



Perspective

Revisiting Essure — Toward Safe and Effective Sterilization

Sanket S. Dhruva, M.D., Joseph S. Ross, M.D., M.H.S., and Aileen M. Gariepy, M.D., M.P.H.

Permanent sterilization is the second-most-common contraceptive approach used by women in the United States, undergone by about 345,000 women per year. For many decades, laparoscopic

surgery was the standard of care. In 2002, a novel hysteroscopic sterilization device was made available after expedited review and premarketing approval by the Food and Drug Administration (FDA): the Essure System (Bayer). With Essure, a coil designed to induce fibrosis and tubal occlusion is placed into each fallopian tube to prevent fertilization. Three months after placement of the coil, women undergo hysterosalpingography to confirm device placement and occlusion before discontinuing use of other contraceptive methods. The device offers clear advantages: no incisions, abdominal entry, or general anesthesia, and it can be implanted in office-based set-

tings. The manufacturer estimates that 750,000 women have received Essure.

On September 24, 2015, nearly 13 years after Essure's approval, the FDA is reconvening its Obstetrics and Gynecology Devices Panel to evaluate its safety and effectiveness and to assess the need for additional postmarketing studies.¹ Safety concerns were raised by women with Essure implants who have reported large numbers of adverse events to the FDA through its Manufacturer and User Facility Device Experience (MAUDE) database, including incomplete procedures, tubal perforations, intractable pain and bleeding leading to hysterectomies, possible device-

related deaths, and hundreds of unintended pregnancies. We believe that these safety concerns, along with problems with the device's effectiveness, might have been detected sooner or avoided altogether if there had been higher-quality premarketing and postmarketing evaluations and more timely and transparent dissemination of study results.

The premarketing approval of Essure in 2002 was based on two nonrandomized, nonblinded, prospective studies that lacked a comparator group and enrolled a total of 926 women. The FDA review concluded that Essure was 97% successful at 1 year, which was described in FDA documents as the reliance rate. This determination of success, however, was not based on an intention-to-treat analysis and considered only women who successfully under-

went the procedure and had 3-month hysterosalpingograms showing correct Essure placement and bilateral tubal occlusion (data presented to the FDA described a 14% failure rate for the first attempt at bilateral coil placement). Because of these exclusions, the declared success rate was based on only 664 (89%) of the 745 women who underwent an implantation attempt and did not account for 181 enrolled women who subsequently chose not to undergo the procedure (for unstated reasons), did not pass screening tests, or were excluded for not meeting other criteria. Among the 745 women who underwent an attempted Essure procedure, only 632 (85%) were followed up at 1 year and 197 (25%) at 2 years, which further limited the evaluation of adverse events and device safety.

Although Essure is designed to remain in place for a woman's lifetime, few women in the premarketing studies were followed for more than 1 year — a limitation that precludes conclusions about longer-term risks. Appropriately, FDA approval was conditional on two mandatory postapproval studies to provide 5-year follow-up data on patients in the premarketing approval studies. However, these studies were not made well known: neither one was registered at ClinicalTrials.gov (though that probably wasn't legally required under the FDA Modernization Act) and their results were not disseminated in a timely way. One postapproval study remains unpublished, and the other was published only recently² — 13 years after device approval and 7 years after study completion and reporting to the FDA.

The recently published study reports no pregnancies during

5 years, suggesting that the device is 100% effective.³ There are, however, concerns about incomplete follow-up and biased results reminiscent of those in the premarketing studies. Five-year follow-up was completed in only 71% of women who underwent implantation (366 of 518). Women who did not have successful bilateral Essure placement, became pregnant before the 3-month hysterosalpingogram, or underwent subsequent hysterectomy were excluded from the effectiveness analysis. Although the FDA's postapproval website states that "one of the strengths of the studies is the observed follow-up rates," the 71% rate suggests that adverse events, including unintended pregnancies, were probably missed and would affect interpretation of study findings.

In addition, the FDA required, as a condition of approval, a third study examining the outcomes achieved when 40 physicians, newly trained in Essure implantation, attempted the procedure in 20 patients each. Although this study was not registered and the only publication was based on a subgroup of the study cohort, FDA reports indicate that the trial was stopped early after physicians attempted implantations in a total of 476 patients. Despite 39 device malfunctions and 13 periprocedural adverse events — and no reported postimplantation follow-up — the device was deemed safe in women who had successful bilateral device placement.³

Since the FDA approval of Essure, the manufacturer has made several modifications to improve device function and to enhance bilateral placement rates. A new Essure model was approved by the FDA in late 2007 through a premarketing approval supplement.

