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May 6, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: “Draft Labeling for Industry on Labeling for Combined Oral Contraceptives;
Availability” (Docket No. 2000D-1350)**

On behalf of the American College of Obstetricians and Gynecologists (ACOG) an organization representing over 40,000 physicians dedicated to improving women’s health care, I am pleased to provide comments on the Food and Drug Administration (FDA) draft guidance for industry on combined oral contraceptives (COCs) (69 Federal Register 44, 10457-10458).

ACOG supports actions by the FDA that increase the usefulness and clarity of labeling of drug products for physicians and patients. It is critical that there be clear and accurate labeling for drug products that require daily use and have a small margin for error, such as COCs. ACOG provided comments in 2000 on the previous revision of this guidance, and we are pleased that some of these comments have been addressed in the current draft. We find the new approach for the patient labeling to be particularly useful and a significant improvement over the previous draft.

We believe, however, that specific areas of the current draft guidance need further clarity and updated literature support. At present, certain areas of the document appear to stray from the science and some changes could be interpreted as politically motivated. Our most significant concerns include outdated evidence for vascular risks, inappropriate requirement of pelvic examination and laboratory tests as a prerequisite for prescribing COCs, and a failure to recognize the substantial noncontraceptive health benefits of COCs.

As we did in our 2000 comments, we are enclosing a copy of the evidence-based ACOG Practice Bulletin “The Use of Hormonal Contraception in Women with Coexisting Medical Conditions,” which differs from the draft guidance in several areas—particularly contraindications. These areas of difference and our other clinical recommendations and comments are as follows.

LABELING FOR PACKAGE INSERT

Indications and Usage

The wording of the indication for the use of COCs is inappropriate and poorly reflects the current scientific knowledge of the excellent effectiveness of COCs with correct use. In addition, to say that COCs are “indicated for use by women to *lower the risk* of becoming pregnant” (italics added), rather than “for the prevention of pregnancy,” as in the 2000 draft, places an unequal and unfair burden on COCs. No pharmaceutical agent is 100% effective, and to single out COCs in this way will inappropriately diminish women’s confidence in the effectiveness of these products. Used as directed, COCs are extremely effective in preventing pregnancy. We strongly recommend that the language in the 2000 draft be reinstated.

We also recommend that a current version of Hatcher and Trussell’s failure rates (as appeared in the 2000 version) be used instead of the simplified chart in this draft. This simplification overestimates the effectiveness of typical use of COCs and underestimates the effectiveness of condom use in preventing pregnancy.

Contraindications

We note with appreciation that several of our comments provided on the 2000 draft of the guidance have been incorporated.

We continue to believe, however, that for some women the use of COCs in women with a history of venous thromboembolism (VTE) ought to be individualized. Women who have had a single episode of VTE in the remote past associated with a nonrecurring risk factor (eg, after immobilization following a motor vehicle accident) may not be at increased risk for VTE.

Although the addition of congenital hypercoagulopathies to this draft of the guidance is consistent with current evidence, we have some concern that this may lead to inappropriate screening of women in order to determine whether they are so affected. As noted in the enclosed Practice Bulletin, screening would identify approximately 5% of COC candidates as having factor V Leiden mutation, but the great majority of these women will never experience VTE, even if they use COCs. It has been estimated that screening more than 1 million COC candidates for thrombophilic markers would, at best, prevent 2 COC-associated deaths. We suggest that it be clarified under “Warnings” that screening of women of unknown status is not recommended.

The addition of “other hormone-sensitive cancer” to this draft requires further explanation as to which cancers are meant. If gynecologic cancers are meant, standard treatment for these cancers generally involves hysterectomy or oophorectomy, which would leave a woman sterile and in no need of contraception. If other cancers are intended, they should be specified.

In addition, we suggest that “active” liver disease be specified on line 108 and that line 111 indicate that superficial thrombophlebitis is not included.

