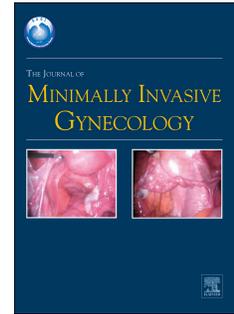


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Hysteroscopic Essure Inserts for Permanent Contraception— Extended Follow-up Results of a Phase III, Multicenter, International Study

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PRÉCIS

This is a report on extended (5-year) follow up of a phase III trial evaluating the effectiveness, safety, tolerability, and satisfaction of hysteroscopically placed Essure inserts for permanent contraception.

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ABSTRACT

Study Objective: To describe safety, tolerability, and effectiveness results through 5 years of follow-up of a phase III trial with Essure inserts.

Design: Multicenter, nonrandomized, single-arm, international study.

Design Classification: Canadian Task Force Classification II-3.

Setting: 13 clinical study centers in the United States, Europe, and Australia.

Patients: 518 previously fertile women seeking permanent contraception.

Intervention: The objective of the hysteroscopic sterilization procedure was bilateral Essure insert placement (ESS205 model) and tubal occlusion. Women with satisfactory device location and tube occlusion (based on modified hysterosalpingogram) were instructed to discontinue alternative contraception and to rely on the Essure inserts for permanent contraception.

Measurements and Main Results: The primary end point for the phase III study was the rate of pregnancies occurring during the first year of relying (ie, confirmed HSG occlusion) on the Essure inserts for permanent contraception (ie, 12 months following HSG). For the full 5 years of follow-up (5 years in total of relying on the Essure inserts for contraception), the end points of interest were safety, prevention of pregnancy, and satisfaction. No pregnancies were reported among women relying on the Essure inserts who completed the full 5 years of follow-up. As of December 5, 2007, 449 women with successful bilateral placement relying on the Essure inserts contributed a total 24,942 woman-months of follow-up for assessing the effectiveness. Overall, the Essure inserts were generally well tolerated, with participant comfort rated as “good” to “excellent” by 99% (382/385) of women after 5 years of wearing. Similarly, overall satisfaction was rated as “somewhat” to “very satisfied” by 98% (376/384) of women after 5 years of wearing. The majority of adverse events reported during the 5 years of follow-up were rated as either “mild” or “moderate” in severity. Three severe events were reported in 2 subjects during follow-up as being “possibly” related to the procedure or inserts (abdominal pain with very heavy periods, and irregular menstrual bleeding).

Conclusions: The findings from extended follow-up of the phase III trial with Essure inserts further support the effectiveness, tolerability, and satisfaction of this nonhormonal, nonincisional, option for permanent contraception.

Key words: hysteroscopic sterilization, Essure insert, permanent contraception

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INTRODUCTION

Unintended pregnancies represent a significant women's health issue (exposing women to morbidity and mortality (1)), and occur despite prevalent use of contraception among women of reproductive age (2). In the United States, nearly 50% of unintended pregnancies occur among contraceptive users (3); however, only 10% result from true method failure, whereas the remainder results from inconsistent or incorrect method use (4).

Female sterilization, which is highly effective and avoids inconsistent and incorrect usage errors, is the most common method of contraception worldwide (used by 19% of women), and ranks second only to oral contraceptive use as the most common method in the United States (used by 27% of women) (5-6). Historically, interval female sterilization has involved laparoscopy, which, because of using small incisions, can be performed as outpatient surgery, offers immediate effectiveness, allows for inspection of the abdomen and pelvic organs, and allows for accelerated return to full activity (7). However, the limitations of the laparoscopic approach are that the procedure is typically performed under general anesthesia; increases the risk of bowel, bladder, and major vessel injuries; requires 1 to 3 incisions; and is associated with postoperative pain and loss of productivity due to surgical recovery time (7). Furthermore, various access barriers may limit the availability of female sterilization as a permanent contraception option, even for women who wish to undergo the procedure (8).

A hysteroscopic approach to female sterilization obviates the need for incisions and entering the abdominal cavity, thereby decreasing the risk of injury to abdominal organs, significantly reducing postoperative pain, and allowing for faster recovery and resumption of normal activities relative to laparoscopic approaches (7-9). In addition, hysteroscopic sterilization can be performed as an in-office procedure, with or without paracervical block or sedation (oral or intravenous), and it may be a preferable option for women who are not ideal candidates for laparoscopic procedures (7). Since approval of the Essure System by the FDA in 2002 (10), more than 750,000 units have been sold (11); and this minimally invasive, nonincisional approach has become an attractive method for permanent contraception. The increasing popularity of hysteroscopic sterilization may be a contributing factor in the decreasing rate of interval tubal ligation procedures (12-13).

Results from a phase III trial with the Essure System have been published previously, focusing on safety, reliance on the Essure inserts for contraception, and effectiveness 15 months following the hysteroscopic sterilization procedure (9). The purpose of this report is to describe

safety, effectiveness, tolerability, and satisfaction results from 5 years of follow-up of this phase III trial with the Essure System.

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METHODS

Detailed methods of the phase III trial are described elsewhere (9). Briefly, the study enrolled previously fertile women of childbearing age seeking permanent contraception between May 2000 and February 2001. Women 21 to 40 years of age and weighing between 90 and 300 pounds, who were seeking permanent contraception, were engaged in a monogamous relationship, and were willing to use a temporary contraceptive method for the first 3 months following Essure insert placement, were eligible for participation. Those women who met the eligibility criteria gave their written, informed consent.

