

# DIALOGUES



## IN CONTRACEPTION®

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## Return to Fertility After Use of Reversible Contraception

Lee P. Shulman, MD, and Carolyn L. Westhoff, MD, MSc

### Educational Objectives:

The health care provider should be able to:

- address misperceptions regarding fertility after discontinuation of contraceptive use
- describe and compare fertility resumption profiles associated with various reversible contraceptive methods
- assist individual women in selecting contraceptive methods that best suit their childbearing goals

Women who elect to use reversible contraception to prevent unintended pregnancy do so for a variety of reasons, often depending on their individual ages and/or stages of life. Many are seeking to delay pregnancy while preserving their fertility; these include adolescents and young adults who wish to prevent pregnancy until their societal/educational/professional/financial goals have been achieved. Many parous women who desire another child wish to space their pregnancies in accord with their goals for family size. Other women wish to prevent any future pregnancies but do not want to have a sterilization procedure; among them are many women aged 35 and older who want contraception until menopause.

### Addressing Misperceptions Regarding Fertility After Contraceptive Use

Women who use contraception to delay pregnancy until they are older may believe the former contraceptive method is the reason for their inability to conceive after discontinuation of use. In fact, however, both aging and parity affect fertility in women, whether or not they have used contraception.<sup>1-3</sup> Data from the Oxford Family Planning Association contraceptive study cohort indicate that, among 6199 episodes of women having planned pregnancies after discontinuing contraception, parity was strongly associated with fertility rates.<sup>1</sup> Women of parity 3 or more experienced almost twice as high a relative fertility rate (1.86,

confidence interval [CI] 1.58-2.20) as nulliparous women (referent). The relation between age and fertility was found to be different for parous and nulliparous women. In parous women, modest decreases in fertility were demonstrated from age 32 (fertility rates ages 30-31, 1.00; 32-33, 0.90; 34-35, 0.86) and then were followed by larger decreases (fertility rates ages 38-39, 0.64;  $\geq 40$ , 0.49). In nulliparous women, a significant decrease ( $p$  for trend,  $<.0001$ ) in fertility occurred gradually after age 28.

Even among nulliparous women aged 30 to 34, there was no evidence in the Oxford study that use of combination oral contraceptives (COCs; eg, Desogen®, Mircette®) causes permanent infertility.<sup>2</sup> The percentages of women remaining undelivered 72 months after contraceptive method discontinuation were very similar among those having used COCs (10.0 $\pm$ 1.8) and those having used nonhormonal contraception (12.7 $\pm$ 2.2).

The cumulative effects of medical, endocrinologic, and gynecologic problems also interact with age to further decrease fertility, regardless of contraceptive use.<sup>4</sup> Such problems include endometriosis, polycystic ovarian syndrome, diabetes, obesity, thyroid dysfunction, and sexually transmitted infections. There is no evidence that elective abortion decreases fertility.<sup>5</sup>

Among the misperceptions about contraception is the belief that use of hormonal or intrauterine contraception impairs future fertility. Use of exogenous hormones does not cause sterility.<sup>6</sup> In both parous and nulliparous women, there is no evidence of an increased incidence of permanent infertility after discontinuing use of COCs.<sup>2</sup> Tubal infertility associated with an increased incidence of pelvic inflammatory disease (PID) following use of one early type of intrauterine contraceptive (IUC) with a multifilament tailstring negatively and erroneously affects opinions of current IUCs, which do not increase risk of either PID or infertility in women not infected with pathogenic organisms.<sup>7,8</sup>

Another erroneous belief is that users of hormonal contraceptives require periodic temporary discontinuation from use of the method in order to preserve future fertility. There is no need to discontinue method use periodically to allow resumption of fertility unless the woman intends pregnancy. Fertility resumes promptly after discontinuation of most hormonal contraceptive methods (see method discussions below) regardless of duration of use.

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## Combination Hormonal Methods

Both the estrogen and progestin components of combination hormonal methods (COCs [eg, Nordette®-28, Estrostep® FE]; transdermal contraceptive patch [ORTHO-EVRA®]; vaginal ring [NuvaRing®]) contribute to their mechanism of contraceptive action. These agents prevent ovulation by inhibiting gonadotropin secretion via effects on both pituitary and hypothalamic centers.<sup>9</sup> The progestin component suppresses luteinizing hormone (LH) secretion, preventing ovulation, and thickens cervical mucus, blocking sperm transport. Estrogen suppresses follicle-stimulating hormone (FSH), preventing the development of a dominant follicle.

