

## Promoting the Safety and Use of Hormonal Contraceptives

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### ABSTRACT

Nearly one half of all pregnancies in the United States are unintended despite the availability of safe and effective contraceptives. The morbidity and mortality from unintended pregnancy are not insignificant. Currently available hormonal contraceptives are very effective, safe, and available for most American women. National and international institutions have removed the pelvic examination as a requirement for initiating the prescription for hormonal contraceptives, substituting instead a medical history and a blood pressure measurement. However, problems with uneven access, prescription requirements, conflicting information on the package instructions for initiating and continuing use, and incorrect perceptions of excess risk of contraceptive products may lead women to use them less than effectively or not at all. Newer progestins have been shown to have more risk of thrombosis than older formulations, instead of improved safety. In considering how hormonal contraceptives might be made safer, recommendations are made for improved availability and effective use. These include expanding the numbers and types of providers and the compensation for these services; reconsidering the need for prescription; revising labels to reflect the safety of the current formulations; communicating the safety of the current formulations; encouraging the use of the older progestins; exploring alternate schedules, such as extended or continuous oral contraceptive (OC) use; promoting same-day initiation of methods rather than waiting for menses; and ensuring universal access to emergency contraception as an adjunct to effective ongoing contraceptive methods.

### INTRODUCTION

UNLIKE THE OTHER CONTRIBUTORS to this issue, we have the privilege of discussing a class of drugs about which a great deal is known. The issue with hormonal contraceptives is not that too little information exists about them but that despite all that is known about them, nearly half of U.S. pregnancies continue to be unintended,<sup>1</sup> women continue to die from unintended pregnancy,<sup>2</sup> and adverse consequences of unintended

pregnancy can be felt throughout families, communities, and the larger society.<sup>3,4</sup> More than one half of the 3 million unintended pregnancies annually in the United States occur in women who are using contraception.<sup>5</sup> Therefore, any discussion of making contraceptives safer for women must include consideration of why available safe products are not meeting the needs of women. We discuss some of the problems relating to access to contraceptives and proper use of contraceptives, and we make recommendations to

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improve contraceptive access and use. Some problems preventing effective contraceptive use lend themselves to the research and advocacy agenda of the Agency for Healthcare Research and Quality (AHRQ), as well as collaborating government agencies. Larger issues of access, such as continued funding of Title X family planning services for poor women,<sup>6</sup> are beyond the scope of this paper but are very much at the forefront of the national priorities debate.

### POLICIES AFFECTING CONTRACEPTIVE ACCESS

Some of the current problems with women's irregular access to effective contraceptives have their roots in the family planning movement of the early 20th century. Ironically, the medical establishment's resistance to Margaret Sanger's ardent crusade to give women control over their reproductive lives led her to partner with physicians to break down that barrier.<sup>7</sup> As women's contraceptive options and family planning services expanded, access to them was largely dependent on public health institutions and physicians in private practice. Over time, the rationale for the concentration of services within the medical community and the prescription requirement shifted from one of expanding access to a belief that it is in the best interest of the woman. Women visiting a physician for family planning services could then also be examined for other gynecological conditions, including cervical and breast cancer and sexually transmitted infections (STIs).<sup>8,9</sup> For poor women, the publicly funded family planning visits often were their primary source for all reproductive health services.<sup>10</sup> This evolution firmly established the periodic pelvic examination within mainstream medical institutions as a *sine qua non* of contraceptive access.

When John Rock, a Roman Catholic, was involved in the trials of the first oral contraceptive (OC) in 1960, he anticipated strong opposition from the church. In an attempt to make the artificial control of ovulation by exogenous hormones appear more natural, the inventors of the pill established a regimen of administration that would replicate normal menstrual cycles.<sup>11</sup> Thus, the 21/7 or 28-day birth control pill cycle was born with the expectation that hormonal contraceptives be planned around the menstrual calendar. The progestin in the OC was one of the first

drugs to be patented, and even the concept of a package dispensing patent was initiated with the OC. For example, to preserve the 28-day cycle, pharmaceutical manufacturers added 7 placebo tablets to the dispenser to prompt women to remember to take the tablets every day. Although there was no physiological rationale for the regimen, over the following 40 years, the OC continued to be prescribed in a strict 3-week-on/1-week-off pattern.

