.: American College of Obstetrics and Gynecology; 2000.
2. Mishell DR Jr. Premenstrual disorders: epidemiology and disease burden. *Am J Manag Care*. 2005;11(16 Suppl):S473–S479.
3. Mortola JF, Girton L, Yen SS. Depressive episodes in premenstrual syndrome. *Am J Obstet Gynecol*. 1989;161(6 Pt 1):1682–1687.
4. Mortola JF, Girton L, Beck L, Yen SS. Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument: the calendar of premenstrual experiences. *Obstet Gynecol*. 1990;76(2):302–307.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-Text Revision*. 4th ed. Washington, DC.: American Psychiatric Association; 2000.
6. Johnson SR. Premenstrual syndrome, premenstrual dysphoric disorder, and beyond: a clinical primer for practitioners. *Obstet Gynecol*. 2004; 104(4):845–859.
7. Speroff L, Fritz MA. *Clinical Gynecologic Endocrinology and Infertility*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
8. Halbreich U, Borenstein J, Pearlstein T, Kahn LS. The prevalence, impairment, impact, and burden of premenstrual dysphoric disorder (PMS/PMDD). *Psychoneuroendocrinology*. 2003;28 Suppl 3):1–23.

9. Mortola JF. Premenstrual syndrome – pathophysiologic considerations. *N Engl J Med*. 1998;338(4):256–257.
10. Steiner M, Pearlstein T. Premenstrual dysphoria and the serotonin system: pathophysiology and treatment. *J Clin Psychiatry*. 2000; 61(Suppl 12):17–21.
11. Halbreich U. The diagnosis of premenstrual syndromes and premenstrual dysphoric disorder—clinical procedures and research perspectives. *Gynecol Endocrinol*. 2004;19(6):320–334.
12. Freeman EW. Luteal phase administration of agents for the treatment of premenstrual dysphoric disorder. *CNS Drugs*. 2004;18(7):453–468.
13. Rapkin AJ. YAZ in the treatment of premenstrual dysphoric disorder. *J Reprod Med*. 2008;53(9 Suppl):729–741.
14. Schmidt PJ, Nieman LK, Danaceau MA, Adams LF, Rubinow DR. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. *N Engl J Med*. 1998;338(4):209–216.
15. Borenstein J, Chiou CF, Dean B, Wong J, Wade S. Estimating direct and indirect costs of premenstrual syndrome. *J Occup Environ Med*. 2005;47(1):26–33.
16. Borenstein JE, Dean BB, Leifke E, Korner P, Yonkers KA. Differences in symptom scores and health outcomes in premenstrual syndrome. *J Womens Health (Larchmt)*. 2007;16(8):1139–1144.
17. Borenstein JE, Dean BB, Endicott J, et al. Health and economic impact of the premenstrual syndrome. *J Reprod Med*. 2003;48(7):515–524.
18. Hylan TR, Sundell K, Judge R. The impact of premenstrual symptomatology on functioning and treatment-seeking behavior: experience from the United States, United Kingdom, and France. *J Womens Health Gend Based Med*. 1999;8(8):1043–1052.
19. Yang M, Wallenstein G, Hagan M, Guo A, Chang J, Kornstein S. Burden of premenstrual dysphoric disorder on health-related quality of life. *J Womens Health (Larchmt)*. 2008;17(1):113–121.
20. Robinson RL, Swindle RW. Premenstrual symptom severity: impact on social functioning and treatment-seeking behaviors. *J Womens Health Gend Based Med*. 2000 Sep;9(7):757–768.
21. Lustyk MK, Gerrish WG, Shaver S, Keys SL. Cognitive-behavioral therapy for premenstrual syndrome and premenstrual dysphoric disorder: a systematic review. *Arch Womens Ment Health*. 2009;12(2):85–96.
22. Braverman PK. Premenstrual syndrome and premenstrual dysphoric disorder. *J Pediatr Adolesc Gynecol*. 2007;20(1):3–12.
23. Rapkin AJ. New treatment approaches for premenstrual disorders. *Am J Manag Care*. 2005;11(16 Suppl):S480–S491.
24. Emans S, Laufer MR, Goldstein DP, eds. *Pediatric and Adolescent Gynecology*. 5th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2005.
25. Freeman EW, Sondheimer SJ, Rickels K. Gonadotropin-releasing hormone agonist in the treatment of premenstrual symptoms with and without ongoing dysphoria: a controlled study. *Psychopharmacol Bull*. 1997;33(2):303–309.
26. Dimmock PW, Wyatt KM, Jones PW, O'Brien PM. Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review. *Lancet*. 2000;356(9236):1131–1136.
27. Freeman EW, Rickels K, Sondheimer SJ, Polansky M, Xiao S. Continuous or intermittent dosing with sertraline for patients with severe premenstrual syndrome or premenstrual dysphoric disorder. *Am J Psychiatry*. 2004;161(2):343–351.
28. Freeman EW, Sondheimer SJ, Sammel MD, Ferdousi T, Lin H. A preliminary study of luteal phase versus symptom-onset dosing with escitalopram for premenstrual dysphoric disorder. *J Clin Psychiatry*. 2005;66(6):769–773.
