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Over half of all pregnancies in the United States (US) are unintended; an estimated 42% of these unintended pregnancies result in induced abortion or miscarriage.[1-3] Unintended pregnancies have profound adverse effects not only on maternal health, but also on infant and child health outcomes, including increased risk of low birth-weight, neonatal mortality, and infant developmental delay.[4] To decrease unintended pregnancy, clinicians must collaborate with their patients to optimize correct and consistent contraceptive use. Offering the full range of contraceptive options and providing counseling to help a woman choose a method that meets her individual needs is critical to optimal contraceptive success and family planning. Advances in contraceptive technology offer women today many options, from shorter-acting daily and nondaily options to longer-acting contraceptive methods. While oral contraceptives (OCs), which require daily use to prevent pregnancy, are still the most popular method in the US, long-acting reversible contraceptives (LARCs) have gained favor, as they provide user convenience and satisfaction and the lowest probability of method failure.[3,5,6]

Recent advances in contraceptive technology offer women today a wide range of contraceptive choices, from shorter-acting daily and nondaily options to longer-acting methods

LONG-ACTING REVERSIBLE CONTRACEPTIVE METHODS

According to the recent American College of Obstetricians and Gynecologists guideline, LARCs, including intrauterine devices (IUDs) and contraceptive implants, should be first-line choices for preventing unintended pregnancy.[7] These methods can be used by most women, including adolescents, nulliparous women, and women with contraindications for estrogen use. LARCs provide advantages not offered by shorter-acting methods, as they are not user-dependent, do not require daily/frequent adherence, have high rates of satisfaction and continuation, and provide top-tier effectiveness during typical use.[3,6,8] A recent, large, prospective cohort study found that participants using shorter-acting methods such as OCs, the transdermal patch, or a vaginal ring, had a risk of contraceptive failure that was 20 times higher than women who used LARCs.[3]

Between daily pills and the long-acting methods are intermediate methods, such as depot-medroxyprogesterone acetate (DMPA). Both intramuscular and subcutaneous injections are available in the US. The failure rate with typical use is 6.8%.[3] DMPA for subcutaneous injection (DMPA-SC) may facilitate (off-label) self-administration,[9,10] and like DMPA, is a highly effective contraceptive when used consistently.[3] Both injectable formulations are required every 3 months and are attractive to women who find daily dosing challenging or inconvenient.[11]

Despite the advantages of LARCs and DMPA, utilization may be diminished by lack of access due to cost, limited access to trained healthcare providers,[12] or

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Dr. Prabhakaran reports that she has no financial relationships to disclose.

patient preferences.[4,7,12] Problems with early IUDs and misperceptions regarding safety and liability issues with IUDs may discourage use of these contraceptives.[13] Concerns regarding menstrual changes and other side effects also may result in discontinuation of LARCs and DMPA or curtail their use.[7,12]

Some women may prefer more control over their contraceptive method and favor reversible, user-dependent contraception, such as barrier methods, that may not require the intervention of a healthcare provider. Women who are considering child bearing in the near future may be less amenable to LARCs or DMPA and favor shorter-acting nondaily or daily hormonal options.

SHORT-ACTING HORMONAL CONTRACEPTIVE METHODS

Oral Contraceptives

Oral contraceptives are the most frequently prescribed form of contraception in the US and are used by over 12 million American women, representing 38% of reproductive-age women.[5,8] When oral contraception was developed more than 50 years ago, it provided women for the first time a safe, effective, and nonintrusive way to avoid pregnancy. Since its development, women in the US have equated contraception with "the Pill." There has been a steady evolution from the first formulations, combination OCs (COCs) that combined high estrogen and progestin doses in 21/7 packaging.[14] The dosage of ethinyl estradiol (EE) has decreased to as low as 10 mcg; one new pill uses estradiol valerate as its estrogen rather than EE. New progestins have been introduced with different metabolic effects and different noncontraceptive benefits. New formulations with monthly multiphasic combinations of estrogen and progestin and formulations that reduce the number of scheduled bleeding episodes offer women new approaches and allow for more individualization of pill selection. Other ingredients, such as iron and folate, have been added to provide direct health benefits.