### Combination Oral Contraceptives (COCs)

Most studies have found a slightly delayed return to fertility but no absolute impairment of fertility following discontinuation of COC use.<sup>2,10-13</sup> In a survey of UK women attending antenatal clinics, the mean time to pregnancy (TTP) following discontinuation of long-term (>2 years) use of COCs was 2-fold longer (8.2 months, CI 7.2-9.1) than mean TTP after long-term condom use (4.2 months, CI 2.5-6.1;  $p < .001$ ).<sup>10</sup>

The dose of estrogen in a COC formulation may influence the length of conception delay following discontinuation. An observational study of women at their first prenatal visits found that, among women whose last contraceptive method was COCs containing less than 50 mcg of estrogen, the mean TTP after discontinuation was 4.01 cycles (CI 3.59-4.43), similar to the mean TTP after discontinuation of nonhormonal methods (3.18 cycles, CI 3.03-3.33).<sup>11</sup>

Nested case-control data from the Nurses' Health Study II cohort indicate that the multivariate relative risk (RR) of ovulatory causes of delayed fertility in women who had ever used COCs was small and nonsignificant (1.2; CI 0.9-1.7).<sup>12</sup> There was no statistically significant trend of increasing risk with increasing duration of COC use; 88% of nulliparous women who had not become pregnant for at least 1 year following method discontinuation reported an eventual pregnancy in 4 years or less, indicating that absolute fertility was not impaired. A prospective study of 8497 planned pregnancies found that previous prolonged use of COCs ( $\geq 5$  years) was associated with more rapid conception than previous use of shorter durations (Table).<sup>14</sup> A 1995 analysis of control-group data from the case-control Cancer and Steroid Hormone

Study found that past use of monophasic COCs containing either more or less than 50 mcg of estrogen was associated with lower frequencies of primary infertility (odds ratio [OR] 0.64, CI 0.3-1.14; OR 0.59, CI 0.37-0.93, respectively) than nonusers (referent).<sup>13</sup>

### Transdermal Contraceptive Patch

The patch releases 20 mcg of ethinyl estradiol (EE) and 150 mcg of norelgestromin (NGMN), the primary active metabolite of norgestimate, into the bloodstream every 24 hours.<sup>15</sup> No long-term studies have yet assessed time to return of fertility after discontinuation of patch use, but the effects are expected to be similar to those of COCs. Gonadotropin levels return to baseline values by 6 weeks after patch discontinuation, similar to COCs, suggesting that return of fertility after patch discontinuation is also rapid.<sup>15</sup>

### Vaginal Ring

The vaginal ring releases 15 mcg of EE and 120 mcg of etonogestrel, the biologically active metabolite of desogestrel, per day.<sup>16</sup> No long-term studies have yet assessed return to fertility after discontinuation of the vaginal ring, but effects are expected to be similar to those of COCs. In one arm of an open-label, randomized study of ovarian function during vaginal ring use, women (n=15) used the method for 2 cycles.<sup>17</sup> Serial ultrasounds to determine follicle diameter and progesterone level measurements to determine when ovulation occurred were then undertaken. The median time to ovulation was 19 days (range 13 to >28 days) after the second ring was removed.

After minor delays in fertility resumption, use of combination hormonal contraception does not adversely affect the incidence of future fertility. Preservation of future fertility may in fact be enhanced with use of these methods through the protection they afford against PID<sup>18</sup> and ectopic pregnancy.<sup>19</sup> One study suggests that use of COCs, and possibly other combination hormonal methods, might prevent ovarian failure caused by chemotherapeutic agents.<sup>20</sup>

## Injectable Progestin-Only Methods

Depot medroxyprogesterone acetate (DMPA; Depo-Provera® CI; depo-subQ provera 104™) inhibits release of LH, preventing ovulation, without suppressing the secretion of FSH.<sup>21</sup> The clearance of progestin from serum after the final injection of DMPA IM (150 mg) has been found

**Table. Percentages of Planned Conceptions Within 12 Months After Discontinuing COC Use**

	Total (N)	Duration of COC Use				$\chi^2$ p-value
		$\geq 5$ y (0%)	3-4 y (0%)	1-2 y (0%)	<1 y (0%)	
		(56.8%)	(20.3%)	(11.0%)	(7.0%)	(4.9%)
No. conceived in 12 mo. (%)	7139 (88.1)	4122 (89.5)	1444 (88.0)	761 (85.2)	474 (83.5)	338 (85.4)
						30.7 (<.0001)

COC=combination oral contraceptive.

Adapted with permission from Farrow et al<sup>14</sup>

to take a mean of 160.9 days (standard deviation [SD]  $\pm 72.3$  days; range 55–440 days).<sup>22</sup> Mean time to first ovulation (as measured by serum progesterone concentrations reaching luteal phase levels) is 211.1 days (SD  $\pm 66.9$  days; range 77–425 days). For this reason, DMPA has a prolonged contraceptive effect. Only 68% of women who discontinue DMPA IM use to become pregnant do so within 12 months, but 83% conceive within 15 months and 93% within 18 months from the last injection.<sup>21,23</sup> The median time to conception for those who wish to conceive has been found to be about 10 months (range 4–31 months).<sup>21,24</sup> A comparative study among former users of various contraceptives found that mean TTP among DMPA IM users of 2 to 4 years' duration was about 8 months longer than among DMPA IM users of 1 to 2 years' duration.<sup>10</sup> Despite these delays in return to fertility, fertility is not permanently impaired; cumulative pregnancy rates have been found to be similar between past users of DMPA IM and of IUCs.<sup>24</sup>

Product labeling for subcutaneous DMPA (DMPA SC; 104 mg) states that return to ovulation and return to fertility are likely to be delayed after method discontinuation.<sup>25</sup> Among 15 women who had received multiple doses of DMPA SC, median time to ovulation was 10 months after the last injection. The earliest return to ovulation was 6 months after the last injection, and 12 women (80%) ovulated within 1 year of last injection.<sup>25</sup> In a prospective, randomized single-dose trial of DMPA IM and DMPA SC, median time to return of ovulation (defined as the first occurrence of serum progesterone levels  $\geq 4.7$  ng/mL) in 39 women discontinuing DMPA SC was 30 weeks (212 days, range 106–358 days).<sup>26</sup> In 19 women discontinuing DMPA IM, the median time to return of ovulation was 26 weeks (183 days; range 70–315 days). In this study, cumulative rates of ovulation at the end of 12 months postinjection were 97.4% (38/39) in the DMPA SC group and 94.7% (18/19) in the DMPA IM group (Figure).<sup>26</sup>

Although fertility is not permanently impaired after discontinuation of DMPA, there is a substantial delay of about 6 to 10 months for return to fertility. Time to conception for some women may be delayed up to 2 years.

