

# Individualizing Selection of Hormonal Contraception

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## KEYWORDS:

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Multiple hormonal contraception methods are available to prevent unintended pregnancies. The initial selection of a hormonal method includes consideration of contraception cost, frequency of use, failure rates, timing to return to fertility after discontinuation, and medical contraindications. The Centers for Disease Control and Prevention U.S. Medical Eligibility Criteria for Contraceptive Use provides an extensive, standard reference for reviewing contraindications for contraceptive use. Following the initial selection of the hormonal contraceptive, anticipating and managing adverse effects improves adherence and consequently, prevention of unintended pregnancy. Approaches to improve tolerability include reducing the hormone free interval, adjusting the estrogen and progestin doses, and switching to a different route of administration.

## 1.0 INTRODUCTION

Reducing the number of unintended pregnancies is a national public health goal.<sup>1</sup> Among the 6.7 million pregnancies in the United States each year, approximately half are unintended.<sup>2</sup> This number is highest among women who are poor or have low-incomes, women aged 18-24, cohabiting women and minority women.<sup>2</sup> Additionally, more than half of all American women will experience an unintended pregnancy by the age of 45.<sup>3</sup> In 2006 an estimated 11.1 billion dollars of U.S. public expenditures were used for unintended pregnancies.<sup>3</sup> National efforts include the U.S. Department of Health and Human Services' Healthy People 2020 campaign focusing on a reduction in these numbers by 10% over the next 10 years.<sup>1</sup>

Critical to this issue includes education on family planning and contraception options. There are several hormonal and non-hormonal options available for patients. This article will discuss the prescription of both estrogen-progestin and progestin-only hormonal contraceptives, focusing on the selection of hormonal contraceptives and managing adverse effects. Understanding these issues, clinicians will be able to match the best contraceptive option to each patient's preference and health condition. Table 1 provides a summary of hormonal contraceptive options available in the United States.

## 2.0 SELECTING HORMONAL CONTRACEPTION METHODS

Contraception selection is uniquely patient specific. Patient considerations include cost, ease of use, contraception failure rates, concomitant medical conditions, and the time it takes to return to fertility after discontinuation.<sup>7</sup> (See Table 1) A clinician must not only consider patient preferences and health conditions, but also have knowledge of current contraceptive recommendations. In some cases, hormonal contraception is not appropriate, and nonhormonal options such as the copper intrauterine system (IUS) or barrier methods must be considered.

The American Congress of Obstetricians and Gynecologists (ACOG) recommends IUS and subdermal implants as first line options over other contraceptive methods.<sup>8</sup> Further guidance for contraceptive selection is provided by the U.S. Medical Eligibility Criteria (U.S. MEC) for Contraceptive Use. This document was initially published by the Centers for Disease Control and Prevention (CDC) in 2010 and offers an extensive, standard reference for reviewing contraindications for contraceptive use.<sup>9</sup> Demonstrated in Table 2, the U.S. MEC recommends appropriate contraceptive use by condition, method, and contraindication by assigning a category from 1-4. The ACOG endorses the use of this CDC reference.<sup>10</sup> The complete chart addressing more than sixty medical conditions can be found at <http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/USMEC.htm> and an application can also be downloaded to electronic devices.

The initial office visit should include a complete medical history, baseline measurements of blood pressure, height, weight, and a physical exam. Although performed regularly, the pelvic exam with cervical inspection and bimanual palpation is not required before prescribing contraceptives, but is required before the placement of any IUS.<sup>7</sup> Overall, the

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**Table 1: Hormonal Contraception Options<sup>4-6</sup>**