These policies, however well-intended in their conception, contribute to the difficulties of hormonal contraceptive access for women today. First, a woman must have a prescription from a medical provider who most likely requires a scheduled appointment. This may necessitate waiting up to a month, and the visit will involve cost and time, as access to the contraceptive prescription has generally required a physical examination. Next, initiation of the method requires coordination with the menstrual calendar and then some form of reminder to obtain a resupply. The Sunday start for the OC was developed to schedule the withdrawal bleeding during the week so the weekends are period free, yet this translates into the need for a new pill package on Sunday. Depending on financial resources or medical insurance policies, only a 1–3-month supply of these contraceptives may be allowed at one time. Because of the entrenched 21/7 OC cycle, the woman using a contraceptive pill is dispensed only 21 active tablets, whereas if she were purchasing a month's supply of antihypertensive tablets, she would get 34 for her insurance copay and her month's medication supply. Thus, running out of hormonal contraceptives and introducing long delays between taking the last dose and obtaining the next package or, sometimes, injection is a commonly cited barrier to uninterrupted and effective hormonal contraceptive use.<sup>12</sup>

Since 1994, a growing number of respected medical institutions have formulated guidelines for prescribing hormonal contraceptives that do not require a pelvic examination for initiation of the method. These institutions include the U.S. Food and Drug Administration (FDA), the U.S. Agency for International Development, Planned Parenthood Federation of America, the World Health Organization (WHO), the International Planned Parenthood Federation, the American College of Obstetricians and Gynaecologists (ACOG), The Society of Obstetricians and Gy-

naecologists of Canada, the Royal College of Obstetricians and Gynaecologists, and some state and local health departments. The guidelines vary somewhat in their recommendations, but all acknowledge that hormonal contraceptives may be safely initiated and prescribed based on a self-reported medical history and measurement of blood pressure. The relaxation of these longstanding requirements recognizes not only that the examination represents a significant barrier to hormonal contraceptive use, particularly for adolescents<sup>13,14</sup> and for women in developing nations, but also that the current methods are much safer for most women than pregnancy.<sup>15</sup>

### COMMUNICATING THE SAFETY OF HORMONAL CONTRACEPTIVES

From the earliest availability of the combined OC in the Western world, large cohort studies of their safety were initiated and continued for decades. These studies, which followed women who were prescribed high doses of both estrogen and progestin, helped to establish the risks and benefits of the regimen. Consistent with regulatory requirements in developed countries, pharmaceutical manufacturers include all the known and suspected risks in package labeling for hormonal contraceptive products. These package inserts, written for both prescribers and users, are generally not updated as quickly as new information becomes available. The safety profile of the modern lower-dose combination OC evolved significantly over 40 years, and most currently used regimens contain one tenth of the hormones originally prescribed, yet the package insert contains essentially the same warnings and precautions as the insert for higher-dose products:

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

—Prescribing information: Ortho Tri-CyclenLo 2003

OrthoPharmaceutical Corp., Raritan, NJ

The application of evidence-based clinical guidelines can be at odds with the prescribing in-

formation available from the manufacturers. Consequently, women who read their package inserts may be confused or concerned and believe that they cannot manage effective hormonal contraception without medical monitoring and intervention.<sup>16</sup>

