Drospirenone: pharmacology and pharmacokinetics of a unique progestogen

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Abstract

The pharmacology and pharmacokinetics of drospirenone, a unique progestogen, are reviewed in this paper. Unlike other progestogens, drospirenone, an analogue of spironolactone, has biochemical and pharmacologic profiles similar to endogenous progesterone, especially regarding antimineralocorticoid and antiandrogenic activities. Drospirenone counteracts the estrogen-induced stimulation of the renin-angiotensin-aldosterone system and blocks testosterone from binding to androgen receptors. Because of these characteristics, it has the potential to reduce body weight, blood pressure, and low-density lipoprotein levels and to enhance high-density lipoprotein levels. As a combination oral contraceptive, drospirenone with ethinyl estradiol is effective and has positive effects on weight and lipid levels. Additionally, it relieves menstrually related symptoms (e.g., negative affect and water retention) that are commonly observed with other combination oral contraceptives. Based on the biochemical and pharmacodynamic data, drospirenone appears to be a viable alternative to the currently available progestogens. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Drospirenone; Progestogen; Oral contraceptive; Renin-angiotensin-aldosterone system; premenstrual syndrome

1. Introduction

Improving the safety and tolerability of oral contraceptives (OCs) without affecting efficacy has been a major research goal for over 20 years. Developing new progestogens has been considered one means of achieving this goal [1,2]. Ideally, a progestogen should have a pharmacologic profile similar to progesterone. Currently available progestogens are structurally related to either 19-nortestosterone (e.g., norethisterone, norethisterone acetate, levonorgestrel, gestodene, desogestrel, norgestimate, and dienogest) or 17α-hydroxyprogesterone (e.g., medroxyprogesterone acetate, megestrol acetate, chlorpromazine acetate, and cyproterone acetate) [3,4]. While some of these agents have antiandrogenic properties (e.g., dienogest, cyproterone acetate, megestrol acetate, and chlorpromazine acetate), they all lack antimineralocorticoid activity when used in clinically relevant dosages [3,5,6]. Adverse effects associated with OCs containing these progestogens may be due, in part, to the absence of these specific antihormone characteristics [1,7–9]. These effects include breast tenderness, weight gain, increased blood pressure (BP), and mood swings. Adverse effects such as these are the major reason why women discontinue the use of OCs [8].

Drospirenone is an analogue of the aldosterone antagonist, spironolactone, and is a unique progestogen [10]. The pharmacologic profile of drospirenone is more closely related to that of progesterone, especially with regard to antimineralocorticoid and antiandrogenic activities, than that of any other synthetic progestogen [11–14]. This suggests that adverse effects commonly observed with combination OCs may be decreased with an OC containing drospirenone. In a recent study, the contraceptive efficacy and adverse effects of drospirenone/ethinyl estradiol combination treatment were evaluated with favorable results [2].

The purpose of this article is to review the distinctive biochemical and pharmacologic characteristics and pharmacokinetics of drospirenone. In addition, contraceptive efficacy and the potential health benefits beyond contraception associated with drospirenone/ethinyl estradiol will be discussed.
2. Biochemistry