Contraceptive	Frequency or Duration	Reversibility	Cost	Failure Rate <sup>a</sup>
<b>Combination Estrogen-Progestin</b>				
Oral Contraceptive Pill (OCP)	Daily	Immediate	\$20-100 (monthly) <sup>b</sup>	9%
Extended-Cycle OCP	Daily	Immediate	\$200-300 (every 3 months) <sup>b</sup>	9%
Contraceptive Patch (Ortho Evra)	Weekly application	Immediate	\$156 (monthly) <sup>b</sup>	9%
Contraceptive Ring (Nuvaring)	Monthly insertion	Immediate	\$120 (monthly) <sup>b</sup>	9%
<b>Progestin-Only</b>				
Norethindrone OCP	Daily	Immediate	\$30-50 (monthly) <sup>b</sup>	9%
Long-acting injectable (depot medroxyprogesterone, Depo-Provera 150 mg IM, Depo-Provera Subcutaneous-104 mg)	Every 3 months	May be delayed	\$130 (every 3 months) <sup>b</sup>	6%
Single-rod implantable device Etonogestrel 68 mg (Nexplanon, Implanon)	Up to 3 years	Immediate	\$659.42 (3 years) <sup>c</sup>	0.05%
LNG IUS	Skyla LNG-13.5 IUS: up to 3 years <sup>d</sup>	Immediate	\$780.38 (3 years) <sup>d</sup>	0.4% <sup>e</sup>
	Mirena LNG-20 IUS: up to 5 years	Immediate	\$843.60 (5 years) <sup>e</sup>	0.2%

<sup>a</sup>Unintended pregnancy rate after one year of typical use.

<sup>b</sup>Estimated retail price of generic and brand name products. <http://www.epocrates.com>; Accessed 27.10.13.

<sup>c</sup><http://secure.medicalletter.org/w1383d>; Accessed 27.10.13.

<sup>d</sup><http://hcp.skyla-us.com/index.php>; Accessed 27.10.13.

<sup>e</sup><http://www.mirena-us.com/how-to-get-mirena/if-mirena-isnt-covered.php>; Accessed 27.10.13.

**TABLE 1 ABBREVIATIONS:**

OCP = Oral Contraceptive Pill; IM = Intramuscular; LNG IUS = Levonorgestrel-containing intrauterine system

**Table 2: U.S. Medical Eligibility Criteria for Contraceptive Use Category Definitions<sup>9</sup>**

Category Number	Category Definition
1	The method can be used without restriction.
2	The advantages of the method generally outweigh the risks.
3	The risks of the method usually outweigh the advantages.
4	The method is associated with unacceptable health risks and should not be used.

pelvic exam does not substantially contribute to the efficacy or safety of contraceptive methods.<sup>11</sup> With respect to certain medical histories, the U.S. MEC recommendations for women with hypertension, tobacco use, venous thromboembolism (VTE), and breast cancer will be addressed.

## 2.1 HYPERTENSION

According to the CDC, blood pressure evaluation is mandatory before the prescription of combined estrogen-progestin contraceptives. If the systolic blood pressure is greater than or equal to 160 mm Hg or the diastolic blood

pressure is greater than or equal to 100 mm Hg, combined estrogen-progestin contraceptives are considered category 4 and should be avoided. If the systolic blood pressure is greater than or equal to 140 mm Hg or the diastolic is 90-99 mm Hg, the combined estrogen-progestin contraceptives are assigned to category 3, indicating that the risks may outweigh the advantages.<sup>7</sup> Women younger than thirty-five years of age with well-controlled hypertension that is carefully monitored may use combined estrogen-progestin contraceptives.<sup>12</sup> Blood pressure elevations, on average of 5 mmHg, which occur after initiation of combined estrogen-progestin contraceptives are not considered clinically significant. Any other blood pressure increase from baseline requires discontinuation of the contraceptive. Blood pressure should normalize within 3 to 6 months after stopping therapy.<sup>13</sup>

## 2.2 SMOKING

Smoking is associated with increased risk of stroke, VTE, and myocardial infarction (MI). Given these risks it is important to consider tobacco use when selecting hormonal contraceptives. Patients who smoke and are less than 35 years of age may use combined estrogen-progestin contraceptives, although efforts to support cessation should be encouraged.<sup>9,12</sup> For women who

smoke and are 35 years of age or older, combined estrogen-progestin contraceptives are contraindicated. Progestin-only methods may be appropriate in these patients. (See Table 1)