The lay press also contributes to concerns about hormonal contraceptive safety. Periodic pill scares over the decades have caused many women to discontinue use of the OC on the basis of newspaper and television reports of risks, which are rarely if ever presented in contrast to proven benefits or to other common risks, such as driving a motor vehicle.<sup>17</sup> A report of a doubling of the risk of venous thromboembolism among third-generation OC users compared with second-generation OC users resulted in no fewer than 554 articles about the “dangerous pills” in the Swedish press over the following 6 months<sup>18</sup> and an increase in the elective abortion rate in the United Kingdom. This continuing one-sided presentation of known or alleged OC risks perpetuates a discomfiting feeling among women that the “pill kills.” Articles and controversy about hormone replacement therapy (HRT) also add to the confusion about the balance between the benefits and adverse effects of hormones. These articles usually do not acknowledge that a 65-year-old woman beginning to use estrogen, years after her menopause, is not physiologically the same as a reproductive-aged woman with ovarian activity choosing to use the OC to control her fertility or menstrual cycle. The fears of hormones are spread without clear recognition that endogenous hormones have their own risks, and often the hormones and the doses used in the OC are not the same as used for HRT.

### RECOMMENDATIONS FOR IMPROVED ACCESS AND USE OF HORMONAL CONTRACEPTIVES

*Educate effectively about safety and benefits of hormonal contraceptives*

An educational campaign is needed to reassure women that current hormonal contraceptives are safe and effective and that their benefits far outweigh their risks for most women. Such a campaign should include information about the existence of the evidence-based prescribing guidelines. The importance of the evidence-based

guidelines needs to be translated into popular media, particularly women's health outlets—magazines and websites, TV spots, local newspaper articles—to make women more comfortable and to demystify the decision making about hormonal prescriptions. The cooperation of the Kaiser Family Foundation with Viacom, *Glamour* Magazine, and other media outlets to introduce safe-sex messages and emergency contraception information into mainstream programming has provided a successful model for dissemination of targeted health information.<sup>19</sup>

Changes need to be made in the package insert information currently dispensed with hormonal contraceptives. Information must be updated to reflect experience with current low-dose formulations, and warnings relevant only to formulations no longer used should be removed or modified. The package insert is particularly irrelevant and unhelpful with respect to the use of combined OCs in the Yuzpe method of emergency contraception.<sup>20</sup> Despite the 1996 FDA approval of several marketed brands of OCs for emergency contraception,<sup>21</sup> to date, their package inserts do not contain instructions for their potential use as an emergency contraceptive. Even the dedicated emergency contraception product Preven<sup>®</sup> (Barr Laboratories, Pomona, NY), which consists of four combined OCs to be administered in divided doses 12 hours apart, includes all the warnings and lists of adverse effects as if the user is planning ongoing OC use.<sup>22</sup>

#### *Increase number and types of contraceptive providers*

The relaxation of the hormonal contraceptive prescribing guidelines allows for provision of contraceptives in nonclinical settings. A demonstration project conducted by the California Office of Family Planning in nonclinical locations, including Women, Infants, and Children (WIC) program offices, a housing project, a community center, and a social service department, was successful in increasing access.<sup>23</sup> Women were offered two hormonal contraceptives (oral and injectable) as well as over-the-counter (OTC) methods. Risk factors for adverse events were obtained from the women directly at the visit and later verified through review of medical records. The low-income women who participated in the project adopted a more effective method than used at last sexual encounter (38%), followed through on referrals for other reproductive

healthcare (73% of those referred), and considered it important to be able to receive pills or injections without a pelvic examination (76%). Pharmacists in another model community—who have shown themselves to be effective and accessible providers of emergency contraception<sup>24</sup>—are participating in a demonstration project in Seattle in which they screen women for safe use of hormonal contraceptives and prescribe oral, vaginal, or transdermal contraceptives.<sup>25</sup> A self-administered standardized questionnaire screens for medical history and for the likelihood of current pregnancy,<sup>26</sup> and the pharmacists take weight and blood pressure measurements. Contraceptives are prescribed according to a protocol developed by the Direct Access Study.<sup>27</sup> Other models can be developed to increase the number and distribution of providers, and efforts should be made to reassure women that they may safely use contraceptives obtained from nonclinicians. It is also necessary to reconsider the need for a prescription to obtain contraceptives.<sup>9</sup> Similarly, OTC availability of emergency contraceptives can signal their safety for self-medication and increase their accessibility to young women, particularly if they are purchased in advance of need.<sup>28</sup>

