Oral Contraceptive Reduced Heavy Bleeding

BY PATRICE WENDLING

ATLANTA — An oral contraceptive known in Europe as Qlaira significantly reduced menstrual blood loss in women suffering from idiopathic heavy and/or prolonged menstrual bleeding, in a multinational, double-blind phase III trial.

Among 135 evaluable women, complete resolution of abnormal menstrual symptoms was achieved in 44% of those receiving the oral contraceptive containing estradiol valerate/dienogest (E2V/DNG) vs. 4% of those given placebo.

The mean change in menstrual blood loss volume, as quantified using the alkaline hematin method, was –353 mL in the E2V/DNG arm vs. 130 mL in the placebo arm (*P* less than .0001).

The dramatic reduction in blood loss was apparent in 3 months, and was accompanied by improvements in iron metabolism parameters, said lead researcher Dr. Jeffrey T. Jensen, professor of obstetrics and gynecology at the Oregon Health and Science University in Portland.

Significant improvements were observed at 196 days with E2V/DNG vs. placebo in the mean change from baseline in the hematocrit (1.4% vs. –0.05%), ferritin (2.9 ng/mL vs. –0.4 ng/mL), and hemoglobin (0.6 g/dL vs. 0.1 g/dL) levels.

E2V/DNG was approved for contraception in Europe under the trade name Qlaira in 2009, and may become available in 2010 in the United States where duel indications for contraception and heavy menstrual bleeding are being discussed, Dr. Jensen said at the annual meeting of the American Society for Reproductive Medicine. While dienogest is a new progestin in the United States, it is available in Europe as a single-agent pill to treat endometriosis, and in combination with ethinyl estradiol for contraception.

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Major Finding: Among 135 evaluable women, complete resolution of abnormal menstrual symptoms was achieved in 44% of those receiving an oral contraceptive containing estradiol valerate/dienogest (E2V/DNG) vs. 4% of those given placebo.

Data Source: The mean change in menstrual blood loss volume was quantified using the alkaline hematin method.

Disclosures: The study was funded by Bayer Schering Pharma AG, which is developing E2V/DNG. Dr. Jensen has received research support from Bayer and Warner-Chilcott, and served as consultant for Bayer and Schering Plough. His coauthors disclosed employment with Bayer Schering and consultant roles with Bayer.

During a discussion of the study, audience members questioned the lack of an active comparator in the study and the high number of patients excluded from analysis. Dr. Jensen said that it was a weakness not to have an active comparator, but that the study design was required by the Food and Drug Administration. An identically designed trial conducted in Europe and Australia produced similar results.

Furthermore, unpublished data from a third trial showed a similar reduction in bleeding at 3 months with E2V/DNG and the approved levonorgestrel-releasing intrauterine system (LNG-IUS) and a better response at 6 months with LNG-IUS.

"Having placebo-controlled data is very useful as far as getting a benchmark, and there's lots of women out there that aren't currently using any other products," he said. "Now whether this is a better treatment than other oral contraceptives, we don't know. The data [don't] support that," he said.

A recently published comparative trial conducted by one of Dr. Jensen's coinvestigators in 798 healthy women seeking contraception, reported significantly fewer bleeding/spotting days among women given E2V/DNG than those given ethinyl estradiol 20 mcg/levonorgestrel 100 mcg (EE/LNG): 17.3 vs. 21.5 days (*P* less than .0001). No unintended pregnancies occurred with E2V/DNG and only one occurred with EE/LNG, while adverse drug reactions occurred in 10% vs. 8.5% of women (Contraception 2009;80:436-4).

Estradiol-containing oral contraceptives have demonstrated effective contraception, but have been problematic in terms of cycle control, notably with bleeding irregularities leading to premature discontinuation. E2V/DNG is administered using a dynamic estrogen step-down and progestin step-up dosing regimen designed to overcome unacceptable cycle control.

In the current study, a total of 190 women from the United States and Canada with heavy and/or prolonged menstrual bleeding without recognizable pelvic pathology were randomized in a 2:1 ratio to E2V 3 mg on days 1-2, E2V 2 mg/DNG 2 mg on days 3-7, E2V 2 mg/DNG 3 mg on days 8-24, E2V 1 mg on days 25-26, and placebo on days 27-28 or placebo on days 1-28. Their mean age was 37 years.