### 2.3 VENOUS THROMBOEMBOLISM

Combined estrogen-progestin contraceptives are contraindicated for use with any current VTE or past history of VTE and a high risk for recurrence (category 4). Women with a past history of VTE and low risk for recurrence are also poor candidates for these methods (category 3).<sup>9</sup> The progestin-only methods (subdermal and IUS) are considered category 2 and generally acceptable for use in women with VTE.<sup>9</sup> A meta-analysis of eight studies found no increased risk for VTE with oral or intrauterine progestin-only contraception; but, injectable depot medroxyprogesterone acetate (DMPA) appeared to have an increased risk.<sup>14</sup> A clear delineation of thromboembolic risks associated with progestin-only methods requires further study.

### 2.4 BREAST CANCER

All hormonal contraceptives are contraindicated in patients with a current or past history of breast cancer. According to the U.S. MEC, any history of current breast cancer is category 4 and past history is category 3. There are no restrictions for contraceptive use in patients with a family history of breast cancer, category 1.<sup>9</sup>

After considering patient preferences and reviewing medical eligibility, contraception can be selected. Following up with these patients is recommended to assess response to therapy, satisfaction, and adverse effects. Modification of the contraceptive method may be necessary and critical to prevent unintended pregnancy.

### 3.0 MANAGING ADVERSE EFFECTS OF HORMONAL CONTRACEPTIVES

While hormonal contraceptives are highly effective, bothersome adverse effects are a common reason for discontinuation.<sup>15,16</sup> Patients can benefit from different therapeutic strategies to improve contraceptive tolerability. These options are discussed and summarized in Table 3.

#### 3.1 SHORTENED HORMONE-FREE INTERVAL

Traditionally, combined oral contraceptives (COC) containing estrogen and progestin included 21 days of active pills and 7 days of placebo pills to allow sufficient time for a withdrawal bleed. Because current COCs contain lower estrogen and progestin doses, the hormone-free interval can be reduced. Products with a 24 day active phase followed by a short 4 day placebo phase may improve ovarian suppression and efficacy.<sup>17,18</sup> Benefits include reduced symptoms associated

**Table 3: General Strategies to Improve Tolerability of Combined Hormonal Contraceptives**

Complaint	Potential Adjustments to Contraceptive Regimen
Nausea	<ul style="list-style-type: none"> <li>• Lower oral estrogen dose</li> <li>• Use intravaginal ring</li> <li>• Switch to progestin-only</li> </ul>
Acne, hirsutism	<ul style="list-style-type: none"> <li>• Use less androgenic progestin</li> <li>• Increase oral estrogen dose</li> </ul>
Breast tenderness	<ul style="list-style-type: none"> <li>• Lower oral estrogen dose</li> <li>• Switch to progestin-only</li> </ul>
Hormone withdrawal symptoms (i.e. headache, mood changes)	<ul style="list-style-type: none"> <li>• Reduce hormone-free interval</li> <li>• Use extended cycle/ continuous dosing</li> </ul>
Non-adherence	<ul style="list-style-type: none"> <li>• Use non-oral combined hormonal contraceptive</li> <li>• Use non-oral progestin-only contraceptive</li> </ul>

with hormone withdrawal including headache, mood changes, and gastrointestinal symptoms. A shortened placebo phase may further suppress androgen production, improving acne and hirsutism.<sup>13</sup> Several COCs provide 10 mcg of ethinyl estradiol (EE) in place of placebo pills. This regimen also reduces the hormone-free interval and many of the symptoms mentioned above.<sup>19</sup>

#### 3.2 EXTENDED CYCLE OR CONTINUOUS USE

Historically cyclic bleeding has been incorporated into combined estrogen-progestin contraceptive regimens. Although some women prefer having a monthly period to assure they are not pregnant; a monthly period is not physiologically necessary. For women who experience adverse symptoms upon hormone withdrawal in the placebo phase, extended or continuous use of a combined estrogen-progestin formulation may be beneficial. Symptoms include premenstrual syndrome and premenstrual dysphoric disorder as well as exacerbations of hormonally-mediated migraine headaches, asthma, and seizure disorders.<sup>13,19-21</sup> Reducing the frequency of withdrawal bleeding also suppresses androgen production improving acne and hirsutism.<sup>13</sup>