#### *Reimburse nonclinician providers*

A barrier to expanding the number and types of contraceptive providers beyond the clinic walls is reimbursement policy. Title X funds require that contraceptive providers also be able to provide comprehensive reproductive health services, and many insurers do not compensate for contraceptive counseling and prescription outside of traditional healthcare facilities. Therefore, alternative providers who use simple screening tools combined with counseling and education to make contraceptives accessible to low-income women cannot be reimbursed for such services. Similarly, few private insurers will reimburse nonclinician providers for services that make contraceptives more accessible for their beneficiaries, although the cost-effectiveness of nonclinician providers has been shown for both public and private payers.<sup>29</sup> Work is needed to enable more qualified providers to be paid for their services.

#### *Use same-day start*

Requiring the start of hormonal contraceptives with menstrual bleeding commonly delays the start of the method. Before the sensitive preg-

nancy test, it was important to have menstruation as evidence of the nonpregnant state because the original high dose of androgenic progestins was associated with genitourinary anomalies in accidentally exposed fetuses. Neither of these barriers exists today, however, and there is no reason to enforce a delay between the day a woman receives a supply of contraceptives and the day on which she starts to use them. A written prescription does not always translate into a pill package, and some women who obtain OCs never begin to take them.<sup>12</sup> Research has demonstrated that women who begin using the hormonal contraceptive on the day of the clinic visit, regardless of the day of their menstrual cycle, are more likely to continue to the second package than comparable women who took pills home intending to begin according to instructions with the onset of their menstrual bleeding.<sup>30</sup> This practice of same-day administration requires provider education to screen for the absence of pregnancy, including administration of a pregnancy test or emergency contraception if indicated and facilitation of access to backup methods of contraception to be used until the hormonal contraceptive becomes effective. Westhoff et al.<sup>31</sup> found in another study that there was no increase in intermenstrual bleeding for women who use the same-day start compared with women who began using hormonal contraceptives in conjunction with their menstrual cycles.

#### *Increase extended or continuous use*

Recent renewed interest in continuous use of combined hormonal contraceptives to eliminate cyclic bleeding, as well as such attendant adverse events as pelvic pain, migraines, and bloating, inspired a review of the literature on the effects of extended use.<sup>32</sup> There is high acceptability of the extended regimens, and skipping the withdrawal week significantly reduced problematic method side effects, such as headaches.<sup>33</sup> Extending the use of an OC from a 28-day regimen to a 49-day cycle reduced bleeding, without a mean increase in spotting.<sup>34</sup> A later study comparing continuous or daily active pill use for a year reported increased spotting in the first 6 months, but by 1 year, 90% of the continuous OC users had amenorrhea.<sup>35</sup> It is very likely seven "spacer" days or "period" week in the standard low-dose regimen with ethinyl estradiol products allows breakthrough ovulation in some women. If, indeed, up

to 20% of women are ovulating with cyclic low-dose OC use,<sup>36</sup> then it is no wonder that the typical OC failure rates continue to be at least 5%, and even one missed pill following the week without hormone use could result in conception.

A commercial product (Seasonale, Duramed Pharmaceuticals, Inc., Pomona, NY) is now available in an 84-day regimen.<sup>36</sup> However, the every-three-month withdrawal bleeding week, an artifact of the product's patent, may contribute to high rates of irregular bleeding with this extended formulation.<sup>37</sup> There is no FDA-approved OC product for continuous use, and the dose and formulation for daily use, especially for use for years at a time, are unknown. It is unlikely that elimination of the pill-free week would change the safety profile, but until there are supportive data, it is prudent to use only very low-dose estrogen products for continuous use. For example, a year of cyclic 30  $\mu\text{g}$  ethinyl estradiol use causes more estrogen exposure than daily use of a 20  $\mu\text{g}$  ethinyl estradiol product for a year. Exploration of the acceptability and safety of extended or continuous administration of other combined hormonal contraceptives, such as the vaginal ring and the contraceptive patch, continue to be needed.<sup>38</sup> In addition, a long-term implant containing a combination of estrogen and progestin could eliminate the irregular bleeding profile typically experienced with the progestin-only implant systems that currently make them less acceptable to users.<sup>39</sup>