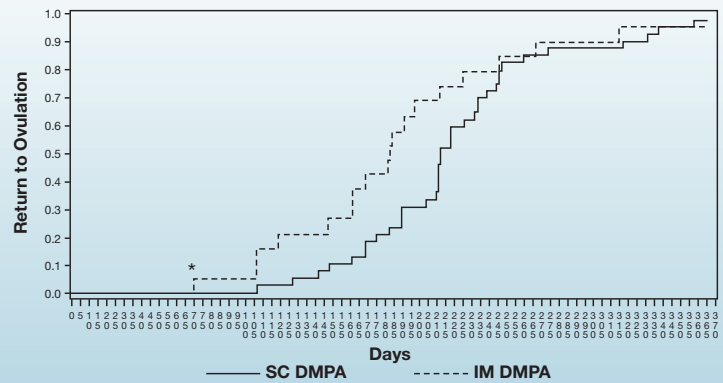
## Intrauterine Contraceptives (IUCs)

The 2 IUCs currently available in the United States are the copper IUC (ParaGard® Copper T 380A) and the levonorgestrel-releasing IUC (LNG-IUS; Mirena® Intrauterine System). The mechanism of contraceptive action of the copper IUC is primarily a foreign-body reaction to the device in the endometrium, causing a sterile inflammatory response and resulting in a spermicidal intrauterine environment.<sup>27</sup> This foreign-body reaction is enhanced by the copper ions released by the copper IUC, which may also inhibit sperm transport in the cervical mucus and in the endometrial cavity.<sup>27–29</sup> The LNG-IUS initially releases 20 mcg of LNG into the uterine cavity daily, with the rate decreasing to half after 5 years of use.<sup>30</sup> Local progestogenic effects in the uterine cavity cause cervical mucus thickening in addition to the foreign-body reaction, inhibiting sperm transport to the oviduct.<sup>27,30</sup>

Studies have found no impairment of resumption of fertility after removal of the copper IUC<sup>27,31</sup> or the LNG-IUS.<sup>32,33</sup> In a randomized comparative study of the 2 IUCs, median TTP after copper IUC removal was 3 months and after LNG-IUS removal 4 months, with lifetable rates of achieving planned pregnancy by 12 months of 91.1% and 96.4%, respectively.<sup>33</sup> In a prospective study of rates and outcomes of planned pregnancy, the 1-year and 2-year lifetable pregnancy rates after discontinuation of the copper IUC were 77% and 88%, respectively, and after discontinuation of the LNG-IUS 84% and 88%, respectively.<sup>34</sup> Among former copper IUC users wishing to conceive, 43% were pregnant within 3 months; the 3-month rate among former LNG-IUS users was 34%. It should be recognized that women discontinuing IUC use in these and other studies were primarily parous, therefore with proven fertility. Studies of pregnancy rates after discontinuation of other contraceptive methods typically include parous and nulliparous women; some of the latter may have been infertile before initiating the method.

Previous use of copper IUCs has been found not to be associated with an increased risk of infertility among nulligravid users compared with gravid users.<sup>8,35</sup> The US Food and Drug Administration (FDA) has approved the use of the copper IUC in nulliparous women aged 16 years and older.<sup>36</sup> The LNG-IUS is approved by the FDA for use in parous women only.<sup>30</sup>

**Figure. Kaplan-Meier curve of time to return of ovulation\* after single injection of DMPA IM or DMPA SC.**



DMPA IM=150 mg/mL; DMPA SC=104 mg/0.65 mL.

\*Based on progesterone levels  $\geq 4.7$  ng/mL.

DMPA=depot medroxyprogesterone acetate; IM=intramuscular; SC=subcutaneous.

Adapted from Jain J, Dutton C, Nicosia A, Wajszczuk C, Bode FR, Mishell DR Jr. Pharmacokinetics, ovulation suppression and return to ovulation following a lower dose subcutaneous formulation of Depo-Provera®. *Contraception*. 70:11–18; copyright 2004, with permission from Elsevier<sup>26</sup>

Use of IUCs does not impair future fertility, and fecundability resumes promptly following discontinuation of use as the foreign-body reaction disappears rapidly.

