EMORY UNIVERSITY SCHOOL OF MEDICINE
THOMAS K. GLENN MEMORIAL BUILDING
69 Butler Street, S.E. Atlanta, Georgia 30303

DEPARTMENT OF GYNECOLOGY
AND OBSTETRICS

(404) 659-0289

To: Nonprescription Drugs Advisory Committee

VAGINAL CONTRACEPTIVE SPONGE

Background

The use of sponges in the vagina to prevent pregnancy goes back in time as far as the ancient Egyptians. Medical history tells us that once women connected sexual intercourse and the ejaculate with pregnancy, they began to gather sponges from the ocean and cut them into pieces, which they placed in their vaginas prior to coitus.

In modern times, various types of sponges were developed and tested. However, only one product, the Today Sponge for vaginal contraception, underwent sufficient laboratory and clinical testing over a period of seven years to meet the requirements for submission to the US Food and Drug Administration (FDA). A formal presentation was made by the manufacturer, the VLI Corporation, to the FDA's medical advisory committee on October 28, 1982. Approval for marketing was given by the FDA in March of 1983. The Sponge was widely distributed and used, becoming the most popular over-the-counter (OTC) vaginal contraceptive method. It was sold to Whitehall Robbins Healthcare, a division of American Home Products, in 1987, which then sold the Sponge until 1995 when they voluntarily halted production.

The FDA had recently established more "stringent" manufacturing requirements, and questioned the purity of the air and water at the plant where the Sponges and other products were made. Since the upgrading of the plant to meet these requirements would have been very time consuming and expensive, it was decided to cease production and close the plant. It is important to note that there was never any question about the safety of the use of the Sponge, and it remained and continues to remain approved by the FDA. (FDA Talk Paper attached).

The loss of the Sponge was disturbing to many users, particularly younger women, since its discontinuation removed one of their contraceptive options. Marketing data reported that over one quarter of a billion were sold over a 13-year period of time. Within both the medical and consumer communities, the hope was frequently expressed that it would soon again become available.

DESCRIPTION

The Sponge is made out of polyurethane foam and it contains an aqueous solution of Nonoxynol 9 (N9), a spermicide that is a nonionic surfactant. This is one of the ingredients reviewed by the FDA's Panel for Contraceptive and Other Vaginal Drug Products. Following evaluation of all of the available laboratory and clinical data, our Panel concluded (Federal Register/Vol 45, No. 241/Friday, December 12, 1980/Proposed Rules, pp. 82028-82031) "that Nonoxynol 9 (a nonionic surfactant) is safe and effective for OTC use as a vaginal contraceptive as specified in the dosage section below." The Panel also went into considerable detail about what should be in the labeling, both the principle display panel and the patient package insert. It stated "the directions for use should be clearly stated and illustrated in order to provide easily understandable guidance to the consumer".

The Sponge contains 1 gram of N9, and releases approximately 125-150 mg in 24 hours. This is 10-20 percent of the total amount, and is less that that found with some other vaginal contraceptives, particularly if multiple applications are made.

MECHANISMS OF ACTIONS

The Sponge provides protection against pregnancy in three ways:

1. It releases the spermicide, N9, into the vagina.
2. It physically blocks the entrance of sperm into the cervical os.
3. It absorbs sperm in the male ejaculate.

SAFETY

The Sponge has been and continues to be classified by the FDA as safe. However, several concerns have been raised over the years.

TOXIC SHOCK SYNDROME

Cases of TSS began to be reported in the late 1970's primarily in users of high absorbency menstrual tampons. The infection is caused by strains of staphylococcus aureus, which produce a specific exotoxin. Subsequently, this disease was found in non-menstruating women, children and men. No cases of TSS were reported in the clinical trials of the Sponge involving1847 women. Since sales to the public began, several cases have been reported. However, the diagnosis was not confirmed in all the cases, and none of the women had used the Sponge as directed on the labeling. Data from the CDC show the total incidence has gone down progressively, and no surveillance data have been summarized since 1997. There is no clinical evidence at the present time that the Sponge causes the development of TSS. In addition, laboratory testing (USP Antimicrobial Test) shows that N9 has a bacteriostatic effect on the growth of staphylococcus aureus and retards toxin production. The current FDA approved labeling (1995) adequately describes the clinical picture of TSS and contains a warning against use of the Sponge during menses.