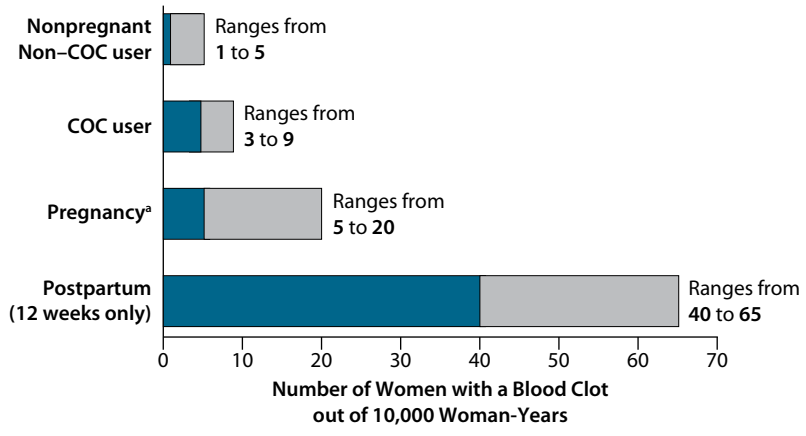
A large body of evidence demonstrates the noncontraceptive health benefits of COC use (presumed to also be relevant to transdermal and vaginal ring combination methods), including a lower incidence of ovarian, endometrial, and colorectal carcinoma and benign breast disease and reduction of menstrual irregularity, dysmenorrhea, ectopic pregnancy, and gonococcal-related hospitalizations for pelvic inflammatory disease, with no increase in breast cancer.[15,16] Several COCs are approved for the treatment of acne[15,17]; one formulation is approved for the treatment of premenstrual dysphoric disorder,[18] while another is approved for treatment of heavy menstrual bleeding.[19]

Progestin-only oral contraceptives (POPs, or minipills) can be used virtually by every woman[20] but, unlike combined hormonal methods, do not provide more predictable bleeding. Bleeding episodes with POPs are also usually more frequent, as well as longer or shorter, but POP users have fewer days of spotting than with COCs.[21] Failure rates in typical use of POPs are the same as with COCs but failure rates for POPs may be higher than COCs if the COCs are taken correctly and consistently.[22] POPs are more susceptible to interaction with drugs that increase hepatic cytochrome P450 activity.

Safety/Side Effects/Efficacy Challenges

The association of COCs with venous thromboembolism (VTE) is well known and prompted the substantial reduction of estrogen found in current COCs as noted earlier.[23] Doses of EE above 35 mcg have been shown to have higher VTE risk, but the increased safety of sub–35-mcg formulations is not clearly documented.[24] Whether or not the type of progestin also contributes

FIGURE 1 Likelihood of developing a blood clot



COC, combination oral contraceptives.

[a] Pregnancy data are based on actual duration of pregnancy in relevant studies; based on a model assumption that pregnancy duration is 9 months, the rate would be 7 to 27 per 10,000.[28]

to VTE risk remains controversial and uncertain, with studies employing varying methodologies reaching different conclusions.[23,25-27] Patient selection remains important because of the significant contributions of age, obesity, smoking, and sedentary lifestyles to VTE risk. However, a more important issue is the profound increase in VTE risk with pregnancy and following childbirth (Figure 1).[28]

As the prevalence of obesity among women in the US continues to increase, attention has also focused on the efficacy of shorter-acting contraceptives in obese women.[29] Incomplete ovarian suppression due to lower serum levels of both estrogens and progestins in obese women compared to normal-weight women has been suggested as a plausible mechanism for the observed higher failure rates. While pharmacokinetic studies show that peak hormone levels are lower in obese women compared with normal-weight women, the levels seen in obese women are still above the minimum needed to suppress ovulation.[29] Based on available evidence, lower OC efficacy in obese women does not seem to reflect any biologic trends. Rather, in the US, obesity and low socioeconomic status are correlated, and correct and consistent utilization of OCs is lower in women of low socioeconomic status.[30]

Utilization/Dosing Regimens

Finally, while COCs are effective when used consistently, perfect use is seldom achieved. Over 1 million unintended pregnancies among OC users can be attributed to incorrect use, gaps in use, discontinuation due to side effects, and method failure.[31] Cost and insurance coverage impact OC usage, and insurance companies' requirement for dispensing of OCs on a monthly basis can cause a delay in obtaining timely refills.[32] Dispensing adequate supplies of pills has been shown to reduce both pregnancy rates and abortion rates.[33] Although the traditional dosing regimen, 21 active pills and 7 placebo pills, has been a gold standard for contraception, new COCs are available that utilize shorter hormone-free intervals, and these appear to be more effective than 21/7-day COCs.[34] Extended 91-day COC formulations reduce the necessity for prescription filling, but acceptance of these new methods has been limited by some women's belief in the importance of monthly bleeding as well as the initial higher incidence of unscheduled bleeding with extended COC use.[35]

