

# Drospirenone vs norethindrone progestin-only pills. Is there a clear winner?

Among progestin-only contraceptive pills, compared to norethindrone, drospirenone has superior performance on key dimensions



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Contraception and family planning have improved the health of all people by reducing maternal mortality, improving maternal and child health through birth spacing, supporting full education attainment, and advancing workforce participation.<sup>1</sup> Contraception is cost-effective and should be supported by all health insurers. One economic study reported that depending on the contraceptive method utilized, up to \$7 of health care costs were saved for each dollar spent on contraceptive services and supplies.<sup>2</sup>

Progestin-only pills (POPs) are an important contraceptive option for people in the following situations who<sup>3</sup>:

- have a contraindication to estrogen-containing contraceptives
- are actively breastfeeding
- are less than 21 days since birth
- have a preference to avoid estrogen.

POPs are contraindicated for women who have breast cancer, abnormal uterine bleeding, or active liver disease and for women who are pregnant. A history of bariatric

surgery with a malabsorption procedure (Roux-en-Y and biliopancreatic diversion) and the use of anti-epileptic medications that are strong enzyme inducers are additional situations where the risk of POP may outweigh the benefit.<sup>3</sup> Alternative progestin-only options include the subdermal etonogestrel implant, depot medroxyprogesterone acetate, and levonorgestrel-releasing intrauterine devices. These 3 options provide superior contraceptive efficacy to POP.

As a contraceptive, norethindrone at a dose of 0.35 mg daily has two major flaws:

- it does not reliably inhibit ovulation
- it has a short half-life.

In clinical studies, norethindrone inhibits ovulation in approximately 50% of cycles.<sup>4,5</sup> Because norethindrone at a dose of 0.35 mg does not reliably inhibit ovulation it relies on additional mechanisms for contraceptive efficacy, including thickening of the cervical mucus to block sperm entry into the upper reproductive tract, reduced fallopian tube motility, and thinning of the endometrium.<sup>6</sup>

Norethindrone POP is formulated in packs of 28 pills containing 0.35 mg intended for daily continuous administration and no medication-free intervals. One rationale for the low dose of 0.35 mg in norethindrone POP is that it approximates the lowest dose with contraceptive efficacy for breastfeeding women, which has the benefit of minimizing exposure of the baby to the medication. Estrogen-progestin birth control pills containing norethindrone as the progestin reliably inhibit ovulation and have a **minimum of 1 mg of norethindrone** in each hormone pill. A POP with 1 mg of norethindrone per pill would likely have greater contraceptive efficacy. When taken daily, norethindrone acetate 5 mg (Aygestin) suppresses ovarian estrogen production, ovulation, and often causes cessation of uterine bleeding.<sup>7</sup> The short half-life of norethindrone (7.7 hours) further exacerbates the problem of an insufficient daily dose.<sup>6</sup> The standard guidance is that norethindrone must be taken at the same time every day, a goal that is nearly impossible to achieve. If a dose of norethindrone is taken >3 hours late, backup contraception is recommended for 48 hours.<sup>6</sup>

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**TABLE Comparison of drospirenone and norethindrone progestin-only pill contraceptives**

Dimension	Drospirenone	Norethindrone
Brand name	Slynd	Camila, and other names
Dosing	4-mg pills (24 hormone pills and 4 inactive pills per pack)	0.35-mg pills (28 hormone pills per pack)
Inhibition of ovulation, percent of cycles	>95%	50%
Androgenicity	Anti-androgenic	Androgenic
Half-life	30 hours	7.7 hours
Missed pills guidance	Backup contraception recommended for 7 days if $\geq 2$ hormone pills are missed	Backup contraception recommended for 48 hours if dose is >3 hours late
Risk of venous thromboembolism	Very low	Very low
Androgenicity	Anti-androgenic	Androgenic
Cost	High average wholesale price, discounts available	Low average wholesale price