Less frequent, scheduled bleeding with extended use or continuous regimens is beneficial for patients with menorrhagia or anemia due to heavy blood loss.<sup>13</sup> The benefit of fewer cycles, however, is often accompanied by unscheduled bleeding (breakthrough bleeding), especially upon initiation.<sup>7,13</sup> Unscheduled bleeding may also be caused by missed pill doses, drug-drug interactions, or other gynecological conditions. Women who experience bothersome unscheduled bleeding where an underlying cause is not identified may discontinue the COC for 3 to 4 days

and resume therapy. However, this is not recommended in the first 21 days of a continuous or extended use regimen, as contraceptive efficacy can be reduced.<sup>7</sup> Addition of 10 mcg EE for 7 days in place of the hormone-free interval following an 84 day extended regimen also resulted in an improved bleeding profile.<sup>22</sup> Overall, a systematic review demonstrated similar or improved bleeding patterns over time with extended cycles compared to monthly.<sup>21</sup>

Commercially available COC formulations include 91-day extended use patterns as well as continuous use for up to 12 months. The continuous use of a monophasic oral contraceptive, intravaginal ring, or transdermal patch can be achieved by skipping the placebo (hormone-free interval). Using contraceptives in this fashion requires additional prescription supply which may be restricted by insurance plans.

### 3.3 VARIED DOSES OR TYPES OF ESTROGEN

The current COCs represent a daily EE dose ranging from 10 mcg to 35 mcg. Increasing or decreasing the dose within this range can be an important modification when individualizing therapy. In general, lower estrogen doses such as 20 mcg EE are associated with lower rates of mastalgia and nausea than 35 mcg products.<sup>13</sup> However, the lower doses also appear to have a higher incidence of unscheduled bleeding, infrequent bleeding, and amenorrhea, which impacts method continuation rates.<sup>23</sup> A higher estrogen dose may be necessary to reduce unscheduled bleeding, especially in the early phase of active pills. Similarly, women experiencing amenorrhea or very light bleeding who prefer to have a predictable cyclic bleeding phase should receive higher doses of estrogen. A higher estrogen dose can also suppress androgen production to a greater degree, which can address acne or hirsutism.<sup>13</sup>

Benefits of varying the type of estrogen in the contraceptive formulation are not clear at this time.<sup>24</sup> EE is the estrogen formulation most commonly utilized in hormonal contraceptives. Mestranol is available in select oral formulations at doses of 50 mcg and is most commonly used for treatment of endometriosis or menorrhagia. Estradiol valerate is the most recent addition to the estrogens incorporated into oral contraceptive formulations. It is a prodrug that is hydrolyzed to 17-beta estradiol after oral administration. Pharmacokinetic studies appear to show a reduced effect on hepatic protein synthesis and subsequent metabolic and hemostatic parameters.<sup>24, 25</sup> Further head-to-head comparison studies of thromboembolic event rates will be required before the clinical implications of this difference can be determined.<sup>24</sup>

### 3.4 VARIED DOSES OR TYPES OF PROGESTINS IN COCS

Comparing the tolerability of progestins is complicated by inconsistent methodologies used in clinical trials.<sup>26</sup> Pharmacologic properties of progestins, such as androgenicity, can provide some guidance for selecting one over another. Levonorgestrel (LNG) in higher doses displays a more pronounced androgenic effect than more recent generations of progestins such as desogestrel, gestodene, norgestimate, and drospirenone. In addition, the progestin effect is dependent on the quantitative estrogen dose in each COC and the phasic pattern of the estrogen and progestin components. Varying the progestin dose may be beneficial to modify bleeding patterns associated with COC use. For example, a product with higher progestin content provides additional endometrial support. This support may prevent unscheduled bleeding that occurs late in the active pill cycle.<sup>13</sup>