SHORT-ACTING NONDAILY HORMONAL CONTRACEPTIVE OPTIONS

Short-acting nondaily contraceptives, such as the vaginal ring and transdermal patch, offer the convenience of less frequent dosing and the elimination of daily hormonal fluctuations while providing comparable contraceptive efficacy.[36]

Short-acting nondaily options, such as the vaginal ring and transdermal patch, offer the convenience of less frequent dosing than OCs with comparable contraceptive efficacy

Vaginal Ring

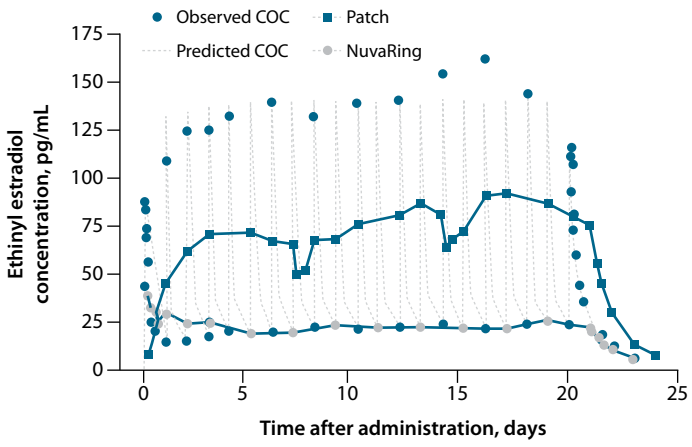
Vaginal ring contraception provides women with effective birth control with once-a-month administration without the need for daily intervention.[36] The EE/etonogestrel vaginal ring (NuvaRing®, Merck & Co, Inc., Whitehouse Station, New Jersey) is a combined contraceptive vaginal ring that releases 15 mcg EE and 120 mcg of the progestin etonogestrel per day. The ring is designed for a once-monthly cycle with 3 weeks of continuous use followed by 1 ring-free week. Pharmacokinetic studies that assessed serum EE concentrations using area-under-the-curve (AUC) parameters showed that exposure to EE was 3.4 times lower among NuvaRing users than among users of the marketed EE/norelgestromin transdermal patch, and approximately twice as low as among users of a COC with 30 mcg EE.[37] The ring is well tolerated and highly acceptable to users, and provides effective contraception, comparable to OCs, with excellent cycle control and a low incidence of side effects.[36,38]

At this time, the same cautions and side effects apply to all estrogen-containing contraceptives. In a national Danish cohort registry study of more than 1.6 million women with over 9.4 million woman-years of observation, users of NuvaRing had a 6.5 times increased risk of VTE compared with nonusers of hormonal contraception of the same age, conferring a 90% higher risk of VTE than a COC containing levonorgestrel.[39] There were serious methodological flaws with the study. The same flaws were also present in a recent US study that reported no higher risk of VTE among ring users compared with women using low-dose COCs.[40] A well-controlled, currently unpublished study presented at the 2012 annual meeting of the American College of Obstetricians and Gynecologists found that the VTE risk with NuvaRing is similar to that associated with use of COCs.[41]

Transdermal Patch

The EE/norelgestromin transdermal patch (Ortho Evra®, Janssen Pharmaceuticals, Inc., Raritan, New Jersey) provides women an effective once-a-week contraceptive option; patches are applied for 3 consecutive weeks followed by a patch-free week.[42] The currently marketed patch can be applied to the outer surface of the upper arm, abdomen, torso, or

FIGURE 2 **Mean EE concentration-versus-time curves for participants (available for pharmacokinetic analysis) using the NuvaRing (n=8), the transdermal contraceptive patch (n=6), and the COC (n=8)**