## Implant Contraception

A single-rod subdermal implant (Implanon®) releasing 60–70 mcg of etonogestrel initially, decreasing to 30 mcg after 2 years, provides effective contraception for 3 years.<sup>37</sup> This implant is expected to become available in the United States during 2006. Plasma concentrations of etonogestrel are sufficiently high to prevent ovulation through suppression of the LH surge.<sup>37–39</sup> Within 1 week after removal of the single-rod implant, etonogestrel serum levels are undetectable<sup>37</sup>; in small studies ovulation and fertility are reported to return within 3 months after implant removal.<sup>40,41</sup> Use of the single-rod implant, therefore, does not appear to impair future fertility, and resumption of ovulation occurs rapidly following method discontinuation.

## Conclusions

With the exception of DMPA, the return to fertility after discontinuation of reversible contraceptive methods is very rapid. Women who desire pregnancy within a relatively short time after stopping contraception should consider alternatives to the use of DMPA. There does not appear to be any significantly increased risk of primary or secondary infertility following use of any of these methods, including DMPA and both IUCs. Counseling regarding return to fertility after contraceptive use should emphasize the importance of each woman's selection of a contraceptive method whose return-to-fertility profile suits her individual childbearing goals. Facts about contraception and the preservation of fertility should be provided to dispel any misperceptions. There is no necessity to discontinue steroid contraception temporarily to preserve future fertility; temporary discontinuation only increases the risk of unintended pregnancy.

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# Improving Continuation With Various Contraceptive Methods

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## Educational Objectives:

The health care provider should be able to:

- define the risks of inconsistent or premature discontinuation of contraceptive use
- identify individual, general, and method-specific factors in consistent contraceptive use and continuation
- implement effective counseling, provision, and follow-up strategies to enhance appropriate contraceptive selection and continuation

Although most nonbarrier reversible contraceptive methods available today are similarly efficacious when used consistently and correctly, the ability of each woman to use her selected method in this manner largely determines whether the maximum contraceptive effect occurs.<sup>1-3</sup> Inconsistent contraceptive use may result in less effective protection against unintended pregnancy as well as increased side effects—which in turn may lead to dissatisfaction, further inconsistent use, and/or premature discontinuation.<sup>4</sup>

The 2002 National Survey of Family Growth (NSFG) reported that in the United States 14% of recent births were unwanted—an increase of 5% from the 9% reported in the 1995 NSFG—and 21% were unplanned (ie, occurred earlier than desired).<sup>5</sup> Among reported US legal abortions in 2000 and 2001, the abortion rate was 16 per 1000 women aged 15 to 44 years.<sup>6</sup> In another national survey of women having abortions in 2000 and 2001, about half of these unintended pregnancies occurred among women reporting having used contraception in the month of conception; however, most contraceptive users cited inconsistent use as the reason for becoming pregnant, including 76% of the oral contraceptive users.<sup>7</sup> Moreover, in the 2002 NSFG, 7.4% of sexually active women aged 15 to 44 years and at risk for unintended pregnancy were not currently using contraception; this increase in contraceptive nonuse from 5.4% in the 1995 NSFG is disturbing, as it represents 1.43 million additional women at risk for unintended pregnancy.<sup>8</sup> The abortion survey found that concerns about contraceptive methods were cited by 32% of nonusers, including past problems with methods (20%) and fear of side effects (13%).<sup>7</sup> A substantial amount of overlap in women's reasons for nonuse and for inconsistent use of contraception was observed.<sup>7</sup>

## Factors in Consistent Use and Continuation of Contraception

In attempting to enhance contraceptive use, consistency, and continuation, clinicians need to recognize the unique needs, preferences, and characteristics of individual women, which have enormous impact on motivation and success for using a particular contraceptive method.<sup>5</sup> The overriding objective of contraceptive counseling, therefore, is to assist each woman to select the contraceptive method that she will best be able to use properly and comfortably for the entire time she wishes to avoid pregnancy.<sup>4,9,10</sup> Such a method is one that is appropriately suited to the particular woman's preferences, needs, and lifestyle. A cross-sectional telephone survey examining the effects of contraceptive counseling and its relationship to contraceptive attitudes and practices found that receiving personalized counseling (rather than no counseling or informational counseling only) significantly increased the likelihood ( $p < .05$ ) of using contraception correctly and of intent to continue contracepting.<sup>11</sup>

A key ingredient of effective counseling is early assessment of any linguistic, cultural/religious, and/or educational barriers to a woman's comprehension of contraceptive information.<sup>9,12,13</sup> The clinician should elicit and consider each woman's age, educational level, literacy, ability to understand counseling, and individual learning style,<sup>9,13</sup> in order to tailor counseling and discussion to her individual characteristics.<sup>11,14</sup>

The active involvement of each woman in the process is crucial for optimal method selection.<sup>4,9</sup> Women should be encouraged to consider and evaluate their individual childbearing goals, beliefs about fertility, priorities of contraception, preferences for contraceptive use, and, eventually, attitudes toward various contraceptive methods.<sup>10,12</sup> When addressing childbearing goals, clinicians should be aware that some women may be ambivalent about becoming pregnant and, therefore, may not be committed to correct, consistent use of their selected contraceptive methods.<sup>15</sup> Such ambivalence can occur in any reproductive-age woman; 4.7% of women of reproductive age obtaining abortions in 2000–2001 cited ambivalence about pregnancy as a reason for not having used a contraceptive in the month of conception.<sup>7</sup> The 2002 NSFG found that 17.3% of respondents who had an unintended pregnancy leading to a live birth and who were not using a contraceptive method at the time of the pregnancy reported that they didn't really mind if they became pregnant.<sup>5</sup>