Drospirenone is a chemical analogue of spironolactone. Drospirenone is a progestin that suppresses LH and FSH and has anti-androgenic and partial anti-mineralocorticoid effects.<sup>8</sup> Drospirenone POP contains 4 mg of a nonmicronized formulation that is believed to provide a pharmacologically similar area under the curve in drug metabolism studies to the 3 mg of micronized drospirenone, present in drospirenone-containing estrogen-progestin contraceptives.<sup>9</sup> It is provided in a pack of 28 pills with 24 drospirenone pills and 4 pills without hormone. Drospirenone has a long half-life of 30 to 34 hours.<sup>8</sup> If  $\geq 2$  drospirenone pills are missed, backup contraception is recommended for 7 days.<sup>9</sup> The contraceptive effectiveness of drospirenone POP is thought to be similar to estrogen-progestin pills.<sup>8</sup> Theoretically, drospirenone, acting as an anti-mineralocorticoid, can cause hyperkalemia. People with renal and adrenal insufficiency are most vulnerable to this adverse effect and should not be prescribed drospirenone. Women taking drospirenone

and a medication that strongly inhibits CYP3A4, an enzyme involved in drospirenone degradation—including ketoconazole, indinavir, boceprevir, and clarithromycin—may have increased circulating levels of drospirenone and be at an increased risk of hyperkalemia. The US Food and Drug Administration (FDA) suggests that clinicians consider monitoring potassium concentration in women taking drospirenone who are also prescribed a strong CYP3A4 inhibitor.<sup>9</sup> In people with normal renal and adrenal function, drospirenone-induced hyperkalemia is not commonly observed.<sup>9</sup>

Drospirenone 4 mg has been reported to not affect the natural balance of pro- and anti-coagulation factors in women.<sup>10</sup> Drospirenone 4 mg daily has been reported to cause a modest decrease in systolic (-8 mm Hg) and diastolic (-5 mm Hg) blood pressure for women with a baseline blood pressure  $\geq 130$  mm Hg. Drospirenone 4 mg daily did not change blood pressure measurement in women with a baseline systolic blood pressure <130 mm Hg.<sup>11</sup> For women

using drospirenone POP, circulating estradiol concentration is usually >30 pg/mL, with a mean concentration of 51 pg/mL.<sup>12,13</sup> Drospirenone POP does not result in a significant change in body weight.<sup>14</sup> Preliminary studies suggest that drospirenone is an effective contraceptive in women with a BMI >30 kg/m<sup>2</sup>.<sup>14,15</sup> Drospirenone enters breast milk and the relative infant dose is reported to be 1.5%.<sup>9</sup> In general, breastfeeding is considered reasonably safe when the relative infant dose of a medication is <10%.<sup>16</sup>

The most common adverse effect reported with both norethindrone and drospirenone POP is unscheduled uterine bleeding. With norethindrone POP about 50% of users have a relatively preserved monthly bleeding pattern and approximately 50% have bleeding between periods, spotting and/or prolonged bleeding.<sup>17,18</sup> A similar frequency of unscheduled uterine bleeding has been reported with drospirenone POP.<sup>14,19</sup> Unscheduled and bothersome uterine bleeding is a common reason people discontinue

POP. For drospirenone POP, the FDA reports a Pearl Index of 4.<sup>9</sup> Other studies report a Pearl Index of 0.73 (95% confidence interval [CI], 0.31 to 1.43) for drospirenone POP.<sup>14</sup> For norethindrone POP, the FDA reports that in typical use about 5% of people using the contraceptive method would become pregnant.<sup>6</sup> The **TABLE** (page 11) provides a comparison of the key features of the two available POP contraceptives. My assessment is that drospirenone has superior contraceptive properties over norethindrone POP. However, a head-to-head clinical trial would be necessary to determine the relative contraceptive effectiveness of drospirenone versus norethindrone POP.

## Maintaining contraception access

Access to contraception without a copayment is an important component of a comprehensive and equitable insurance program.<sup>20</sup> The American College of Obstetricians and Gynecologists (ACOG) advocates that all people “should have unhindered and affordable access to all U.S. Food and Drug Administration-approved contraceptives.”<sup>21</sup> ACOG also calls for the “full implementation of the Affordable Care Act requirement that new and revised private health insurance plans cover all U.S. Food and Drug Administration approved contraceptives without cost sharing,

including nonequivalent options within one method category.” The National Women’s Law Center<sup>22</sup> provides helpful resources to ensure access to legislated contraceptive benefits, including a phone script for speaking with an insurance benefits agent<sup>23</sup> and a toolkit for advocating for your contraceptive choice.<sup>24</sup> We need to ensure that people have unfettered access to all FDA-approved contraceptives because access to contraception is an important component of public health. Although drospirenone is more costly than norethindrone POP, drospirenone contraception should be available to all patients seeking POP contraception. ●

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