COC, combined oral contraceptives; EE, ethinyl estradiol

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buttocks with low rates of detachment.[43] The convenience and ease of use of weekly application provides higher satisfaction and preference for the patch among users of other contraceptive methods.[44] In addition, in clinical trials, women of all ages have reported that they use a transdermal patch more consistently than an OC.[44-46] In a randomized, multicenter clinical trial of 1,417 women, 88% of women allocated to the EE/norelgestromin patch reported perfect use compared to 78% of those allocated to an OC.[45] Breast discomfort and dysmenorrhea were initially more common among the patch users. Some women experienced application site irritation, which led to early discontinuation in 2.6% of patch users. Although this difference was not statistically significant, the EE/norelgestromin patch users had a lower overall failure rate than study participants randomized to OC use, possibly reflecting better utilization with this weekly method compared to daily dosing of OCs.[45]

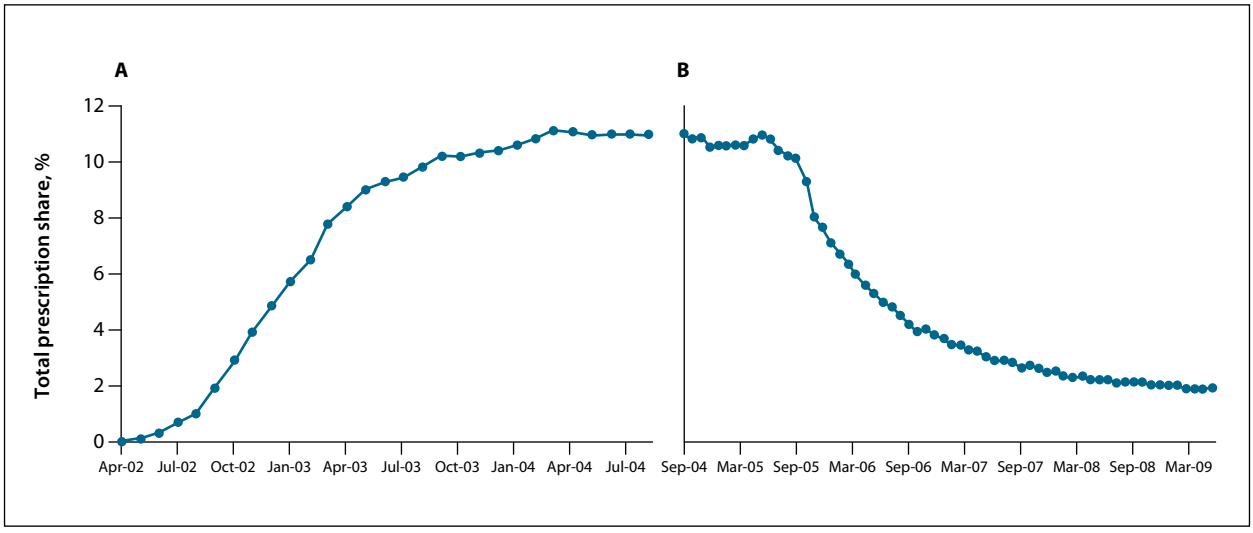
High failure rates with COCs are seen in adolescent women.[3] In the randomized trial described above, although adolescents using OCs experienced substantially lower consistent and correct use than that noted among adult study participants, adolescents randomized to the patch reported using the patch as consistently and correctly as adults and far better than teens randomized to pills.[45] Correct use and contraceptive efficacy reported in clinical trials, as noted, are often higher than with typical contraceptive use. In observational studies, continuation rates were lower in women who used the EE/norelgestromin patch than in women who used an OC or the vaginal ring.[47] Despite expectations that the convenience of transdermal patch use would improve contraceptive utilization, adolescents who use the patch are almost twice as likely as OC users to discontinue use after 1 year,[47,48] with the majority discontinuing by 4 months.[48] Also, the percentage of women experiencing an unintended pregnancy within the first year of typical use is comparable between the marketed patch and OCs.[8]

In the pharmacokinetic clinical trial referred to previously,[37] serum levels for EE over a 24-hour period (AUC) in women using the marketed patch were approximately 60% higher than in women using a 30 mcg EE OC. In contrast, the EE AUC among women using the vaginal ring contraceptive was substantially lower than that for women using the COC (Figure 2).[37,49-51]