The clinician should attempt to determine the importance to each woman of method effectiveness, safety, side effects, regimen timing, convenience, ease of use, and planned duration of use.<sup>9</sup> In addition, the woman's most significant concerns regarding contraceptive use (eg, intolerance of bleeding irregularities, history of incorrect use, preservation of fertility) should be evaluated.<sup>9,10</sup> When describing various available contraceptive methods, the clinician should assess the woman's understanding of method-specific effectiveness, benefits/risks (including the noncontraceptive health benefits afforded by each method), side effects, and correct implementation.<sup>9</sup> Differentiation and comparison of the attributes of each method can enhance selection of the most suitable contraceptive option.<sup>10</sup> Any fears, myths, or misperceptions about various methods should be elicited and addressed using evidence-based findings whenever possible.<sup>10</sup> Partner attitudes toward contraception use and/or specific methods can positively or negatively affect consistent use and continuation.<sup>2,16,17</sup> Accordingly, if possible and appropriate, involvement of the woman's partner in contraceptive selection should be encouraged.

When the woman has made a selection of contraceptive method, it is important to provide anticipatory guidance about possible problems and common side effects. Women who know what side effects to expect, and who understand that many initial side effects are likely to resolve within several months, are less likely to discontinue use prematurely.<sup>4,10</sup> The importance of correct, consistent use of the selected method for contraceptive effectiveness, cycle control, and safety should be emphasized.<sup>4</sup> Despite determination and preparation, however, errors in contraceptive usage can occur. It is advantageous to provide women with emergency contraception (eg, Plan B<sup>®</sup>) to be used ideally within 72 hours (or by 120 hours) after the occurrence of a single act of unprotected or underprotected intercourse.<sup>18,19</sup>

To help avert premature discontinuation of method use, clinicians should provide women with easy telephone access to staff members who are trained to address problems and concerns as they arise. Periodic counseling should reassess the woman's satisfaction with her method, its suitability to her current needs, and any changes in childbearing goals. Information about any new contraceptive methods that may have become available should also be provided at least yearly. Even when women are satisfied with their current contraceptives, awareness of newly available methods may encourage consideration of using more convenient and/or effective ones. Women should know that if the method initially selected proves unsatisfactory, an alternative method, selected to address the source of dissatisfaction, can be substituted.<sup>20</sup> However, women should also be encouraged not to discontinue method use—particularly in reaction to negative media reports—without first calling the clinician or staff; women who stop using one method of contraception without initiating a replacement method increase their risk of unintended pregnancy.

## Facilitating Continued Use of Selected Contraceptive Method

Depending on the woman and the contraceptive method selected, a number of strategies to facilitate consistent and continued method use may be utilized when possible and appropriate (*Table*). A particularly useful approach

to method initiation is Quick Start: the selected hormonal method (combination oral contraceptives [COCs; eg, Levlén®, Brevicon®], transdermal patch [ORTHO EVRA®], vaginal ring [NuvaRing®], depot medroxyprogesterone acetate IM [Depo-Provera® CI], subcutaneous depot medroxyprogesterone acetate [depo-subQ provera 104™]) is started immediately during the clinician visit in which it is prescribed, regardless of the woman's menstrual cycle day, and without waiting for a Sunday start, menses start, or return visit.<sup>21-24</sup> Studies of Quick Start have found that this method initiation approach eliminates much of the counseling and confusion regarding when to start the method, results in short-term continuation rates comparable to or better than those observed with traditional start times for the same methods, produces no differences in the effect of bleeding patterns on continuation compared with conventional starting regimens, and may improve consistency and long-term continuation of contraceptive use.<sup>21-26</sup> Contraception, including intrauterine contraception, should be offered at the time of any spontaneous or elective abortion.

### Table. Strategies to Facilitate Successful Use of Selected Contraceptive Method

- Implement Quick Start approach to immediate initiation of hormonal contraception
- Emphasize importance for hormonal contraceptive effectiveness of not extending the hormone-free interval
- When possible, provide an extra cycle's supply of the selected method, to help avoid delay in use resumption after hormone-free interval
- When possible, prescribe 1 year's supply of method to facilitate prompt refill
- Combine Quick Start of the new method with a prescription for the previous method in case of problems with the new method
- Consider extended-use or continuous-use regimens (ie, few or no hormone-free intervals) for selected women; however, no data support an association between extended use and more consistent method use
- Schedule a telephone consultation after 3 months of use to review method use issues and concerns<sup>20</sup>
- Enable women to have easy access to staff trained to answer contraceptive-use questions and address problems
- Provide emergency contraception prescription in advance, in case of need
- Encourage women to call clinician or staff **before** discontinuing method use, particularly in reaction to negative media reports about the method

## Method-Specific Use and Continuation Factors

Women's individual characteristics can affect the consistency of method use and, therefore, the risk of unintended pregnancy. Methods with high inherent efficacy, independent of user action, have less inherent potential for incorrect use, while methods with high inherent efficacy but dependent to some extent on user action have an increased likelihood of not being used correctly or consistently.<sup>3</sup>