29. Steiner M, Steinberg S, Stewart D, et al. Fluoxetine in the treatment of premenstrual dysphoria. Canadian Fluoxetine/Premenstrual Dysphoria Collaborative Study Group. *N Engl J Med*. 1995;332(23):1529–1534.
30. Freeman EW, Rickels K, Yonkers KA, Kunz NR, McPherson M, Upton GV. Venlafaxine in the treatment of premenstrual dysphoric disorder. *Obstet Gynecol*. 2001;98(5 Pt 1):737–744.
31. Cohen LS, Soares CN, Lyster A, Cassano P, Brandes M, Leblanc GA. Efficacy and tolerability of premenstrual use of venlafaxine (flexible dose) in the treatment of premenstrual dysphoric disorder. *J Clin Psychopharmacol*. 2004;24(5):540–543.
32. Grady-Weliky TA. Clinical practice. Premenstrual dysphoric disorder. *N Engl J Med*. 2003;348(5):433–438.
33. Freeman EW, Rickels K, Sondheimer SJ, Polansky M. A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. *JAMA*. 1995;274(1):51–57.
34. Smith S, Rinehart JS, Ruddock VE, Schiff I. Treatment of premenstrual syndrome with alprazolam: results of a double-blind, placebo-controlled, randomized crossover clinical trial. *Obstet Gynecol*. 1987;70(1):37–43.
35. Harrison WM, Endicott J, Nee J. Treatment of premenstrual dysphoria with alprazolam. A controlled study. *Arch Gen Psychiatry*. 1990;47(3): 270–275.
36. Landen M, Eriksson O, Sundblad C, Andersch B, Naessen T, Eriksson E. Compounds with affinity for serotonergic receptors in the treatment of premenstrual dysphoria: a comparison of buspirone, nefazodone and placebo. *Psychopharmacology (Berl)*. 2001;155(3):292–298.
37. Wang M, Hammarback S, Lindhe BA, Backstrom T. Treatment of premenstrual syndrome by spironolactone: a double-blind, placebo-controlled study. *Acta Obstet Gynecol Scand*. 1995;74(10):803–808.
38. O'Brien PM, Craven D, Selby C, Symonds EM. Treatment of premenstrual syndrome by spironolactone. *Br J Obstet Gynaecol*. 1979;86(2):142–147.
39. Wyatt K, Dimmock PW, O'Brien PM. Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database Syst Rev*. 2005;3:CD001396.
40. Shah NR, Jones JB, Aperi J, Shemtov R, Karne A, Borenstein J. Selective serotonin reuptake inhibitors for premenstrual syndrome and premenstrual dysphoric disorder: a meta-analysis. *Obstet Gynecol*. 2008;111(5):1175–1182.
41. Joffe H, Cohen LS, Harlow BL. Impact of oral contraceptive pill use on premenstrual mood: predictors of improvement and deterioration. *Am J Obstet Gynecol*. 2003;189(6):1523–1530.
42. Appel TB, Kambi AA, Birdsall C, et al. A comparison of a new graduated estrogen formulation with three constant-dosed oral contraceptives. *Contraception*. 1987;35(6):523–532.
43. van Heusden AM, Fauser BC. Activity of the pituitary-ovarian axis in the pill-free interval during use of low-dose combined oral contraceptives. *Contraception*. 1999;59(4):237–243.
44. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. *Contraception*. 2000;62(1):29–38.
45. Rubig A. Drospirenone: a new cardiovascular-active progestin with antiandrogenic and antiandrogenic properties. *Climacteric*. 2003; 6(Suppl 3):49–54.
46. Elger W, Beier S, Pollow K, Garfield R, Shi SQ, Hillisch A. Conception and pharmacodynamic profile of drospirenone. *Steroids*. 2003;68(10–13): 891–905.
47. Foidart JM, Wuttke W, Bouw GM, Gerlinger C, Heithecker R. A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. *Eur J Contracept Reprod Health Care*. 2000;5(2):124–134.
48. Sangthawan M, Taneepanichskul S. A comparative study of monophasic oral contraceptives containing either drospirenone 3 mg or levonorgestrel 150 microg on premenstrual symptoms. *Contraception*. 2005;71(1):1–7.
49. Spona J, Elstein M, Feichtinger W, et al. Shorter pill-free interval in combined oral contraceptives decreases follicular development. *Contraception*. 1996;54(2):71–77.
50. Freeman EW, Kroll R, Rapkin A, et al. Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. *J Womens Health Gend Based Med*. 2001;10(6):561–569.
51. Pearlstein TB, Bachmann GA, Zacur HA, Yonkers KA. Treatment of premenstrual dysphoric disorder with a new drospirenone-containing oral contraceptive formulation. *Contraception*. 2005;72(6):414–421.
52. Yonkers KA, Brown C, Pearlstein TB, Foegh M, Sampson-Landers C, Rapkin A. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. *Obstet Gynecol*. 2005;106(3):492–501.