Epidemiologic studies have estimated VTE risks with the EE/norelgestromin patch to range from a risk that is similar to that of OC use to more than twofold higher than the risk noted with OC use.[52-56] Methodological differences in the studies, including confirmation and classification of a finding of VTE from health insurance claims and medical records, may have contributed to the range of findings.[52] Given the higher estrogen levels associated with Ortho Evra use, women interested in using this method should be counseled regarding the possibility that VTE risk is elevated compared with use of oral contraception but is still substantially lower than that associated with pregnancy and childbirth. The markedly higher exposure to estrogen with the patch prompted the US Food and Drug Administration (FDA) to issue a warning about use of Ortho Evra, and the contraceptive's labeling was updated to include a black box warning that the risk of VTE with the patch may be up to twice the risk experienced with OCs.[57]

Even if VTE risks with patches were higher than with COCs, that risk is substantially lower than the VTE risk seen in pregnancy and following childbirth. The estimated incidence of VTE is as high as 10 per 10,000 women during pregnancy and 50 per 10,000 women in the immediate postpartum period.[58] VTE risks associated with use of estrogen–progestin contraceptives

FIGURE 3 Sales of Ortho Evra (**A**) before black box labeling change and (**B**) after black box labeling change



Data provided by IMS Health (Parsippany, New Jersey).

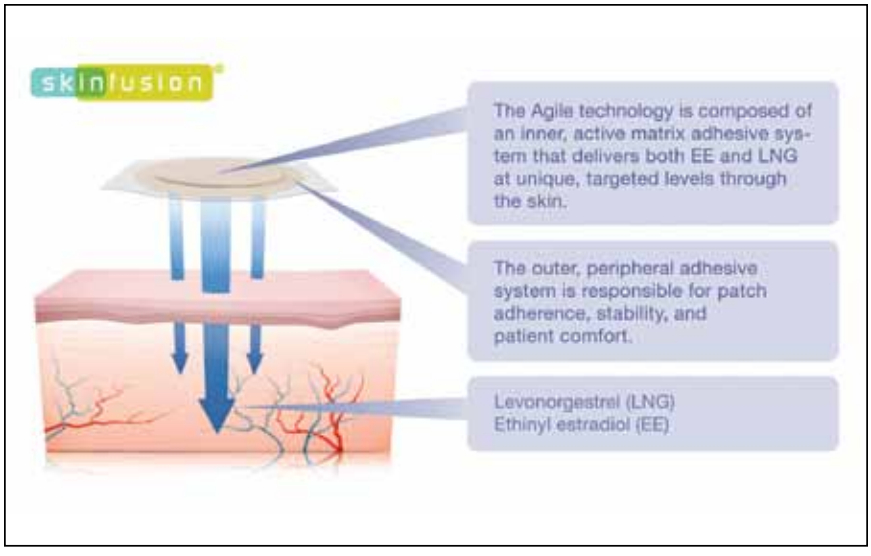
are substantially lower and about one-tenth the risk during pregnancy.[52-56,59] The 2010 Centers for Disease Control and Prevention US Medical Eligibility Criteria for Contraceptive Use states that the transdermal patch provides safety and pharmacokinetic profiles comparable to COCs with similar hormone formulations and makes comparable recommendations for use of COCs and the transdermal contraceptive patch based on a woman's indications and conditions.[20]

Although Ortho Evra was initially an extremely popular contraceptive method, utilization dropped abruptly after safety concerns developed and its packaging added the warning about possible increased VTE risk (Figure 3). This observation underscores that a lower-dose estrogen contraceptive patch would very likely represent an attractive contraceptive option for many women.

A LOWER-DOSE INVESTIGATIONAL CONTRACEPTIVE PATCH: AG200-15

An investigational EE/levonorgestrel transdermal contraceptive patch, AG200-15, offers the advantages of transdermal contraception with substantially lower estrogen release than the currently available contraceptive patch.

FIGURE 4 Technology used in the AG200-15 transdermal patch



AG200-15 is a low-dose transdermal contraceptive delivery system (TCDS), containing 2.3 mg EE and 2.6 mg levonorgestrel in an active matrix core of 15 cm^2 in area, which is then covered and surrounded by the perimeter adhesive system[60] (Skinfusion®, Agile Therapeutics, Princeton, New Jersey; Figure 4).