Drospirenone (6β,7β,15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17 carbolactone) is an analogue of the antimineralocorticoid spironolactone (Fig. 1) that is synthesized from androstenolone [10,15,16]. A comprehensive, comparative biochemical characterization of drospirenone and progesterone examined their interaction with a series of classical steroid hormone receptors such as the progesterone, androgen, glucocorticoid, mineralocorticoid, and estrogen receptors [10]. The relative binding affinities of drospirenone and progesterone to these receptors were determined using cytosol fractions containing the expression vector for the respective animal (rat or rabbit) [10] or human steroid receptor. (Data on file, Schering AG, Berlin, Germany.) The radiolabeled reference compounds for the progesterone, androgen, glucocorticoid, mineralocorticoid, and estrogen receptors were progesterone, methyltrienolone, aldosterone, dexamethasone, and estradiol, respectively, in both the human and animal receptor binding assays. Relative binding affinity values of these reference compounds were arbitrarily set at 100%. Results of both the animal and human steroid receptor binding assays are summarized in Table 1. Of note, (1) drospirenone demonstrated a relative binding affinity of 19% to the human and 40% to the rabbit progesterone receptor; (2) drospirenone and progesterone have high relative binding affinities for the mineralocorticoid receptor (500% and 1000% for the human receptor for drospirenone and progesterone, respectively; both 100% for the rat receptor); (3) both progestogens have ≤3% relative binding affinity to the androgen receptor in all models; (4) drospirenone exhibits a low relative binding affinity to the glucocorticoid receptor (1% and 3% for the animal and human receptor, respectively), whereas progesterone has some binding affinity to this receptor (11% and 35% for the animal and human receptor, respectively); and (5) neither drospirenone nor progesterone demonstrate significant binding to the estrogen receptor [10]. (Data on file, Schering AG, Berlin, Germany.) In contrast, other progestogens such as gestodene, 3-ketodesogestrel (active metab-

![Spironolactone](image1)

**Spironolactone**

![Drospirenone](image2)

**Drospirenone**

![Acid form of drospirenone](image3)

**Acid form of drospirenone**

![4,5-Dihydro-drospirenone-3-sulfate](image4)

**4,5-Dihydro-drospirenone-3-sulfate**

Fig. 1. Chemical structures of spironolactone and drospirenone and major drospirenone plasma metabolites. (Data on file, Berlex Laboratories, Wayne, NJ, USA.)
olite of desogestrel), and levonorgestrel have different receptor-binding profiles than drospirenone and progesterone [17]. All three progestogens have demonstrated higher binding affinities to both the progesterone and androgen receptor than progesterone or drospirenone. Additionally, levonorgestrel and 3-ketodesogestrel have lower binding affinities to the mineralocorticoid receptor than either progesterone or drospirenone, whereas gestodene has a greater binding affinity to this receptor than progesterone or drospirenone.

The effects of drospirenone and progesterone on androgen-, glucocorticoid-, and mineralocorticoid-receptor–mediated induction of transcription were also evaluated using in vitro transactivation assays [10]. These assays were performed in CV-1 cells transfected with either androgen or glucocorticoid receptors and a reporter plasmid containing mouse mammary tumor promotor virus or COS 1 cells transfected with mineralocorticoid receptor and the identical viral promotor [10]. The results showed that (1) drospirenone and progesterone inhibit aldosterone-induced mineralocorticoid activity and weakly induce reporter gene transcription on their own; (2) both progestogens have no androgenic activity but display antiandrogenic activity in terms of inhibition of androgen-receptor–mediated transcription in a dose-dependent manner [10]. The receptor-mediated inhibition of transcription reflects that drospirenone has antiandrogenic activity which is explained by competitive binding to the androgen receptor and is intrinsic to its molecular structure; this direct antiandrogenic effect is in addition to the more indirect antiandrogenic effect of progestogens in general, that is mainly explained by the suppression of androgen production from the adrenals or ovaries. Drospirenone shows no glucocorticoid and antiglucocorticoid activity, whereas progesterone exhibits weak glucocorticoid-receptor–mediated agonistic activity but not antagonist activity [10]. Overall, the results from the steroid-binding and transactivation assays demonstrate that the biochemical profile of drospirenone is similar to that of progesterone, especially regarding its antimineralocorticoid and antiandrogenic activities [10]. This profile distinguishes drospirenone from other synthetic progestogens currently used in OCs (Table 2) [5,6,18].