#### *Study effects of direct-to-consumer advertising on contraceptive choice*

Although most currently available hormonal contraceptives are safe for most women, concerns have been raised about the safety of the third generation of progestogens.<sup>40</sup> These formulations have been associated with increased risk of cardiovascular complications, albeit rare, but because they are new, they are heavily marketed directly to consumers, a practice that results in brand name requests to prescribers by their patients.<sup>41</sup> Similarly, the multiphasic OC regimens have been heavily marketed to consumers, although a review found that they do not provide sought for improvements in cycle control over monophasic formulations containing the same progestogen,<sup>42</sup> and they may be more prone to consumer error because of more complicated packaging.<sup>43</sup> Studies are needed to determine whether direct-to-consumer marketing practices are resulting in

more women being unnecessarily exposed to less effective, more problematic contraceptive regimens. It is very easy to obtain these newly approved products with current patents, such as Yasmin<sup>®</sup> (Berlex, Montville, NJ) and OrthoEvra<sup>®</sup> (Ortho Pharmaceutical Corp.), via the internet with nothing more than a credit card (L. Miller and J. Gardner, unpublished observations).

#### *Return effective contraceptives to market*

A mechanism and resources must be devised to retain accessibility of useful contraceptive products when their sponsors discontinue marketing them for business reasons. There are women who will happily choose a long-acting subdermal contraceptive implant or a combined estrogen/progestin injectable product if they are again made available in the U.S. market.

### RECOMMENDATIONS FOR IMPROVEMENTS IN SAFETY AND USE OF CONTRACEPTIVES

#### *Support studies not undertaken by contraceptive manufacturers*

Despite the evidence of the overall safety of hormonal contraceptives for most women,<sup>44</sup> studies are needed to clarify specific areas of concern. Most contraceptive research is conducted by pharmaceutical companies to obtain patents and regulatory approval to market products. Some of the resulting contraceptive products, although protecting the manufacturers' patents, do not necessarily represent gains in efficacy or safety for women. Examples of these are multiphasic contraceptive products, which are promoted as following a more natural menstrual cycle<sup>45</sup> but have been shown to have no better cycle control than monophasic products,<sup>46</sup> with comparable, not improved, safety and efficacy.<sup>47</sup> A complicating factor in assessing product safety is, of course, that women with risk factors for adverse reactions are excluded from clinical trials, regardless of who sponsors them.<sup>48</sup> Obesity, a growing problem in the United States, has been linked to higher rates of method failure for the contraceptive patch<sup>49</sup> and low-dose OC.<sup>50</sup> Study of how these failures happen or how to tailor a method, such as the OC, for the obese user may not be undertaken by industry sponsors, as these

women have a higher intrinsic risk of complications.

Other needed areas of contraceptive study also may not be undertaken by manufacturers, such as how to improve method compliance, the special needs of mentally ill or disabled women, an update of combined hormonal contraception during lactation,<sup>51</sup> and the effects of contraceptive formulations for perimenopausal women. For many years, two hormonal markets have existed in the United States: the contraceptive market, for which the FDA requires trials to be conducted in women ages 18–35 to correlate with fertility, and the menopausal or HRT market, for which women with established menopause are recruited to study. This has meant that women in perimenopause are often not included in studies of the OC, and questions of how best to transition between a decline in ovarian function to menopause when one is still at risk for pregnancy have not been well studied.