A total of 54 withdrew from the study, 44 discontinued treatment, 5 never took the study medication, and 6 were lost to follow-up. In all, 84 women in the E2V/DNG arm and 51 in the placebo arm were available for analysis.

Dr. Jensen noted that a composite of up to eight individual criteria were used for achieving a complete response. Based on a subjective assessment, 81% of the women given E2V/DNG reported improvement vs. 38% of those given placebo. ■

Ultrasound Deemed Alternative to Biopsy and Mammography

BY RICHARD HYER

CHICAGO — Women younger than 40 years with focal breast signs or symptoms should be evaluated by targeted ultrasound, and probably not mammography or biopsy, according to findings from two studies of more than 1,800 patients treated at one medical center.

"This is particularly timely with the recent [U.S. Preventive Services Task Force] recommendations that women not perform self–breast exam," said Dr. Constance Lehman of the University of Washington in Seattle.

"One of the USPSTF's concerns was that women will go through unnecessary harms and procedures. We think imaging can better guide us in reducing harms that can be associated with a self–breast exam."

The studies' findings could have broad implications for practice patterns and cost. Reducing biopsies and surgical excision of lumps would lessen trauma and cost, while limiting mammography would reduce cost and unnecessary radiation.

Dr. Lehman described the two studies in a press briefing at the annual meeting of the Radiological Society of North America. Both were retrospective reviews of data from the University of Washington.

In the first analysis, investigators reviewed all breast exams performed on women under age 30 from Feb. 1, 2002, to Aug. 30, 2006, and found 1,091 lesions in 830 patients. Three malignancies were found, and all were identified as suspicious by ultrasound. No malignancy was found in any patient with a negative, benign, or probably benign ultrasound.

The rate of biopsy was high, and the yield was low. For example, a third (46/140, 33%) of patients with a Breast Imaging–Reporting and Data System (BI-RADS) 3 lesion (probably benign) underwent tissue sampling, and none of these lesions was found to be malignant.

The authors concluded that mammography was not indicated in this setting, and that close surveillance might be a preferred alternative to tissue sampling.

The second study, which included women aged 30-39 years, also found ultrasound to have 100% sensitivity. In this study, investigators reviewed 1,327 lesions in 1,032 patients, finding that 98% (1,301/1,327) were benign and 2% (26/1,327) were malignant. Ultrasound and mammography had been used to evaluate 91% (1,207/1,327) of cases, yet all cancers at the site of clinical concern were detected by ultrasound and none by mammography alone.

In a solitary case (1/1,327, 0.08%), mammography resulted in detection of a malignancy in an asymptomatic area.

The authors concluded that ultrasound has 100% sensitivity in evaluating women 30-39 years of age presenting with focal signs or symptoms.

"The added value of mammography in this setting is less apparent," Dr. Lehman said. "It did help one woman who had an area of cancer identified in another region of the breast, but in all other women, there was no added value."

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Coauthors (from left) Dr. Constance Lehman, Dr. Michael Portillo, and Dr. Vilert Loving "don't recommend ultrasound" as a screen.

In answer to a question from the audience, Dr. Lehman said that ultrasound is recommended as a diagnostic tool and not as a screening tool.

"We strongly recommend women have screening mammography annually, age 40 and older, and if they are shown to be at high risk, that they add MRI to that. We don't recommend ultrasound as a screening tool," she said, because the specificity of ultrasound is low.

At the scientific session, Dr. Michael Portillo, one of Dr. Lehman's coauthors, was asked whether his institution had changed its practice in the wake of this study. "At this point we're still following the [American College of Radiology guidelines], but we are currently considering changing our practice," said Dr. Portillo, who worked on the project while a fellow at the University of Washington. ■

Disclosures: *Both studies were funded by the University of Washington. Dr. Lehman disclosed work as an instructor with General Electric Co. Dr. Portillo had nothing to disclose.*