

Seventy-Third Meeting of the
Obstetrics and Gynecology Devices Panel

Friday, December 14, 2007
Hilton Washington DC North, Gaithersburg, MD

**General Topic Discussion – Clinical Trial Design Issues for Endometrial Ablation
Devices for Women Seeking Elective Cessation of Menses**

General Topic Overview

To date FDA has approved 5 endometrial ablation devices for the U.S. market. (Two others were reviewed by FDA at open public meetings; however, they did not ultimately receive approval.) The approved devices represent a range of treatment modalities for achieving destruction of the endometrial lining of the uterus. They include microwave, cryosurgery, RF energy, thermal balloon and free circulating heated saline. Device treatment times range from 90 seconds to 10 minutes with a goal of destroying 5-7 mm of tissue without causing thermal injury to unintended tissue/organs. These devices have been approved for the following specific indication for use:

ablation of the endometrial lining of the uterus in premenopausal women with menorrhagia (abnormal uterine bleeding) due to benign causes for whom child bearing is complete.

In the general topic session, we will discuss a new indication for use for these type of devices, i.e.,

elective ablation of the endometrial lining of the uterus in premenopausal women in eliminating (or reducing?) menstrual bleeding for whom child bearing is complete.

This indication differs from the approved indication in that there is no disease state being treated. Instead this elective use is for lifestyle preferences. This may be likened to “cosmetic” procedures such as breast augmentation in that the patient is electing the surgical procedure to improve or enhance her lifestyle. This makes for a different evaluation of the risk/benefit analysis that is required for every new clinical investigation.

The labeling for the approved endometrial ablation devices contains information on the effectiveness of the devices. Study success was based on the 12-month patient success rate defined as a pictorial blood loss assessment chart (PBLAC) score of ≤ 75 . A secondary outcome measure was the rate of amenorrhea which was defined as a diary score of 0 at 12 months. Patients were also followed for an additional 24 months post-procedure to ascertain bleeding status. Patients who indicated by telephone/questionnaire that they had no bleeding were categorized as having amenorrhea.

The following table provides information on the amenorrhea rates for the approved devices. This is just a summary that is intended to give an idea of the rates of amenorrhea achieved in the pivotal studies of these devices in which the new endometrial ablation device was compared against a control group of rollerball or rollerball and resection. In general these rates ranged from about 15-55% with about a 10% difference between treatment and control. Please see the attached table for additional details:

Amenorrhea Rates for Approved Endometrial Ablation Technologies†

	Device A (n=134, 126*)	Device B (n=187, 89*)	Device C (n=193, 86*)	Device D (n=175, 90*)	Device E (n=215, 107*)
12-months	14% v. 25%	35% v. 47%	22% v. 47%	37% v. 31%	55% v. 46%
24-months	12% v. 18%	37% v. 38%	8% v. 20%	37% v. 29%	----
36-months	13% v. 21%	39% v. 35%	11% v. 20%	33% v. 26%	----

† The above rates are calculated using the intent to treat population (ITT) in which study subjects lost to follow-up are counted as treatment failures.

*Each of the identified devices was evaluated in a randomized, controlled, clinical trial in which either rollerball or rollerball and resection was used as the control. The second numbers listed represent those associated with the control group.

FDA is interested in developing a model (or models) for clinical trial design of endometrial ablation devices intended for this new indication. Although one design may not be uniformly applied due to differences in the device designs and their mechanisms of action, establishing a general model would help us to maintain an even playing field while obtaining relevant and clinically meaningful scientific information.

We have put together a bibliography of references that should provide a suitable background for this day’s discussion. There is a section of references related to the issue of menstruation itself and women’s perceptions of it. These references cover the attitude of women as they relate to menstruation suppression. We have also included information on the special needs of some sub-populations, e.g., women in the military.

There are additional references on the use of oral contraceptive to suppress menstruation for varying durations. Of note are the FDA approved extended-cycle and continuous use oral contraceptives. Although these drugs are primarily indicated for non-permanent contraception, there are two drugs (Seasonale and Seasonique from Duramed) that reduce the number of menstrual cycles in a year from 13 to 4 and one drug (Lybrel from Wyeth Laboratories) that can be used continuously. These studies provide insight into the perceived need of women electing non-permanent contraception to suppress their menstrual cycles. However, it is important to remember that these are oral contraceptives first with a secondary “benefit” of suppressing menstruation. The other issue with extended-cycle and continuous oral contraceptives is the fact that unscheduled bleeding can be a significant problem for some women. Any secondary benefit from these oral contraceptives is significantly different from endometrial ablation devices which will be solely indicated for permanent elimination of menstruation.

This new use of endometrial ablation requires a reassessment of the risk/benefit ratio. Although we anticipate the use of these devices in this new population will carry the same risks, the acceptability

will be different. “Global” endometrial ablation devices used for the treatment of women with menorrhagia have been viewed as treatment modalities that are potentially less morbid than earlier hysteroscopic methods as well as hysterectomy. They require less skill on the part of the user and are not associated with the potential complications of hysteroscopic insufflation, e.g., fluid overload. Although the safety profiles of the “global” devices when used to treat women with menorrhagia are acceptable, these devices have been associated with some very rare serious adverse events. Because these serious adverse events are so rare, they did not show up in the pre-market evaluations. They are, however, important to note here for this discussion. The following serious post-market adverse events have been reported to FDA in association with global endometrial ablation devices: uterine perforation; hysterectomy; thermal injury to bowel, bowel resection, post ablation tubal sterilization syndrome, endometritis, hematometra, thermal injury to vagina and perineum, infection and sepsis.

Although the patients in these studies will be need to be carefully consented such that they understand all the risks of this “elective” procedure, there must be some threshold at which the risk/benefit ratio is not considered to be acceptable. One risk that is of particular concern is the potential of the procedure to mask a uterine cancer. There are some references included that specifically address this issue.

Finally, references related to outcome measures have been included to help facilitate the discussion regarding study inclusion and study endpoints.

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Bibliography of Selected Journal Articles*

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