### Coitus-Dependent Methods

Methods designed to be used at the time of coitus (eg, condoms, diaphragm) are frequently not used consistently by many women and their partners.<sup>7</sup> Among the reasons most often cited among condom users who had abortions in 2000-2001 for inconsistent use of condoms included the woman's

belief that she would not become pregnant, not having a condom available, not expecting to have sex, forgetting, not wanting to use it, or partner not wanting to use it.<sup>7</sup>

### Daily Methods

COCs are the most commonly used reversible contraceptive method in the United States, used by 30.6% of reproductive-age women using contraception.<sup>8</sup> COCs are among the most effective contraceptive methods available when used correctly and consistently.<sup>3</sup> However, the need to ingest a tablet daily for maximum contraceptive protection is difficult for many women to achieve. Analysis of self-reported diary data on COC use found that 68% of 141 study participants missed 1 or more active tablets during the 3-month study period; 48.9% reported missing 2 or more tablets at some time.<sup>20</sup> Moreover, in more than one third of missed-tablet instances, participants did not take the required 2 tablets the day after a missed tablet, thus decreasing protection against pregnancy.<sup>20,27</sup> The foregoing figures probably underrepresent instances of missed tablets: in a study comparing self-reported data on COC tablet-taking with data from an electronic device measuring actual tablet-taking, the electronic and self-reported data agreed on the number of missed-tablet days only 45% of the time.<sup>28</sup> In each month, the proportion of women self-reporting no missed tablets was higher than that reported electronically (53%-58% versus 19%-33%, respectively). A French cohort study of COC use found that 42% of instances of missing a tablet occurred during the first week after the hormone-free interval.<sup>29</sup> Missing 3 or more active pills at any time during the cycle warrants additional contraceptive precautions, but the risk of pregnancy is greatest when active pills are missed at the beginning or at the end of the active-pills cycle, ie, when the hormone-free interval is extended.<sup>27</sup> Clinicians should make women aware of the importance of not missing a tablet at the beginning of the cycle, when follicular development is most likely,<sup>30,31</sup> and of the steps they can take to help prevent pregnancy (eg, backup contraception, emergency contraception) if coitus occurs when tablets have been missed. The reasons most commonly cited for missing COC tablets include being away from home without the pill-pack, forgetting to take the tablet, or being unable or forgetting to obtain a new pill-pack in time to begin a new cycle.<sup>7,20</sup>

### Nondaily Combination Hormonal Methods

Methods that do not require daily use are characterized by a smaller difference between perfect-use and typical-use unintended pregnancy rates, providing more effective contraception overall.<sup>1</sup> In surveys, users have found nondaily combination hormonal methods (patch, vaginal ring) to be easier to use than daily COC tablet ingestion.<sup>32,33</sup>

### Transdermal Contraceptive Patch

In North American clinical trials, users of the patch—applied once weekly for 3 weeks, followed by a hormone-free week to allow withdrawal bleeding—achieved perfect regimen implementation more often (87.8% to 91.6% of cycles) than COC (Triphasil®) users (67.7% to 85.2% of cycles).<sup>34</sup> Younger women using the COC (<20 years, 67.7%; 20 to 24 years, 74.4%) had fewer perfect-use cycles than did older women (≥25 years, 79.8% to 85.2%).<sup>34</sup> However, perfect use of the patch was similar in all age categories. Similarly, in a randomized, open-label, parallel-group trial comparing COC use with patch use in 65 centers in Europe and South Africa, the percentage of cycles with perfect regimen implementation for each age group of users up to age 40 years was higher for patch users (90% or more) than for COC users (87% to 89%).<sup>32</sup> In a long-term evaluation (up to 18 months) of adolescent (mean 17.5±2 years, range 13 to 23) patch users, 50% of users were reported to be in their second year of use.<sup>35</sup>

### Vaginal Ring

In noncomparative studies, the vaginal ring, worn for 3 weeks per month followed by a hormone-free week to allow withdrawal bleeding, was found to be used perfectly in 85.6% of cycles (79.9% of cycles in North America, 90.8% in Europe).<sup>36</sup> In a 1-year randomized phase III study in Europe and South America comparing the vaginal ring with a COC (30 mcg ethinyl estradiol [EE]/150 mcg levonorgestrel [LNG]), 87.4% of ring cycles and 86.6% of COC cycles achieved (*p*-value not provided) perfect adherence to the regimen.<sup>37</sup> Incidence of adverse events and discontinuation because of such events were similar in both treatment groups.<sup>37</sup>

(continued on page 7)

# Risk of Venous Thromboembolism With Different Estrogen-Containing Contraceptive Methods

Ronald T. Burkman, MD, and Carolyn L. Westhoff, MD, MSc

Recent labeling changes for the transdermal contraceptive patch (patch; ORTHO EVRA®; ethinyl estradiol [EE]/norelgestromin [NGMN], the active metabolite of norgestimate [NGM]) state that there are differences in pharmacokinetic (PK) profiles between the patch and a combination oral contraceptive (COC; 250 mcg norgestimate/35 mcg EE).<sup>1</sup> The correlation between PK parameters and risk of any adverse event is unknown; therefore, clinicians have difficulty evaluating the clinical implications of the differences in PK profiles of the patch and COCs. The following discussion is intended to help clarify the issues involved.