### Table 1
Relative binding affinities (RBA) of progesterone and drospirenone to steroid hormone receptors [10]*

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Progesterone receptor</th>
<th>Androgen receptor</th>
<th>Mineralocorticoid receptor</th>
<th>Glucocorticoid receptor</th>
<th>Estrogen receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBA (%)</td>
<td>Human</td>
<td>Rabbit</td>
<td>Human</td>
<td>Rat</td>
<td>Human</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>19</td>
<td>40</td>
<td>2</td>
<td>1</td>
<td>500</td>
</tr>
<tr>
<td>Progesterone</td>
<td>100</td>
<td>100</td>
<td>3</td>
<td>1</td>
<td>1000</td>
</tr>
</tbody>
</table>

*Human data on file, Schering AG, Berlin, Germany.

*nc = no competition. The radiolabeled reference compounds for the progesterone, androgen, mineralocorticoid, glucocorticoid, and estrogen receptors were progesterone, methyltrienolone, aldosterone, dexamethasone, and estradiol, respectively in both the human and animal receptor binding assays. RBA values of these reference compounds were arbitrarily set at 100%.

### Table 2
Pharmacologic profile of drospirenone and other progestogens in animal models [5,6,18]

<table>
<thead>
<tr>
<th>Pharmacologic activities*</th>
<th>Progestogenic</th>
<th>Androgenic</th>
<th>Antiandrogenic</th>
<th>Antimineralocorticoid</th>
<th>Glucocorticoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>+</td>
<td>−</td>
<td>(+)</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>(+)</td>
</tr>
<tr>
<td>Desogestrelb</td>
<td>+</td>
<td>(+)</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Dienogest</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Gestodene</td>
<td>+</td>
<td>(+)</td>
<td>−</td>
<td>(+)</td>
<td>−</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>+</td>
<td>(+)</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Norgestimatec</td>
<td>+</td>
<td>(+)</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

* (+) indicates negligible at therapeutic dosages; −, no effect; +, distinct effect.

*b Active metabolite is 3-ketodesogestrel.

c Main metabolites are levonorgestrel-3-oxime and levonorgestrel.

### 3. Pharmacology and bioactivity

The progestational activity of drospirenone has been analyzed by evaluating its antigonadotropic and endometrium-transforming capabilities [11,14]. In male cynomolgus monkeys treated with drospirenone 4 mg/kg/day (orally [p.o.]) on days 5, 7, 10, 12, and 14, drospirenone showed a
strong antagonadotrophic effect by significantly reducing lutetinizing hormone levels compared to the pretreatment phase [11,14]. Additionally, endometrial transformation tests using ovariectomized rabbits initially treated for 6 consecutive days with estradiol (5 µg/animal; subcutaneously [s.c.] or p.o.) and followed by a 5-day treatment of drospirenone (range, 0.1 to 1.0 mg/animal; s.c. or p.o.) demonstrated marked endometrial transformation at a daily dosage of drospirenone 0.3 mg/animal [11,14]. The threshold dose for endometrial reactions (McPhail value of 1.5) occurred in the dose range of 0.1 to 0.3 mg/animal (s.c.) [11,14]. The results from these animal models are consistent with results from receptor-binding assays and demonstrate that drospirenone has progestogenic activity.

Inhibition of ovulation by drospirenone alone or in combination with ethinyl estradiol 30 µg has been demonstrated in humans [19]. Patients had documented normal ovulatory function in their pretreatment cycle. Drospirenone alone was assessed over 3 treatment cycles in 48 women randomized to dosages of 0.5, 1, 2, and 3 mg in a dose ranging study. Dose-dependent efficacy in ovarian suppression was shown. Incidence of ovarian ripening was 9% and 42% in 3 mg and 2 mg drospirenone groups, respectively. Incidence of complete ovarian suppression was 91% and 50% in the 3 mg and 2 mg groups, respectively. All subjects in the 3 mg group were anovulatory, whereas 1 patient in each of the lower dosage groups ovulated. Efficacy in ovulation inhibition of drospirenone 2 mg or 3 mg combined with ethinyl estradiol 30 µg was assessed in 52 women over 3 treatment cycles. Mean values of lutetinizing hormone, follicle stimulating hormone, 17β-estradiol and progesterone serum levels were suppressed during all treatment cycles with the combination of drospirenone 2 mg or 3 mg and ethinyl estradiol 30 µg, compared to pre- and post-treatment cycles. In the 2 mg group, escape ovulation occurred in 1 cycle for each of three patients; complete inhibition of ovulation was observed in 57 of 69 cycles. In the 3 mg group, none of the women ovulated and complete ovulation inhibition was observed in 62 of 69 cycles.