Another population often excluded from study, adolescents under the age of 18, is most at risk for effects on bone density. For example, the long-acting injectable contraceptive depot medroxyprogesterone acetate induces hypoestrogenism, and use in the early adolescent years may cause diminished peak bone mass and later postmenopausal fractures and osteoporosis.<sup>52,53</sup>

There have been no recent prospective studies of the effects of long-term hormonal contraceptives on breast tissue and on the rate of the return to fertility or ovarian reserve. If a method suppresses ovulation, is the effect on the ovary different from when ovulation continues? Many women will choose to delay their families and to have few children. Thus, a method that is protective of fertility would be an advantage for them. Further, in the United States, the average duration of breastfeeding is short; hence, women will be at risk for pregnancy and could potentially use hormonal contraceptives for 30 years. It is well proven that traditional cyclic OC use can reduce endometrial and ovarian cancer, but protection of breast tissue has been absent. Perhaps with a switch to low-dose continuous use and the elimination of cyclic stimulation, the breast could be protected, and research could be done to study breast density.<sup>54</sup> These types of prospective studies, involving long-term use and difficult-to-measure end points, cannot happen without significant resources. These studies will not be funded by pharmaceutical companies, given that the ben-

efit or harm is unlikely to be limited to a single product, and there would be risk to the investment.

More work needs to be done to specify which anti-infective drugs interact with contraceptive preparations to reduce their effectiveness.<sup>55</sup> Women can be given good advice about using backup methods of contraception when they are taking rifampin or griseofulvin,<sup>15</sup> but the effects of other commonly used antibiotic and antifungal preparations are less clearly defined, and the instruction “use another method while taking antibiotics,” although cautious, is vague and non-specific.<sup>56</sup> This question could be well studied by the Centers for Education and Research on Therapeutics,<sup>57</sup> for example.

## CONCLUSIONS

Decades of study have proven the safety and efficacy of widely used contraceptive steroid preparations, particularly at dosages in current use. More research is needed in subgroups of women inadequately studied and in areas of inquiry where resources have not been made available. More than research, however, effective communication is needed of the safety and known benefits of hormonal contraceptives coupled with policies to make existing formulations accessible and easier for women to use. This, along with universal access to emergency contraception as an adjunct to any chosen regular method, will significantly advance women’s health.