Theoretically, a progestin with a lower androgenic profile may improve acne and hirsutism.<sup>13</sup> Interestingly, a systematic review of COCs for the treatment of acne showed beneficial effects from all products, even those containing LNG. The greatest effects were demonstrated by formulations containing cyproterone acetate (not available in the United States) and drospirenone.<sup>27</sup> In contrast, a more androgenic progestin may improve libido, although a clear correlation between libido and serum testosterone levels in premenopausal women is not well established.<sup>13</sup>

Drospirenone is a unique progestin with anti-mineralocorticoid and anti-androgenic properties. It is associated with a reduction in symptoms associated with premenstrual syndrome, such as water retention, bloating and increased appetite.<sup>13, 28</sup> Drospirenone blocks testosterone receptors on the sebaceous gland, providing an additional mechanism for treatment of acne.<sup>13</sup> Drospirenone-containing contraceptives are FDA-approved for treatment of premenstrual dysphoric disorder and acne.

### 3.5 MONOPHASIC VERSUS MULTIPHASIC FORMULATIONS

Dosing of the estrogen and progestin components of current COCs ranges from monophasic to quadriphasic patterns. Monophasic regimens supply the same dose of estrogen and progestin through the cycle. Bi-, tri-, and quadriphasic regimens increase or decrease the estrogen and/or progestin doses through the cycle. Clinical studies have not revealed a clear benefit of one type over another. A recent systematic review comparing monophasic and triphasic preparations found improved bleeding patterns with the triphasic products; however, the authors did not find significant differences in discontinuation rates based upon tolerability between the 2 regimens.<sup>29</sup> A systematic review of trials comparing biphasic

to triphasic formulations yielded no difference in cycle control when comparing products with similar progestins. Authors concluded that the progestin type may be more contributory than the phase pattern, as a triphasic levonorgestrel formulation was associated with a more predictable cycle compared to a biphasic norethindrone formulation.<sup>30</sup> A quadriphasic pattern is the most recent addition to available COCs. A systematic review comparing quadriphasic to monophasic formulations found a similar incidence of unscheduled bleeding, but more women experienced withdrawal bleeding and less mastalgia with the monophasic product.<sup>31</sup>

While the data to support the use of one phasic pattern over another is not well-defined, varying the dosing patterns of triphasic formulations may be useful for a woman experiencing unscheduled bleeding at various stages of the month. For example, a product with a lower progestin dose in the first active phase can increase the volume of scheduled bleeding for women who are experiencing amenorrhea or light bleeding. A higher estrogen dose in the first active phase may alleviate bleeding or spotting that continues after the placebo pills or initiation of a new pill pack. A higher progestin dose in the later active phase provides additional endometrial support for those experiencing unscheduled bleeding before taking the placebo pills. If mid-cycle unscheduled bleeding occurs, a product that increases both estrogen and progestin in the middle active phase may be utilized.<sup>13</sup>

### 3.6 NON-ORAL COMBINED ESTROGEN-PROGESTIN CONTRACEPTIVES

Combined oral contraceptives require daily administration, which may present compliance issues. A non-oral combined formulation such as the intravaginal ring (EE/etonogestrel) or the transdermal patch (EE/norelgestromin) are effective alternatives that require less frequent dosing. A systematic review of trials comparing non-oral combined estrogen-progestin contraceptives with COCs showed higher adherence rates with the patch and ring.<sup>32</sup>

The intravaginal ring is associated with similar or improved cycle control (less breakthrough bleeding and spotting) compared to COCs.<sup>32, 33</sup> Additionally, the lower estrogen dose in the intravaginal ring is associated with less nausea, acne, and mood disturbances. An adverse effect unique to the intravaginal ring is increased vaginal secretions. While this may be bothersome to some women, it may benefit women with vaginal dryness. Overall, the improved tolerability leads to lower discontinuation rates with the vaginal ring compared to COCs.<sup>32</sup>

The transdermal patch is associated with cycle control similar to that of COCs.<sup>32</sup> However, unlike the intravaginal ring, the transdermal patch is associated with more breast tenderness,

dysmenorrhea, nausea, and vomiting than COCs, which leads to higher discontinuation rates.<sup>32</sup> The transdermal patch is also limited by reduced efficacy in women weighing 90 kg or more and its use should be avoided in these patients.<sup>34</sup>

### 3.7 PROGESTIN-ONLY CONTRACEPTIVES

Progestin-only contraceptives (POCs) are important alternatives for women with medical contraindications to estrogen. In addition, women experiencing estrogenic adverse effects such as breast tenderness, nausea, and melasma that do not respond to the strategies previously identified may tolerate a progestin-only option.<sup>13</sup> The choice of product depends on preferences for route and frequency of administration, as well as adverse effect profiles.