The effect of drospirenone on factors influenced by mineralocorticoid activity [e.g., electrolyte and water balance, weight, and blood pressure (BP)] was examined in animal models and humans. Ovariectomized rats fed on a low-sodium diet treated with drospirenone or spironolactone (each, 1 to 10 mg/animal/day) were evaluated for sodium and potassium excretion [11,14]. Drospirenone was more effective than spironolactone in increasing the Na⁺/K⁺ excretion rate and was shown to be a long-term antimineralocorticoid, as a dosage of 10 mg/animal/day produced a sustained stimulation of this electrolyte excretion ratio [11]. Similar studies have shown that progestogens like levonorgestrel, norethisterone acetate, 3-ketodesogestrel, and cyproterone acetate have neither antimineralocorticoid activity nor mineralocorticoid activity. Gestodene, however, is devoid of mineralocorticoid activity but has a rather low antimineralocorticoid activity, which is not considered clinically relevant in contraceptive dosages [13].

Young women on a constant moderately low sodium and potassium diet were treated with drospirenone 2 mg from day 8 to day 13 of their menstrual cycle and evaluated for sodium and potassium excretion [12]. Those on drospirenone had greater sodium excretion than women treated with placebo, except for the third day of treatment; the potassium excretion did not differ between the two groups. Sodium excretion in the drospirenone-treated group rose from a mean of 79.6 to 98.6 mmol Na⁺/day during drug treatment. The difference between average sodium excretion rates of women treated with drospirenone and placebo was close to significance (98.6 mmole/24 h and 81.8 mmole/24 h, respectively; p = 0.053). Weight loss was slightly greater with drospirenone treatment than placebo treatment [12]. Drospirenone also significantly increased plasma renin activity and plasma and urinary aldosterone during treatment [12].

A rise in sodium excretion, plasma renin activity, and plasma and urinary aldosterone levels has been noted during the luteal phase of the menstrual cycle. These effects are thought to be due to the antimineralocorticoid activity of progesterone [12]. A dosage of drospirenone 2 mg administered to normal, healthy menstruating women from day 5 to day 25 inhibited ovulation and prevented the rise in progesterone [12]. In contrast to cyproterone acetate, a progestogen with no antimineralocorticoid activity, drospirenone induced natriuresis and increased plasma renin activity and aldosterone levels during the follicular phase of the menstrual cycle compared to that of the untreated control cycle (Fig. 2). Preliminary studies have demonstrated that drospirenone (2 or 4 mg/day) in combination with ethinyl estradiol (30 µg/day) increases urinary sodium excretion, which is, however, compensated for by increases in plasma aldosterone and angiotensin II levels throughout the menstrual cycle [20]. The natriuresis and rise in plasma renin activity and plasma and urinary aldosterone levels induced by drospirenone in the follicular phase is similar to that induced by progesterone in the luteal phase of the menstrual cycle [3,12].

Drospirenone has been shown to have no clinically significant effects on BP in animal and human studies. During a 4-week treatment with drospirenone (2 mg/day), BP did not change in spontaneously hypertensive male rats, whereas equipotent doses of levonorgestrel and cyproterone acetate increased BP in these animals [21]. Similarly, drospirenone had only a slight effect on systolic BP and no effects on diastolic BP in normotensive female rats [22]. BP and body weight were also evaluated in normal, healthy women who received either drospirenone 3 mg with varying doses of ethinyl estradiol (15, 20, and 30 µg) or levonorgestrel 150 µg with ethinyl estradiol 30 µg for 6 months [16]. Drugs were taken from day 1 to day 21 of the menstrual cycle, followed by a pill-free interval of 7 days. Between the pretreatment cycle and the sixth treatment
cycle, the mean body weight decreased by 0.8 to 1.7 kg in the drospirenone/ethinyl estradiol-treated groups, whereas it increased 0.7 kg in the levonorgestrel/ethinyl estradiol-treated group. The differences in the body weight change of the drospirenone/ethinyl estradiol-treated groups compared to that of the levonorgestrel/ethinyl estradiol-treated group were significant (all, p < 0.05) [16]. In addition, systolic and diastolic BP decreased by 1 to 4 mm Hg in groups treated with drospirenone and ethinyl estradiol, whereas it increased by 1 to 2 mm Hg in the group treated with levonor-