PK data come from 1 study measuring in vivo drug levels over time. Area under the curve (AUC) assesses an individual's total exposure, as measured by levels of the drug in the blood, over time;  $C_{max}$  refers to the highest level (peak) of drug concentration. The new labeling language states: "The PK profile for the...patch is different from the PK profile for (COCs) in that it has higher steady state concentrations and lower peak concentrations. AUC and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using [patch] compared with women using [a COC] containing EE 35 [mcg]. In contrast, peak concentrations for EE are approximately 25% lower in women using [patch].... In general, increased estrogen exposure may increase the risk of adverse events. However, it is not known whether there are changes in the risk of serious adverse events based on the differences in [PK] profiles of EE in women using [patch] compared with women using [COCs] containing 35 [mcg] of EE."<sup>1</sup>

## Pharmacokinetic Data

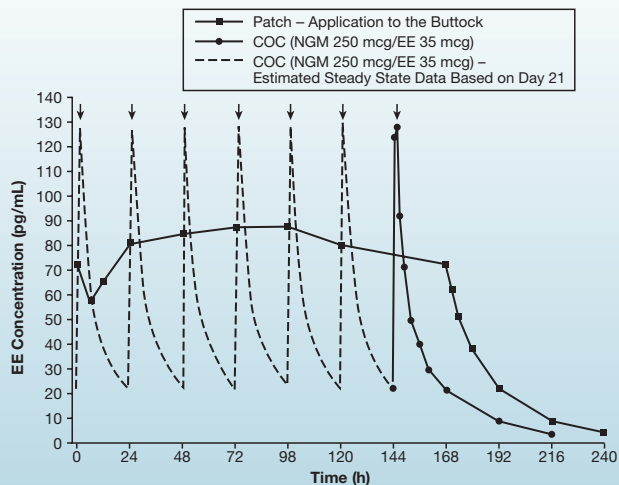
A recent Dutch PK study compared serum hormone levels of a COC (30 mcg EE/150 mcg levonorgestrel [LNG]; n=8) with the patch (n=6) and found that exposure to serum EE, as shown by  $AUC_{0-21}$ , was higher with the patch than with the COC (1.6, confidence interval [CI] 1.3-2.0;  $p < .05$ ) but that peak EE levels were lower with the patch than with the COC ( $C_{max}$  0.63, CI 0.53-0.75;  $p < .05$ ).<sup>2</sup>

The patch product labeling PK data (Figure),<sup>1</sup> based on a different study of 32 women, reflect EE levels similar to those found in the Dutch study.

## Clinical Relevance of PK Data

The PK profiles of orally and transdermally administered EE are different, but it remains to be determined whether the risks of venous thrombosis and embolism (VTE) associated with these contraceptive methods are also different.

**Figure. Mean serum concentration time-profiles of EE, transdermal patch,\* and EE 35 mcg/NGM COC during 7 days of treatment.†**



\*Cycle 2, Week 3; †Cycle 2, Days 15-21  
<sup>a</sup>Cycle 2, Week 3  
<sup>b</sup>Cycle 2, Day 21  
<sup>c</sup>Average weekly exposure, calculated as  $AUC_{24} \times 7$

EE=ethinyl estradiol; NGM=norgestimate; COC=combination oral contraceptive; AUC=area under the curve. Adapted with permission from package insert<sup>1</sup>

As stated in patch labeling, it is not known whether there are differences in risk of serious adverse events based on differences in PK profiles between COCs and the patch.<sup>1</sup>

## Risk of VTE With COCs

A substantial body of evidence has established that the relative risk of VTE associated with COC use is 2 to 4 times that among nonpregnant reproductive-age women not using COCs.<sup>3,4</sup> However, the absolute risk of VTE with COC use is low: 30 to 40 cases of VTE per 100,000 woman-years of use.<sup>3,5-7</sup> The excess risk of VTE attributable to COC use is therefore also low: 20 to 30 cases per 100,000 woman-years of use. In contrast, the risk of VTE with pregnancy is about 6 times the baseline rate.<sup>3</sup>

## New VTE Studies Comparing Patch, COC

In the first epidemiologic comparison of VTE risk between the patch and COCs, a nested case-control study compared VTE incidence among women aged 15 to 44 who started either the patch or COCs containing 35 mcg EE/NGM (Ortho-Cyclen®; Ortho Tri-Cyclen®) after April 1, 2002, when the patch became available in the United States.<sup>8</sup> Exposure to the methods included 58,752 woman-years of patch use and 88,571 woman-years of COC use. Up to 4 controls were age-matched and contraceptive-

matched to each of the 68 identified cases of VTE. The study found that risk of nonfatal VTE with patch use was similar to the risk with COCs containing 35 mcg EE and NGM (unadjusted odds ratio [OR] patch use versus the COC, 0.9 [CI 0.5-1.6]; Table). Overall VTE incidence rates per 100,000 woman-years of method use in the study population were 52.8 (CI 35.8-74.9) for the patch and 41.8 (CI 29.4-57.6) for COCs. Based on this study's findings, the NGM-containing patch appears to have a similar risk of nonfatal VTE as NGM-containing COCs, with relative and absolute risks for both NGM/EE-containing methods within the range observed in studies of VTE risk with COCs in general. Because the current study compared 2 methods containing NGM, a progestin not evaluated to any substantial degree in other studies of VTE risk with COCs, how NGM-containing COCs compare with other specific COCs in regard to risk of VTE remains to be determined.