Ethinyl estradiol exposure from the AG200-15 patch is substantially lower than that of many cur-

An investigational EE/levonorgestrel transdermal contraceptive patch, AG200-15, offers the advantages of transdermal contraception with substantially lower estrogen release than the currently available contraceptive patch

rent EE-containing COCs. A Phase 1 open-label study with a crossover design randomized 36 healthy women to AG200-15 or a COC (Ortho Cyclen®, Janssen Pharmaceuticals, Inc., Raritan, New Jersey) containing 35 mcg EE and 250 mcg norgestimate.[60] The norgestimate and EE COC was selected because of its use as comparator in prior pharmacokinetic studies that evaluated Ortho Evra.[49,50] A comparison of the pharmacokinetic profiles of the 2 contraceptives found marked differences, with EE exposure being significantly lower with AG200-15 treatment than with the COC. The maximum serum concentration (C_{max}) value for EE levels was approximately 60% lower with AG200-15 compared with the COC, and systemic EE exposure (AUC) from the COC was 44% higher than that of AG200-15. In addition, EE exposure (AUC) from the AG200-15 patch was lower than levels reported for COCs containing 30–35 mcg EE. Of importance, EE exposure (AUC) during AG200-15 use was about half the level previously reported for Ortho Evra[61] (Table).[60]

SUMMARY

Despite the availability of many contraceptive options, half of all unintended pregnancies occur in couples who are using contraceptives, usually due to incorrect or inconsistent use. Birth control is a basic health need of sexually active women during their reproductive years. Choosing a contraceptive method is an individual decision that is influenced by factors such as interest in future pregnancy, age, personal preferences, and underlying health issues. Although long-acting reversible methods offer women highly effective and convenient birth control, some women do not have access to IUDs and implants and others prefer to use shorter-acting hormonal methods. Although OC use continues to be popular in the US, high failure rates with typical use suggest the need for alternative shorter-acting hormonal contraceptive choices. The vaginal contraceptive ring represents one such alternative. The high initial popularity of the currently marketed EE/norelgestromin contraceptive patch underscores that many

TABLE Pharmacokinetic parameters for EE: AG200-15 versus norgestimate plus EE during treatment cycles 2 and 3.

	Mean ± SD		Treatment comparison		
Parameter/period	AG200-15 (n=32)	Norgestimate + EE (n=32)	*P* Value[a]	Point estimate, %[b]	90% Confidence interval
Week 1					
C_{max} (pg/mL)	45.5 ± 24.0	135 ± 50.7[c]	<.0001	32.08	27.58–37.30
$AUC_{0\text{-}168\ h}$ (ng h/mL)	5.06 ± 2.26	7.28 ± 2.66[c]	.0001	65.96	56.76–76.65
$C_{ss}1$ (pg/L)	31.4 ± 15.1	43.3 ± 15.8[d]	.0009	67.41	56.30–80.71
$C_{ss}2$ (pg/mL)	32.0 ± 16.2	43.3 ± 15.8[d]	.0007	66.35	55.34–79.55
Week 3					
C_{max} (pg/mL)	51.3 ± 17.3	131 ± 45.4	<.0001	39.01	35.26–43.15
$AUC_{0\text{-}168\ h}$ (ng h/mL)	6.26 ± 2.46	6.97 ± 2.25	.0532	85.96	75.67–97.66
$C_{ss}1$[e] (pg/mL)	35.7 ± 14.5	41.5 ± 13.4[d]	.0167	81.78	71.48–93.57
$C_{ss}2$[f] (pg/mL)	35.7 ± 15.4	41.5 ± 13.4[d]	.0175	80.13	69.00–93.06

[a] ANOVA model with sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect.
[b] Point estimate and 90% confidence interval of the least squares geometric means ratio.
[c] n=29.
[d] C_{ss}: calculated as average concentration at steady-state from the 24-h trapezoidal AUC ($AUC_{0\text{-}24\ h}$/24) for Ortho-Cyclen.
[e] $C_{ss}1$: average concentration within the 48–168-h time interval.
[f] $C_{ss}2$: average concentration at steady-state calculated from trapezoidal AUC within the 48–168-h time interval.
Reprinted with permission from Archer DF, et al.[60]

women find the concept of transdermal patch contraception attractive. Should it receive FDA approval and become available on the US market, the low estrogen release and favorable adhesion characteristics of the investigational EE/levonorgestrel AG200-15 transdermal patch suggest that it could become an attractive contraceptive option for many US women.

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Notes

SUPPLEMENT TO

OBG MANAGEMENT