Fig. 2. Sodium excretion, plasma renin activity, plasma aldosterone levels, and aldosterone excretion in the first and second halves of the untreated control cycle and treatment cycles. *p = 0.05; **p = 0.01. Adapted with permission from J Clin Endocrinol Metabolism [12].
gestrel and ethinyl estradiol. The change in systolic pressure in the group treated with drospirenone 3 mg and ethinyl estradiol 15 µg, and the changes in the diastolic pressures in the groups treated with drospirenone 3 mg and ethinyl estradiol, either 15 or 30 µg, were significantly different from the corresponding changes in the levonorgestrel/ethinyl estradiol-treated group (all, p < 0.05) [16]. Overall, the results from these in vivo studies clearly show that the data from the receptor-binding and transactivation assays translate into antimineralocorticoid activity of drospirenone in animals and humans.

The effect of drospirenone on factors influenced by androgenic activity was examined in animal models and humans. Animal studies demonstrated that drospirenone has antiandrogenic activity in terms of its effects on the growth of accessory sex glands in androgen-treated juvenile castrated rats. Drospirenone at dosages ranging from 0.1 to 10 mg/animal/day (s.c.) caused a dose-dependent inhibition of the growth of both seminal vesicles and the prostate upon 7 days’ application [10,11,14]. Similar effects were seen with progesterone at dosages ranging from 0.3 to 30 mg/animal/day (s.c.) [10].

It has been demonstrated that combined oral contraceptives reduce ovarian and adrenal production of testosterone and its precursors both by direct inhibition of enzymes involved in their biosynthesis and indirectly through suppression of gonadotropin secretion [18,23]. Slight reduction of ovarian androgen production has also been shown with the combination of drospirenone and ethinyl estradiol in normal healthy women. (Data on file, Schering, AG, Berlin, Germany.)

An antiandrogenic effect has also been observed in women administered drospirenone 3 mg with ethinyl estradiol (15 to 30 µg) [16]. These combination treatments produced increases in high-density cholesterol levels (range, 9% to 23%) and triglyceride levels (range, 47% to 73%) above baseline compared to levonorgestrel 150 µg and ethinyl estradiol 30 µg treatment (12% and unchanged from baseline, respectively). The differences in high-density cholesterol and triglyceride levels with the drospirenone combinations are significantly different from the corresponding changes with the levonorgestrel combination (all, p < 0.05). Conversely, drospirenone/ethinyl estradiol treatment decreases low-density cholesterol levels below baseline level (14% to 20%) compared to levonorgestrel/ethinyl estradiol treatment, which had no effect. The results from these studies involving both animals and humans support previous data obtained with receptor-binding and transactivation assays that show drospirenone has antiandrogenic activity.