53. Yonkers KA, Niknian M, Marr J. Premenstrual dysphoric disorder symptom cluster improvement by cycle with an oral contraceptive (drospirenone 3 mg/ethinyl estradiol 20 micrograms 24/4) (Abstract for poster session at ACOG 56th Annual Clinical Meeting). *Obstetrics and Gynecology*. 2008;111:65S.
54. Lopez LM, Kaptein A, Helmerhorst FM. Oral contraceptives containing drospirenone for premenstrual syndrome. *Cochrane Database Syst Rev*. 2008;1:CD006586.
55. Borenstein J, Yu HT, Wade S, Chiou CF, Rapkin A. Effect of an oral contraceptive containing ethinyl estradiol and drospirenone on premenstrual symptomatology and health-related quality of life. *J Reprod Med*. 2003;48(2):79–85.
56. Endrikat J, Sandri M, Gerlinger C, Rubig A, Schmidt W, Fortier M. A Canadian multicentre prospective study on the effects of an oral contraceptive containing 3 mg drospirenone and 30 microg ethinyl oestradiol on somatic and psychological symptoms related to water retention and on body weight. *Eur J Contracept Reprod Health Care*. 2007;12(3):220–228.
57. Taneepanichskul S, Jaisamram U, Phupong V. Efficacy of Yasmin in premenstrual symptoms. *Arch Gynecol Obstet*. 2007;275(6):433–438.
58. Apter D, Borsos A, Baumgartner W, et al. Effect of an oral contraceptive containing drospirenone and ethinylestradiol on general well-being and fluid-related symptoms. *Eur J Contracept Reprod Health Care*. 2003;8(1):37–51.
59. Borges LE, Andrade RP, Aldrighi JM, et al. Effect of a combination of ethinylestradiol 30 microg and drospirenone 3 mg on tolerance, cycle control, general well-being and fluid-related symptoms in women with premenstrual disorders requesting contraception. *Contraception*. 2006;74(6):446–450.
60. Brown C, Ling F, Wan J. A new monophasic oral contraceptive containing drospirenone. Effect on premenstrual symptoms. *J Reprod Med*. 2002;47(1):14–22.
61. Parsey KS, Pong A. An open-label, multicenter study to evaluate Yasmin, a low-dose combination oral contraceptive containing drospirenone, a new progestogen. *Contraception*. 2000;61(2):105–111.
62. Huber J, Foidart JM, Wuttke W, et al. Efficacy and tolerability of a monophasic oral contraceptive containing ethinylestradiol and drospirenone. *Eur J Contracept Reprod Health Care*. 2000;5(1):25–34.
63. Thornycroft H, Gollnick H, Schellschmidt I. Superiority of a combined contraceptive containing drospirenone to a triphasic preparation containing norgestimate in acne treatment. *Cutis*. 2004;74(2):123–130.
64. Maloney JM, Dietze P Jr, Watson D, et al. Treatment of acne using a 3-milligram drospirenone/20-microgram ethinyl estradiol oral contraceptive administered in a 24/4 regimen: a randomized controlled trial. *Obstet Gynecol*. 2008;112(4):773–781.
65. Koltun W, Lucky AW, Thiboutot D, et al. Efficacy and safety of 3 mg drospirenone/20 mcg ethinylestradiol oral contraceptive administered in 24/4 regimen in the treatment of acne vulgaris: a randomized, double-blind, placebo-controlled trial. *Contraception*. 2008;77(4):249–256.
66. Pehlivanov B, Mitkov M. Efficacy of an oral contraceptive containing drospirenone in the treatment of women with polycystic ovary syndrome. *Eur J Contracept Reprod Health Care*. 2007;12(1):30–35.