Recent press releases<sup>9,10</sup> report the preliminary result of a second, separate study also comparing risk of VTE in first-time users of the patch with risk of VTE with a COC containing 35 mcg EE and NGM in a different population of women. In this unpublished study, according to the releases, the risk of VTE in patch users was found to be approximately twice the risk of VTE in the COC users. As the complete data are not yet available, the clinical relevance of these results remains to be determined.

**Table. Odds Ratio for VTE Comparing Users of Contraceptive Patch With Users of NGM-Containing COC**

Exposure	Cases		Controls		Odds ratio	95% CI
	n	%	n	%		
COC	37	54	139	52	1.0	Reference
Patch	31	46	127	48	0.9	0.5–1.6

VTE=venous thrombosis and embolism; NGM=norgestimate; COC=combination oral contraceptive. Adapted from Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 µg of ethinyl estradiol. *Contraception*. 73:223-228; copyright 2006, with permission from Elsevier<sup>8</sup>

## Summary

Despite reported findings of higher EE serum levels among patch users than among COC users, one recent epidemiologic study reported that the patch does not have a significantly different nonfatal VTE risk than COCs containing the same hormones. Results of the second, unpublished study found the VTE risk was higher with the patch than with COCs. Pending publication and evaluation of the findings from the second epidemiologic study, women should be counseled regarding the published study findings

and, if concerned, consider their contraceptive options. VTE risk, even if somewhat higher with use of estrogen-containing contraceptives than with nonuse, is still lower than the risk associated with pregnancy.<sup>3,8</sup> Further, even if the preliminary findings in the newest study are confirmed, it appears the absolute risks of VTE with the patch and with COCs are of small magnitude. Clinicians can advise women that selection of an appropriate combination hormonal method should be made based on individual preference for regimen or administration route, including possible differences in risk of VTE.

*Improving Continuation With Various Contraceptive Methods (continued from page 5)*

## Long-Acting Nonestrogen Methods

### Depot Medroxyprogesterone Acetate (DMPA)

DMPA IM 150 mg, injected intramuscularly every 3 months, requires no user action except to return for reinjection when scheduled. However, continuation rates with DMPA are less than optimal. In 1 study of inner-city adolescents, continuation rates were found to be 70.3% at 6 months, 48.3% at 9 months, 32.5% at 12 months, and 12.8% at 24 months.<sup>38</sup> Side effects (primarily irregular bleeding and weight gain) and missed appointments were the most common reasons for discontinuation.

A new, lower-dose (104 mg; DMPA-SC) version of DMPA, injected subcutaneously every 3 months, is now available. In 2 1-year phase III studies—1 in North America and South America and the other in Europe and Asia—13.9% and 5.3%, respectively, of participants discontinued use of DMPA-SC because of adverse events, most commonly increased or irregular vaginal bleeding.<sup>39</sup> Injection-site reactions (eg, injection-site pain, granuloma, atrophy) were reported in 1.6% of women in the European/Asian trial and in 9.7% of women in the Americas trial.

### Intrauterine Contraception

Intrauterine contraceptives (IUC; copper IUC [ParaGard<sup>®</sup>], levonorgestrel-releasing IUC [LNG-IUS; Mirena<sup>®</sup> Intrauterine System]) provide the longest-acting reversible protection against pregnancy: copper IUC 10 years, LNG-IUS 5 years.<sup>40,41</sup> Particularly for women who do not desire pregnancy for several years or ever (eg, perimenopausal women), IUC may be an appropriate option.

In large, international, multicenter studies of long-term IUC use, removal rates of the copper IUC for total medical reasons decreased from approximately 6% in the first year of use to approximately 4% annually in Years 2 to 10.<sup>42</sup> In a multicenter prospective randomized comparison of the 2 IUCs, the 5-year continuation rate was 33.0 per 100 women using the LNG-IUS and 40.6 per 100 women using the copper IUC.<sup>43</sup>

Altered bleeding patterns may occur with use of either IUC. Increases in the number of menstrual bleeding days and in amount of menstrual blood loss are common in the early cycles of copper IUC use, and may continue for the duration of method use<sup>44,45</sup>; bleeding irregularities are among the reasons most commonly cited for first-year discontinuation of copper IUC use.<sup>40</sup> While bleeding episodes may also increase during the first few months of LNG-IUC use, bleeding days and amount of menstrual blood loss gradually decrease over time, with amenorrhea experienced by 40% to 50% of users within 2 years of use.<sup>46</sup>

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## Conclusions

Clinicians can help women become aware of specific contraceptive methods that may improve their successful use of contraception. For many women, nondaily (eg, patch, vaginal ring) or long-acting methods (eg, DMPA, IUC) can facilitate correct and continued use. The Quick Start approach to hormonal contraception initiation, with immediate method start in the presence of the clinician, may benefit many women. Long-term method prescriptions and/or an additional month's supplies when possible can facilitate contraceptive continuation from 1 cycle to the next. Advance provision of emergency contraception in case of unprotected intercourse may help avert unintended pregnancies if the contraceptive method is not used correctly.

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## Return to Fertility After Use of Reversible Contraception (continued from page 3)

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