4. Pharmacokinetics

Drospirenone was initially detected and identified during pharmacokinetic studies of spirorenone in the monkey [26]. Subsequent pharmacokinetic studies of drospirenone in man demonstrated that its absorption is rapid and complete, with peak plasma concentrations of drospirenone occurring within 1 to 2 hours after oral administration. (Data on file, Berlex Laboratories, Wayne, NJ, USA.) The absolute bioavailability of drospirenone after oral administration to young, healthy women was on average 76%. There is a linear relationship between the dose of drospirenone (range, 1 to 10 mg) and the pharmacokinetics of drospirenone. Steady-state is achieved after about 7 daily administrations of drospirenone 3 mg in combination with ethinyl estradiol 30 µg. The average maximum drospirenone plasma concentration ranges between 60 and 87 ng/mL, and the mean drospirenone trough level ranges between 20 and 25 ng/mL. Plasma levels of drospirenone decline biphysically. After oral administration the mean half-lives are about 2 hours for the distribution phase and range from 25 to 33 hours for the disposition phase. Approximately 95% to 97% of drospirenone is bound to serum protein, thought to be albumin. Drospirenone does not bind to sex-hormone-binding globulin or corticosteroid-binding globulin and does not attenuate the ethinyl estradiol induced increase in these proteins.

Following oral or intravenous administrations, drospirenone is extensively metabolized. The major plasma metabolites of drospirenone are the acid form of drospirenone generated by the opening of the lactone ring and the 4,5-dihydro-drospirenone-3-sulfate (Fig. 1). The major metabolites are generated independently of the cytochrome P450 enzyme system. Excretion of drospirenone is nearly complete after 10 days with trace amounts of drospirenone excreted unchanged in urine and feces. At least 20 different metabolites are observed in urine and feces. Less than 10% of the metabolites in urine are freely extractable, while about 38% to 47% are excreted as glucuronide and sulfate conjugates. In feces, about one-third of the metabolites are freely extractable and about 17% to 20% are excreted as glucuronides and sulfates.

5. A new OC with drospirenone

Recently Yasmin (Berlex Laboratories, Wayne, NJ, USA), a new low-dose OC tablet containing drospirenone 3 mg and ethinyl estradiol 30 µg, was evaluated in a year-long, open-label, multicenter study for contraceptive efficacy and safety [2]. The results showed Yasmin is an effective, safe, and well-tolerated OC. One pregnancy occurred in 3201 cycles of 326 subjects; this subject reported 1 intake error. After correcting for cycles without recorded use of other contraceptives (3192 cycles), the Pearl Index was 0.4. The pregnancy ratio was 0.46 since 1 pregnancy occurred among the 220 subjects completing 13 cycles without using alternative contraception. No serious adverse events related to the contraceptive occurred. Additionally, 71% of subjects (230/326) reported at least one adverse event during the study, and 6% of subjects (20/326)
Fig. 3. Mean changes in menstrually related symptoms from baseline to cycle 6 for the three phases of the menstrual cycle. The three phases include the premenstrual phase (4-day period prior to menstruation), menstrual phase (first through last day of menstruation), and postmenstrual phase (remainder of the cycle). Reprinted with permission from Contraception [2].

Fig. 4. Mean (SD) changes from baseline weight by cycle. Reprinted with permission from Contraception [2].
discontinued the study because of adverse effects. Emotional lability, headache, nausea, dysmenorrhea, intermenstrual bleeding, and depression, that occurred at frequencies of 1.5% or less, were the most frequently reported adverse events cited for discontinuation. The incidence of these adverse events is comparable to that of other low-dose
combination OCs; the antimineralocorticoid actions of drospirenone would not be expected to impact the occurrence of these particular side effects [2].

During the same open-label study, the Menstrual Distress Questionnaire [27] was adapted and used to assess menstrually related symptoms such as impaired concentration, negative affect, water retention, increased appetite, feelings of well-being, and undesirable hair change during three phases of the menstrual cycle (i.e., premenstrual, 4 days prior to menstruation; menstrual, first through the last day of menstruation; and postmenstrual, remainder of the cycle) [2]. For water retention and negative affect, there was a statistically significant decrease from baseline to cycle 6 for all subjects in all phases of the menstrual cycle (Fig. 3). The severity level of increased appetite was significantly lower at cycle 6 compared to baseline for all phases of the menstrual cycle, except the postmenstrual phase. There were no significant changes for impaired concentration, undesirable hair change, or feelings of well-being throughout the entire menstrual cycle (Fig. 3). Overall, drospirenone has a favorable impact on the common menstrual cycle symptoms cited above. These symptoms are often reported among patients suffering from premenstrual syndrome.