Warnings

This draft appropriately recognizes that the decision to use COCs in women with medical conditions is not made in a vacuum but should take into consideration the woman's risk of pregnancy and possibility of use of other contraceptive methods. We suggest, therefore, that lines 148 and 176 include the risk of thromboembolic disease associated with pregnancy (60/100,000 women) vs. the 10-15 cases/100,000 women per year among users of older, low-dose COCs.

The decision whether to discontinue COCs before surgery appears to be properly nuanced. We do recommend, however, that the "elective surgery of a type associated with an increase in risk of thromboembolism" be defined as major surgery; discontinuation of COCs is not necessary before laparoscopic tubal sterilization or other brief surgical procedures. The possibility of other prophylactic measures, such as heparin, should be considered as well.

The data on vascular risks appear to be quite old, and a new literature search would be beneficial. For example, at line 183, the relative risk of heart attack for current OC users ("two to six") appears incorrect unless the data refer to older, higher-dose pills. There is little to any increased risk for healthy users of the currently available low-dose pills. See, for example Pettiti et al 2003 N Engl J Med. Similarly, the risk of stroke appears not to reflect current data. We recommend that lines 199-200 say: "Some observational studies show an increased risk of stroke among women using COCs. However, other studies have found no increase in the overall risk of arterial stroke (either ischemic or hemorrhagic) among current low-dose OC users." (See Pettiti DB et al N Engl J Med 1996;335:8-15 and WHO Collaborative study of cardiovascular disease and steroid hormone contraception. Lancet 1996;348:498-505)

In the section on liver disease, it should be noted that liver tumors are extremely rare among young women—stating only the attributable risk without the absolute risk is distorting. Also, it should be noted that WHO data show no increased risk of liver cancer with OC use (Leon DA, Int J Cancer 1989;43:254-9).

Regarding diabetes, newer data indicate that COCs do not enhance the progression of diabetes (see, for example, Klein BEK et al, Diabetes Care 1990;13:895-8 and Garg SK et al, JAMA 1994;271:1099-1102). Regarding high blood pressure, the Nurses Health Study II found only 42 cases of elevated blood pressure per 10,000 person-years of low-dose COC use. (Chasan-Taber L, et al. Am J Epidemiol, 1996 Aug 1;94:483-9).

Precautions

In the general section, we oppose the new requirements for physical examinations and laboratory tests. Although preventive services, such as cervical cytology, are an important part of women's health care, it is questionable whether they are useful in informing the decision whether to prescribe COCs. Making such services a prerequisite to obtaining COCs undeniably poses a barrier to obtaining necessary services for those who most critically need reliable contraception.

ACOG recommends that the physical examination may be deferred at the woman's request or in appropriate circumstances, particularly in young teens. We strongly urge that this section incorporate the following language from the FDA Advisory Committee Recommendation: "Physical examination may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician."

As medicine continues to limit the morbidity and mortality associated with human immunodeficiency virus (HIV) infection yet infections continue to occur, more HIV-positive women of reproductive age will need effective means of contraception. We believe that providing information on drug interactions of COCs with anti-HIV protease inhibitors will be useful to clinicians in prescribing contraception for HIV-positive women. However, non-nucleoside reverse transcriptase inhibitors (NNRTIs) may have a similar effect, and one of these (nevirapine) is in common use in the obstetric–gynecologic community as it is used to prevent maternal–fetal transmission—a current government priority. We recommend that NNRTIs be addressed here as well. Similarly, more women are turning to complementary and alternative therapy, and it will be beneficial for clinicians to know the drug interactions of herbal products such as St. John's wort with COCs.

Adverse Experiences

Because breakthrough bleeding is relatively common, it should be added to the side effects, as it is in the patient labeling.