CARCINOGENICITY

Questions have been raised in the past about the possible induction of malignancies by the use of the Sponge. The allegations have fallen into four categories:

1. Urethane is carcinogenic in mice. There are thousands of urethanes. The Sponge is made of a urethane specifically developed for biomedical devices and has been used with no problems in artificial hearts, coronary blood vessels, etc. Moreover, tests for carcinogenicity and mutagenicity (Ames Salmonella Mutagenicity Test, Mouse Lymphoma Forward Mutation Assay) have all been negative.
2. 1,4 dioxane has been found in N9 in low parts per billion. The allowable level in foods is 1/1000.
3. 2,4 Toluene Diamine also claimed to be a carcinogen, is undetected at 1 part per million (ppm) in the Sponge.
4. Ethylene oxide is found in N9 at 0.7 ppm, far below the allowable level of 250 ppm.

Studies in rats, rabbits and dogs have all shown no potential for the development of malignancies. Even more important, widespread use of the Sponge by several million women for more than 20 years has indicated no evidence of potential risk.

LOCAL SIDE EFEFCTS

Nonoxynol 9 has been shown to produce vaginal irritation in about 1-4 percent of users; a similar incidence of sensitivity has been observed in sexual partners. About 8 percent of users have complained of vaginal itching, soreness or

dryness. It has been suggested that damage to the vaginal mucosa might increase the risk of STD transmission but this has not been clinically documented with statistical validity. In addition, studies showing a decrease in lactobacillus and an occasional increase in pathogenic organisms have also caused apprehension about the local effects of N9, but have yet to be shown to have clinical importance.

In general, the Sponge has been shown to produce less vaginal irritation than those products that use foaming and effervescent vehicles for the introduction of spermicides into the vagina. Moreover, one Sponge may be used up to 30 hours, whereas all other vaginal contraceptives require additional applications for repeated acts of intercourse.

One study has measured the frequency of genital ulcers and vulvitis following use of the Sponge by sex professionals in Africa. The sex workers had a higher prevalence of genital ulcers than the placebo group prior to the initiation of the study. During the study the sex workers used multiple Sponges per day. No reduction in HIV infection was found in the Sponge users who averaged 40 to 50 partners per week. Clearly, this study cannot be used to compare to consumer use where frequency is expected to be about three times per week.

EFFICACY

The efficacy of the Sponge in preventing unwanted pregnancy has long been the subject of ongoing debate. The results from certain sites, but not all sites, reported in the original clinical study of the Sponge suggested a disparity between the rates found in parous and nulliparous users, particularly when US and international data were compared. This apparent difference disappeared when the total data from all of the reviewed studies was compared. These data are the ones in the currently used, FDA-approved Table for contraceptive effectiveness. There continues to be a considerable difference of opinion as to what the actual rates really are given the inconsistent rates obtained from small studies and beta analyses. However, the best assessment of efficacy is made from the total submitted clinical data from the 1800 users followed for a year of use.

Even more important is how one would best explain the variable results from a number of studies for potential users, so that they can make an informed decision when choosing a contraceptive method.

There are several variables that must be noted when trying to assess effectiveness data. First, it was noted in one study that pregnancy rates were

higher in new users of both the Sponge and the diaphragm than rates obtained in women experienced in the use of vaginal contraceptives. These comparisons of data from new users and prior users will inevitably favor the subjects with prior experience. Similarly, continuation rates are higher in prior users.

Second, success rates vary considerably depending on patient characteristics such as levels of education, language skills and motivation. Finally, the amount and quality of instruction in the use of a method clearly impact the outcome data.