The route and frequency of administration of the POCs vary widely. The progestin-only “mini pill,” for example, must be dosed on a daily basis at the same time each day to ensure efficacy.<sup>7</sup> The DMPA intramuscular or subcutaneous injection allows for extended dosing at a 3 month interval. The subdermal etonogestrel implant is approved for 3 years of use and the 2 levonorgestrel IUS are approved for 3 and 5 years, respectively. These non-oral formulations support increased compliance and efficacy.

Progestin-only contraceptives are associated with irregular, unscheduled bleeding that differs from the combined estrogen-progestin contraceptives. The non-oral progestin-only options are associated with bleeding patterns that may result in amenorrhea. For example, the LNG IUS are associated with irregular bleeding patterns and prolonged bleeding during the first six months of use. By the end of the first year of use, the 14 mcg/day levonorgestrel IUS is associated with infrequent bleeding (1 to 2 bleeding episodes in 90 days) in 20% of users and amenorrhea in 6%.<sup>35</sup> Approximately 20% of women using the 20 mcg/day levonorgestrel IUS report amenorrhea after the first year of use.<sup>36</sup>

The most common bleeding irregularity reported with the use of the etonogestrel subdermal implant is infrequent bleeding (less than 3 episodes during a 90 day interval), reported by 34% of users. Amenorrhea is reported by 22%, while prolonged (bleeding episode lasting longer than 14 days during a 90 day interval) and frequent (more than 5 episodes during a 90 days period) bleeding are reported by 18% and 7%, respectively.<sup>37</sup> Various approaches to reduce frequent bleeding or spotting have been investigated in small clinical trials, including the short term administration of estrogen, COCs, oral LNG, tamoxifen, or tranexamic acid.<sup>7</sup>

A systematic review of clinical trials with the DMPA intramuscular injection found that the prevalence of amenorrhea increased with each successive 90-day interval:

12%, 25%, 37%, and 46%.<sup>38</sup> The product labeling reports amenorrhea in 55% of users at 1 year of use.<sup>39</sup> The bleeding pattern with the subcutaneous formulation is similar, with 39% and 57% of users reporting amenorrhea after 6 months and 1 year, respectively.<sup>40</sup>

Weight gain is a common concern associated with POCs. Product information for the DMPA intramuscular injection and the etonogestrel implant includes weight gain of 8.1 pounds and 3.7 pounds after 2 years of use, respectively.<sup>37,39</sup> However, a recent systematic review of weight gain with POCs found a mean weight gain of less than 4.4 pounds over a 12 month period, which is not significantly different from other contraceptive methods.<sup>41</sup>

Another potential concern is the effect of POCs on mood disorders. Data from clinical trials are inconsistent and difficult to interpret due to differing diagnostic classification systems.<sup>42</sup> For example, the DMPA intramuscular injection has been reportedly associated with depression, although some recent analyses show little impact.<sup>43,44</sup> Monitoring for individual mood changes upon use of a POC is warranted.

Regardless of the POC chosen, side effects of weight gain, unpredictable bleeding, and possible mood changes should be discussed. With education, patients can make informed decisions. Studies show that proactive counseling improves continuation rates of contraceptive choices.<sup>7</sup>

#### 4.0 CONCLUSION

The initial selection of hormonal contraception involves careful consideration of health conditions, cost, preferences for routes of administration, and frequency of use. Further modifications to hormonal methods and dosing patterns should be based upon tolerability. Individualizing this approach should maximize patient satisfaction, compliance and prevention of unintended pregnancy.

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