Possible Health Benefits

Use of COCs has many significant well-established noncontraceptive health benefits for women, and the omission of several of these is inexplicable. There is abundant high-quality evidence supporting the role of COCs (including lower-dose formulations) in protecting against endometrial cancer and ovarian cancer and decreasing the incidence of ectopic pregnancy. (CDC CASH study, JAMA 1983;249:1600-4, JAMA 1983;249:1596-9; Grimes DA and Economy KE, Am J Obstet Gynecol 1995;172:227-35; Schlesselman JJ, Obstet Gynecol 1995;85:793-801; Franks AL et al, Am J Obstet Gynecol 1990;163:1120-3; Marchbanks P, et al. JAMA 1988;259:1823-7.) Failing to include these well-supported benefits would suggest that something other than the scientific evidence is motivating the FDA process. Additionally, benefits should be described as being "beyond preventing pregnancy," not "beyond lowering of risk of becoming pregnant" as in the current draft.

PATIENT LABELING

The approach to patient labeling in this draft is clearer than the same section in the 2000 draft. Requiring manufacturers to address just the formulation that is packaged (ie, 21-day pack or 28-day pack) will help women understand the important information in this section. The inclusion of illustrations of the pill pack and the direction in which pills are taken will also be helpful.

The section on how well pills work is important to giving patients a clear understanding of what to expect with pill use. As the section notes, the failure rate is dependent on whether use is “typical” or “perfect,” so—as for the package insert—we suggest that the Hatcher and Trussell data be provided here instead of the simplified table. Because COCs are quite effective in preventing pregnancy, this section appears to be overly negative.

The section on management of missed pills will be crucial for women’s effective use of COCs. We are very pleased that the directions on what women should do if they miss a pill(s) have been made more explicit, but we have concerns that the current labeling would require excessive use of both back-up contraception and additional pills. For example, the management recommended in the current draft when women missed two active pills is very similar to the Yuzpe regimen of emergency contraception. This regimen is clearly effective in women who have had unprotected intercourse around the time of ovulation, but it is also associated with significant side effects. Whether it is warranted in this circumstance is less certain. We encourage FDA to reexamine this important issue, perhaps by consulting some of the international groups that have done work in this area.

In the “Who Should Not Take (OC Name)?” section, women cannot be expected to know which cancers are hormonally sensitive and which are not; specific cancers should be mentioned instead. Line 572 should specify “active” liver disease. While previous heart attack is a clear contraindication, “chest pains” are insufficiently specific to serve as a contraindication and ought to be deleted. In addition, angina is not addressed in the package insert. “Severe migraine headaches” may not be specific enough to guide women; we recommend that the neurologic effects be included (ie, “Severe migraine headaches with aura, numbness, weakness, or visual changes”).

In the “Side Effects” section, the most frequent side effect is breakthrough bleeding—it ought to be listed first. Also, the less common side effects do not match the similar section in the package insert. The two inserts should be in agreement.

In the “Most Serious Risks” section, reference to blood clots in the eyes and gallbladder problems should be reconsidered. The package insert indicates that COCs have been associated with retinal vein thrombosis on the basis of case reports. This level of evidence may be insufficient to warrant including effects on the eyes. Similarly, the current draft of the package insert now describes the risk on gallbladder disease as “minimal,” so it may be preferable to omit gallbladder disease. At line 682, it should be specified that pain is in one leg. At line 684, “or sudden neurologic symptoms like visual changes, weakness, numbness” ought to be added. Line 686 ought to specify “sudden severe headache unlike any previous headaches.”

CONCLUSION

Combined oral contraceptives remain the most popular reversible form of contraception for women. Ensuring that the labeling of COCs is clear and accurate is vitally important to the appropriate prescribing and use of these products. ACOG appreciates the opportunity to

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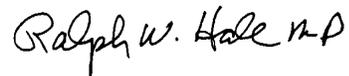
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comment on the FDA draft guidance on COCs. As an organization dedicated to improving women's health care, we welcome the opportunity to work further with the FDA on this issue and would be pleased to discuss our views in more detail.

Sincerely,

A handwritten signature in black ink that reads "Ralph W. Hale MD". The signature is written in a cursive style.

Ralph W. Hale, MD, FACOG

Executive Vice President

Attachment

cc: Paula J. Adams Hillard, MD, FACOG
Herbert Peterson, MD, FACOG