It is currently believed that with perfect use of the Sponge, levels of effectiveness are 90% as indicated on the current label. With average or less than perfect use, this figure falls to 86% as indicated on the current approved label. In general, increased efficacy rates are found with increased duration of use.

Generalizations have also been made about the comparative effectiveness of the various vaginal contraceptives. It has been suggested that the Sponge is more effective than foams, jellies and suppositories, but less effective than the diaphragm. However, it must be noted that comparative randomized clinical trials have never been carried out-making it impossible to give a potential user any valid comparative pregnancy rates.

LABELING

In recent years, there has been growing attention paid to the importance of accurate, explicit, understandable and easily retained labeling of products for the consumer. It has been shown in multiple studies that both verbal and written instructions including clear illustrations are critical to the proper use and effectiveness and compliance with medical products. This is particularly important for OTC methods, where there may be no professional guidance.

In the case of the Sponge, instructions for use must be given in easily understood language and pictures. This includes both the procedure for insertion and for removal. Also to be included are the length of time of insertion prior to intercourse required, and the duration of use allowed (30 hours). Warnings about local irritation and the possibility and signs of TSS must be included.

Even more important, the presentation of variable results from a number of studies will be confusing to potential users. The inclusion of additional efficacy rates as in the suggested added Table would need then, to be further explained to women making a choice for a contraceptive method.

In the past, labeling for the Sponge underwent considerable review, resulting in improvements in the final version. As currently written, (1995 FDA approved labeling), it should meet the needs of those women who elect to use it. In

addition, an "800" number was added to the label to answer additional consumer questions.

ADVANTAGES

The vaginal contraceptive Sponges offer consumers a number of advantages. In brief, these include:

- There are available over-the-counter, obviating the need for professional intervention.
- They are made in only one size, so that fitting is not required.
- They are easy to insert and, in most instances, easy to remove.
- They may be inserted immediately before or up to 24 hours prior to intercourse, timing being under control of the woman.
- They are effective for 24-30 hours after insertion for multiple acts of sexual intercourse without the addition of more spermicide.
- They have minimal side effects and avoid the potential adverse effects of IUD's and hormonal contraceptives.
- They are less messy than other vaginal barrier methods.
- They are disposable.
- They may protect against the transmission of certain STD's
- Men can be unaware of their use

DISADVANTAGES

- The Sponge (like all barrier methods) is less effective than the IUD and hormonal contraceptives.
- For maximum protection, the Sponge must be properly inserted and be in place with every act of intercourse.
- The Sponge may occasionally cause discomfort to one or both sexual partners.
- 1-4% of both men and women may be sensitive to Nonoxynol 9.
- There have been problems with removal of the Sponge, particularly with new users.
- Leaving the Sponge in place for longer than the recommended time may cause a malodorous vaginal discharge.
- There may be a rare association with TSS.
- There may be local vaginal irritation.

SUMMARY AND CONCLUSIONS

The vaginal contraceptive Sponge played a considerable role in the total contraceptive armamentarium for a number of years. Its removal from the marketplace was perceived as a loss by many women who wish to see it available soon again as one of their contraceptive options.

While the efficacy rate of the Sponge is lower than the rates of IUDs and hormonal methods, the Sponge was often selected by those who did not want to use, or could not use, for personal or medical reasons, the more effective methods. The Sponge is safe, except for occasional local adverse effects and has no serious side effects.

Currently FDA approved labeling (1995) adequately reflects the efficacy and safety of the Sponge and has adequate warnings for irritation, TSS, instructions for use and advice as to when to seek medical assistance.

On balance, the risk-vs.-benefit ratio is clearly in favor of making the Sponge available again to those women who wish to use it as their contraceptive method of choice.

Sincerely,

Elizabeth B. Connell, M.D.

Elizabeth B. Connell MD
Professor Emeritus Department of Gynecology & Obstetrics
Emory University School of Medicine

6/6/00