67. Batukan C, Muderris II. Efficacy of a new oral contraceptive containing drospirenone and ethinyl estradiol in the long-term treatment of hirsutism. *Fertil Steril*. 2006;85(2):436–440.
68. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab*. 1961;21:1440–1447.
69. Bachmann G, Sulak PJ, Sampson-Landers C, Benda N, Marr J. Efficacy and safety of a low-dose 24-day combined oral contraceptive containing 20 micrograms ethinylestradiol and 3 mg drospirenone. *Contraception*. 2004;70(3):191–198.
70. Oelkers W, Foidart JM, Dombrovicz N, Welter A, Heithecker R. Effects of a new oral contraceptive containing an antiminerocorticoid progestogen, drospirenone, on the renin-aldosterone system, body weight, blood pressure, glucose tolerance, and lipid metabolism. *J Clin Endocrinol Metab*. 1995;80(6):1816–1821.
71. Foidart JM. The contraceptive profile of a new oral contraceptive with antiminerocorticoid and antiandrogenic effects. *Eur J Contracept Reprod Health Care*. 2000;5(Suppl 3):25–33.
72. Foidart JM. Added benefits of drospirenone for compliance. *Climacteric*. 2005;8(Suppl 3):28–34.
73. Bayer HealthCare Pharmaceuticals. YAZ combination brief and detailed patient labeling (package insert). Wayne, NJ: Bayer HealthCare Pharmaceuticals, Inc; 2007. p. 1–8.
74. Schürmann R, Blode H, Benda N, Cronin M, Kufner A. Effect of drospirenone on serum potassium and drospirenone pharmacokinetics in women with normal or impaired renal function. *J Clin Pharmacol*. 2006;46(8):867–875.
75. Schütt B, Kunz M, Blode H. Coadministration of estradiol/drospirenone and indomethacin does not cause hyperkalemia in healthy postmenopausal women: a randomized open-label crossover study. *J Clin Pharmacol*. 2007;47(6):774–781.
76. Dinger JC, Heinemann LA, Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142, 475 women-years of observation. *Contraception*. 2007;75(5):344–354.
77. Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol*. 2007;110(3):587–593.
78. Gaspard U, Scheen A, Endrikat J, et al. A randomized study over 13 cycles to assess the influence of oral contraceptives containing ethinylestradiol combined with drospirenone or desogestrel on carbohydrate metabolism. *Contraception*. 2003;67(6):423–429.
79. Klipping C, Marr J. Effects of two combined oral contraceptives containing ethinyl estradiol 20 microg combined with either drospirenone or desogestrel on lipids, hemostatic parameters and carbohydrate metabolism. *Contraception*. 2005;71(6):409–416.

International Journal of Women's Health

Publish your work in this journal

The International Journal of Women's Health is an international, peer-reviewed open-access journal publishing original research, reports, reviews and commentaries on all aspects of women's healthcare including gynaecology, obstetrics, and breast cancer. Subject areas include: Chronic conditions (migraine headaches, arthritis, osteoporosis);

Submit your manuscript here: <http://www.dovepress.com/international-journal-of-womens-health-journal>

Dovepress

Endocrine and autoimmune syndromes; Sexual and reproductive health; Psychological and psychosocial conditions. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.