## REFERENCES

1. Henshaw SK. Unintended pregnancy in the United States. *Fam Plann Perspect* 1998;30:24, 46.
2. Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance—United States 1991–1999. *MMWR* 2003;52(SS02):1.
3. Brown SS, Eisenberg L, eds. *The best intentions: Unintended pregnancy and the well-being of children and families*. Washington, DC: National Academy Press, 1995.
4. Koenig JD, Strauss MJ, Henneberry J, Wilson TG. The social costs of inadequate contraception. *Intl J Technol Assess Health Care* 1996;12:487.
5. Jones RK, Darroch JE, Henshaw SK. Contraceptive use among U.S. women having abortions in 2000–2001. *Perspect Sex Reprod Health* 2002;34:294.
6. Stewart FH, Shields WC, Whang AC. The 2005 United States budget: Wasteful expenditures, foregone opportunities. *Contraception* 2004;70:87.
7. Tone A. *Devices and desires: A history of contraceptives in America*. New York: Hill and Wang, 2001.
8. Stewart FH, Harper CC, Ellertson CE, Grimes DA, Sawaya GF, Trussell J. Clinical breast and pelvic examination requirements for hormonal contraception: Current practice vs. evidence. *JAMA* 2001;285:2232.
9. Trussell J, Stewart F, Potts M, Guest F, Ellertson C. Should oral contraceptives be available without prescription? *Am J Public Health* 1993;83:1094.
10. Frost JJ. Public or private providers? U.S. women’s use of reproductive health services. *Fam Plann Perspect* 2001;33:4.
11. Gladwell M. John Rock’s error. *New Yorker* 2000; 15:52.
12. Oakley D, Sereika S, Bogue E-L. Oral contraceptive pill use after an initial visit to a family planning clinic. *Fam Plann Perspect* 1991;23:150.
13. Millstein SG, Adler NE, Irwin CE Jr. Sources of anxiety about pelvic examinations among adolescent females. *J Adolesc Health Care* 1984;5:105.
14. Armstrong KA, Stover MA. SMART START: An option for adolescents to delay the pelvic examination and blood work in family planning clinics. *J Adolesc Health* 1994;15:389.
15. Hatcher RA, Nelson AL, Ziemann M, et al. *A pocket guide to managing contraception, 2003–2004 edition*. Tiger, GA: Bridging the Gap Foundation, 2003.
16. Williams-Dean M, Potter LS. Current oral contraceptive use instructions: An analysis of patient package inserts. *Fam Plann Perspect* 1992;24:111.
17. Grimes DA. Dispelling OC myths and misperceptions. *Dialogues Contracept* 1994;4:1.
18. Mills A, Edwards IR. Venous thromboembolism and the pill: The combined oral contraceptive pill—Are poor communication systems responsible for loss of confidence in this contraceptive method? *Hum Reprod* 1999;14:7.
19. The Henry J. Kaiser Family Foundation. Available at [www.kff.org](http://www.kff.org)
20. Cheng L, Gulmezoglu A, Oel C, Piaggio G, Ezcurra E, Look P. Interventions for emergency contraception. *Cochrane Database Syst Rev* 2004;3:CD001324.
21. U.S. Food and Drug Administration. Prescription drug products: Certain combined oral contraceptives for use as postcoital emergency contraception: Notice. *Federal Register Part V*, 1997;62(37):8609.
22. Preven<sup>®</sup> prescribing information. Available at [www.preven.com](http://www.preven.com)
23. Harper C, Balistreri E, Boggess J, Leon K, Darney P. Provision of hormonal contraceptives without a mandatory pelvic examination: The first stop demonstration project. *Fam Plann Perspect* 2001;33:13.
24. Gardner JS, Hutchings J, Fuller TS, Downing D. Increasing access to emergency contraception through community pharmacies: Lessons from Washington state. *Fam Plann Perspect* 2001;33:172.
25. Shotorbani S, Gardner JS, Miller L, Downing D, Le S, Blough DK. The direct access study. Presented at Re-