Effects of drospirenone and ethinyl estradiol on weight, BP, and lipids were also assessed in this study [2]. There was a trend toward weight loss in cycles 1, 3, and 9, whereas significant weight loss occurred at cycle 6 ($p = 0.025$). Weight gain, however, was significant at cycle 13 ($p = 0.0319$; Fig. 4). During the study, BP remained within normal limits and no significant changes from baseline in mean systolic or diastolic BP occurred. Finally, lipids also remained within normal limits throughout the study, but total cholesterol, triglycerides, high-density lipoprotein, and the ratio of high-density lipoprotein to low-density lipoprotein showed significant increases from baseline at cycle 13 ($p <0.0001$). Thus, drospirenone/ethinyl estradiol OC has a favorable profile with respect to weight and lipids [2].

Estrogenic components of OCs can contribute to many of their reported adverse effects [3]. Estrogens such as ethinyl estradiol, a common component of OCs, can stimulate the synthesis of hepatic proteins such as sex-hormone-binding globulin and angiotensinogen. High levels of angiotensinogen can cause small increases in angiotensin II, thereby stimulating aldosterone secretion that in turn increases sodium reabsorption and water retention. By activation of the renin-angiotensin-aldosterone system, ethinyl estradiol may cause sodium retention, weight gain, and high BP in susceptible women. In the later half of the menstrual cycle, progesterone has been shown to induce sodium loss and a compensatory increase in renin secretion, plasma renin activity, angiotensin II, and plasma aldosterone because it has potent antimineralocorticoid activity. These effects counteract the estrogen-induced increase in sodium retention, weight, and BP [3]. Like progesterone, drospirenone is an aldosterone antagonist and has demonstrated strong antimineralocorticoid activity by counteracting estrogen-induced increase in sodium retention, weight gain, and high BP [3].

For water retention and negative affect, there was a statistically significant decrease from baseline to cycle 6 for all phases of the menstrual cycle (Fig. 3). The severity level of increased appetite was significantly lower at cycle 6 compared to baseline for all phases of the menstrual cycle, except the postmenstrual phase. There were no significant changes for impaired concentration, undesirable hair change, or feelings of well-being throughout the entire menstrual cycle (Fig. 3). Overall, drospirenone has a favorable impact on the common menstrual cycle symptoms cited above. These symptoms are often reported among patients suffering from premenstrual syndrome.

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duced effects from the activation of the renin-angiotensin-aldosterone system. In contrast, other available combined OCs contain progestogens without antimineralocorticoid activity and are frequently associated with adverse effects.

6. Conclusions

The reviewed in vitro and in vivo animal studies show that drospirenone is a unique progestogen which has a biochemical and pharmacologic profile that closely resembles natural progesterone [10]. Unlike other currently available synthetic progestogens derived from 17α-hydroxyprogesterone or 19-nortestosterone, drospirenone demonstrates both antimineralocorticoid and antiandrogenic activities [11]. As such, drospirenone is a viable progestogenic alternative that may, in some cases, be preferable to other choices. The actions of this unique progestogen in 3 physiologic pathways are summarized in Fig. 5. First, the progestogenic action results in inhibition of ovulation [2,11, 14]. Second, the antiandrogenic activity of drospirenone could lead to suppression of unwanted symptoms such as acne and hirsutism through blockade of androgenic receptors in the skin [6]. Finally, the antimineralocorticoid activity of drospirenone balances the aldosterone-stimulating mineralocorticoid effect of estrogens (e.g., ethinyl estradiol) and may reduce estrogen-induced sodium and water retention. Therefore, Yasmin, an effective and safe low-dose OC containing drospirenone and ethinyl estradiol, provides health benefits beyond contraception. These benefits include a favorable impact on menstrually related symptoms (e.g., water retention and negative affect) and a favorable profile with respect to skin, weight, and lipids.

References