As a condition of this approval, a new postmarketing study involving 800 patients was required. This study was never registered at ClinicalTrials.gov, despite the 2007 FDA Amendments Act requirement, and was stopped early at the manufacturer's request after 578 patients underwent attempted implantation. Its findings are minimally informative, since no follow-up data were collected and nearly all study results reported on the FDA website are redacted.

Given the limitations of the relevant studies, it's not surprising that so many years passed before safety issues with Essure were recognized. To identify adverse events occurring in day-to-day practice, the FDA relies on voluntary reporting through its MAUDE system. Although passive adverse-event reporting is known to underestimate adverse-event rates, as of June 2015, a total of 5093 adverse-event reports related to Essure had been made to MAUDE, most of which listed multiple safety concerns. These reports led the FDA to update the device label in 2013 to include information about risks of chronic pain and device migration and to reconvene its Obstetrics and Gynecology Devices Panel to reassess safety and effectiveness.

Though Essure offers possible advantages to women seeking sterilization, the evidence suggests that it is neither as effective nor as safe as the premarketing-approval evaluation indicated. An intention-to-treat analysis using a Markov model and incorporating all relevant available data, including data from the manufacturer and elsewhere, suggests that there's a 5.7% annual risk of pregnancy after hysteroscopic sterilization,⁴ and in 2012 the instructions for use of Essure were updated to

acknowledge the occurrence of hundreds of unintended pregnancies.

The upcoming meeting of the Obstetrics and Gynecology Devices Panel represents a clear opportunity to impose requirements that will more fully elucidate the safety and effectiveness of Essure. A new study focused on patient-centered end points — unintended pregnancy, device migration, tubal perforation, bleeding, pain, and events such as hysterectomy and death — in all enrolled women is needed to provide clear estimates of device performance. We believe such a study should compare outcomes in women receiving Essure with those in women undergoing laparoscopic sterilization, the standard of care, and should be overseen by an impartial, off-site data and safety monitoring board performing periodic, planned reviews with follow-up for at least 5 years.

The problems of inadequately rigorous premarketing and postmarketing studies, unregistered clinical trials, and incomplete and

delayed dissemination of results are not unique to Essure. Most FDA-required postapproval studies are smaller than the premarketing studies, most follow patients for 1 year or less, and nearly half lack comparator groups.⁵ The 13-year history of Essure emphasizes the necessity for thorough examination and timely reporting of patient outcomes in well-conducted premarketing clinical trials and dedicated follow-up in postmarketing studies. Only then will we better understand the risks and benefits of various devices. In the case of Essure, these data would allow women to make more informed decisions regarding hysteroscopic sterilization.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Robert Wood Johnson Foundation Clinical Scholars Program (S.S.D., J.S.R.), the Section of General Internal Medicine (J.S.R.), and the Department of Obstetrics and Gynecology (A.M.G.), Yale University School of Medicine; the Department of Health Policy and Management, Yale University School of Public Health (J.S.R.); and the Center for Outcomes Research and Evaluation, Yale–New Haven Hospital

(J.S.R.) — all in New Haven, CT; and the Veterans Affairs Connecticut Health System West Haven, CT (S.S.D.).

This article was published on September 23, 2015, at NEJM.org.

1. Federal Register. Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee: notice of meeting (<https://www.federalregister.gov/articles/2015/07/22/2015-17985/obstetrics-and-gynecology-devices-panel-of-the-medical-devices-advisory-committee-notice-of-meeting>).

2. Chudnoff SG, Nichols JE Jr, Levie M. Hysteroscopic Essure inserts for permanent contraception: extended follow-up results of a phase III multicenter international study. *J Minim Invasive Gynecol* 2015;22:951-60.

3. Food and Drug Administration. Essure summary of study results extracted from PAS study status web page for the two PAS ordered in conjunction with original PMA approval (<http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/UCM452291.pdf>).

4. Garipey AM, Creinin MD, Smith KJ, Xu X. Probability of pregnancy after sterilization: a comparison of hysteroscopic versus laparoscopic sterilization. *Contraception* 2014;90:174-81.

5. Rathi VK, Krumholz HM, Masoudi FA, Ross JS. Characteristics of clinical studies conducted over the total product life cycle of high-risk therapeutic medical devices receiving FDA premarket approval in 2010 and 2011. *JAMA* 2015;314:604-12.

DOI: 10.1056/NEJMp1510094

Copyright © 2015 Massachusetts Medical Society.