- productive Health 2004, Annual Meeting of the Association of Reproductive Health Professionals, September 8–12, 2004, Washington, DC.
26. Zidar VM. Helping women use the pill. Population Reports, Series A, No. 10. Baltimore, MD: The Johns Hopkins University School of Public Health Population Information Program, 2000.
  27. Fuller TS, Christensen DB, Williams DH. Satisfaction with prescriptive authority protocols. *J Am Pharm Assoc* 1996;NS36:739.
  28. Grimes DA. Switching emergency contraception to over-the-counter status. *N Engl J Med* 2002;347:846.
  29. Marciantie KD, Gardner JS, Veenstra DL, Sullivan SD. Modeling the cost and outcomes of pharmacist-prescribed emergency contraception. *Am J Public Health* 2001;91:1443.
  30. Westhoff C, Kerns J, Morroni, Cushman LF, Tiezzi L, Murphy PA. Quick start: A novel oral contraceptive initiation method. *Contraception* 2002;66:141.
  31. Westhoff C, Morroni C, Kerns J, Murphy PA. Bleeding patterns after immediate vs. conventional oral contraceptive initiation: A randomized controlled trial. *Fertil Steril* 2003;79:322.
  32. Clark AK, Miller SJ. The debate regarding continuous use of oral contraceptives. *Ann Pharmacother* 2001;35:1480.
  33. Sulak PJ, Kuehl TJ, Ortiz M, Shull BL. Acceptance of altering the standard 21-day/7-day oral contraceptive regimen to delay menses and reduce hormone withdrawal symptoms. *Am J Obstet Gynecol* 2002;186:1142.
  34. Miller L, Notter K. Menstrual reduction with extended use of combination and oral contraceptive pills: Randomized controlled trial. *Obstet Gynecol* 2001;98:771.
  35. Miller L, Hughes JP. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: A randomized trial. *Obstet Gynecol* 2003;101:653.
  36. Pierson RA, Archer DF, Moreau M, Shangold GA, Fisher AC, Creasy GW. OrthoEvra/Evra versus oral contraceptives: Follicular development and ovulation in normal cycles and after an intentional dosing error. *Fertil Steril* 2003;80:34.
  37. Anderson FD, Hait H, the Seasonale 301 Study Group. A multicenter, randomized study of an extended cycle oral contraceptive. *Contraception* 2003;68:89.
  38. Mulders TMT, Dieben TOM. Use of the novel combined contraceptive vaginal ring for ovulation inhibition. *Fertil Steril* 2001;75:865.
  39. Makarainen L, van Beck A, Tuomivaara L, Asplund B, Coelingh Bennink H. Ovarian function during the use of a single contraceptive implant: Implanon compared with Norplant. *Fertil Steril* 1998;69:714.
  40. Döring A, Fröhlich M, Löwel H, Koenig W. Third generation oral contraceptive use and cardiovascular risk factors. *Atherosclerosis* 2004;172:281.
  41. Direct-to-consumer advertising affects provider/patient relationship. *Contracept Technol Update* 1998;19:153.
  42. Van Vliet HA, Grimes DA, Helmerhorst FM, Schulz KF. Biphasic versus triphasic oral contraceptives for contraception. *Cochrane Database Syst Rev* 2003;2:CD003283.
  43. Weisberg E. Triphasics: Have they fulfilled their promise? *Curr Ther (Seaforth)*. 1992;33:11.
  44. Hannaford PC, Webb AMC. Evidence-guided prescribing of combined oral contraceptives: Consensus statement. *Contraception* 1996;54:125.
  45. Ortho-McNeil Pharmaceutical. OrthoTri-Cyclen: How it works. Available at [www.orthotri-cyclen.com](http://www.orthotri-cyclen.com)
  46. Chavez A, DelConte A. A comparison of cycle control with monophasic levonorgestrel/ethinylestradiol 100 micrograms/20 micrograms versus triphasic norethindrone/ethinylestradiol 500-750-1000 micrograms/35 micrograms: A multicenter, randomized, open-label study. *Eur J Contracept Reprod Health Care* 1999;4:75.
  47. Cedars MI. Triphasic oral contraceptives: Review and comparison of various regimens. *Fertil Steril* 2002;77:1.
  48. Dieppe P, Bartlett C, Davey P, Doyal L, Ebrahim S. Balancing benefits and harms: The example of non-steroidal anti-inflammatory drugs. *Br Med J* 2004;329:31.
  49. Ortho-McNeil Pharmaceutical. Prescribing Information, OrthoEvra®. Available at [www.orthoevra.com](http://www.orthoevra.com)
  50. Holt VL, Cushing-Haugen KL, Daling JR. Body weight and risk of oral contraceptive failure. *Obstet Gynecol* 2002;99:820.
  51. Truitt ST, Fraser AB, Grimes DA, Gallo MF, Schulz KF. Hormonal contraception during lactation: Systematic review of RCT. *Contraception* 2003;68:233.
  52. Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. Injectable hormone contraception and bone density: Results from prospective study. *Epidemiology* 2002;13:581.
  53. Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. The association between depot medroxyprogesterone acetate contraception and bone mineral density in adolescent women. *Contraception* 2004;69:99.
  54. Pike MC, Spicer DV. Hormonal contraception and chemoprevention of female cancers. *Endocr Relat Cancer* 2000;7:73.
  55. Dickinson BD, Altman RD, Nielsen NH, Sterling ML. Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol* 2001;98:853.
  56. Lindsey JL, Hugin M. Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol* 2002;99:841.
  57. Centers for Education and Research on Therapeutics. Available at [www.certs.hhs.gov](http://www.certs.hhs.gov)

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