The objective of the hysteroscopic sterilization procedure was bilateral Essure insert placement and tubal occlusion. Women who received unilateral placement were followed for safety only, unless they had a subsequent HSG that confirmed contralateral proximal tubal occlusion and the women chose to rely on the unilateral Essure insert and the contralateral proximal tubal occlusion for contraception, or if they had a unicornuate uterus. These women were followed for safety and effectiveness, but were not included in the long-term effectiveness rate calculations in the Instructions for Use.

Optimum placement of the Essure inserts is defined as 3 to 8 visible trailing coils of the proximal device at the tubal ostium (visible within the uterine cavity on hysteroscopy). A pelvic x-ray was conducted within 24 hours after device placement to serve as a baseline evaluation of device location. Modified hysterosalpingogram (HSG) scheduled for 3 months after Essure insert placement was used to evaluate device location and fallopian tube occlusion.

Follow-up via telephone was scheduled for months 3, 6, and 18 post-HSG, soliciting information on coital activity, reliance on the Essure inserts, any changes in their partner's fertility status, satisfaction and comfort of wearing devices, and plans for any intrauterine procedures or extirpative surgery of reproductive organs, as well as any adverse events or unusual symptoms. Office visits were scheduled annually at years 1 through 5. Visits at years 1, 2, and 5 of follow-up included a pelvic exam, pregnancy test, and x-ray verification of Essure insert retention, in addition to the same assessments conducted during telephone follow up. For follow-up visits at years 3 and 4, a pelvic exam, pregnancy test, or x-ray assessments were excluded. Women who had one or more Essure inserts placed, but were not able to rely on them for contraception, were followed for safety, with annual visits at years 1 through 5 for continuing intention to treat analysis.

The phase III study was designed to include 5 years of follow-up, 1 year of which was to be completed prior to a premarketing approval filing. The remaining 4 years of follow-up was completed as part of a post-approval study. The primary end point for the first year of follow-up study was the rate of pregnancies occurring during the first year of relying on the Essure inserts for permanent contraception (12 months after HSG confirmation test) (9). Reliance on Essure inserts required 3-month HSG-confirmed bilateral occlusion and appropriate device location. Additional end points of interest include safety and satisfaction of the Essure insert placement procedure, safety and satisfaction of wearing, and bilateral placement rate. For the 4 additional years of follow-up (5 years in total of relying on the Essure inserts for contraception), the end points of interest were safety and satisfaction, reliance on the Essure inserts for contraception, and prevention of pregnancy.

Data analysis was conducted using SAS 8.0 statistical software (SAS Institute, Cary, North Carolina), including the PROC MIXED procedure and GLIMMIX macro; and Microsoft Excel (Redmond, Washington).

RESULTS

Disposition of Study Participants

A total of 518 women met the entry criteria and were scheduled to undergo the hysteroscopic sterilization procedure, thus comprising the intention-to-treat population. The demographics and baseline characteristics of study participants are summarized in Table 1, and the disposition of participants through 5 years of follow-up is summarized in Figure 1. Bilateral placement rates, confirmation test results, and reliance rates for the first year (ie, 15 months following device placement) have been published previously (9).

A total of 453 women were able to rely on the Essure inserts for permanent contraception, which represents 87.5% of the intention-to-treat population, or 89.3% (453/507) among those in whom Essure insert placement was attempted (9). Overall, 366/453 women (n=364 with bilateral placement, n=2 with unilateral placement) who relied on the Essure insert for contraception completed 5 years of follow-up, representing 71% of the intention-to-treat population. Sixty-five women (n=27 after 24 months, and n=38 more after 48 months) were lost to follow-up throughout the course of the study. In addition, termination of study participation prior to the completion of 5 years of follow-up occurred in 22 women. Reasons for early termination included 9 women who underwent subsequent hysterectomy, 8 women who voluntarily terminated participation, 1 patient who was terminated by study investigators for protocol violation (missed the 6-month post-HSG follow-up), 1 patient with unsatisfactory device placement, 1 patient who died from unrelated causes (leukemia), and one patient who became incarcerated. Lastly, 1 woman voluntarily chose to undergo bilateral salpingectomy to become pregnant via in-vitro fertilization.

An additional 25 women were followed throughout the study for safety assessments only, which included 8 women who underwent unilateral placement of the Essure insert; 11 who had unsatisfactory device location (based on 3-month HSG); and 6 women who underwent subsequent hysterectomy after Essure insert placement. Of these women followed for safety assessments only, 20 completed the full 5-year study period (n=5 lost to follow-up). Data from these participants were included in all assessments related to safety, patient comfort, and satisfaction, but are not included in effectiveness calculations.

Effectiveness

No pregnancies were reported by any participant completing the study throughout the full 5 years of follow-up. As of December 5, 2007, 449 women with successful bilateral placement of Essure inserts contributed a total 24,942 woman-months of follow-up for assessing effectiveness, with the mean wearing time of 55.5 months. Similarly, no pregnancies were reported among the 4 women with intentional unilateral placement (with confirmed contralateral proximal tubal occlusion or unicornuate uterus) who were relying on Essure inserts for permanent contraception (2 of whom completed 5 years of follow-up). The only pregnancy reported among women relying on Essure inserts occurred in a woman (who had successful bilateral placement) who voluntarily terminated study participation at 45 months to undergo bilateral salpingectomy to become pregnant (intentionally) via in vitro fertilization. There were four luteal phase pregnancies that occurred in women prior to HSG confirmation of Essure insert placement and occlusion.

Tolerability/Satisfaction

The tolerability of the hysteroscopic sterilization procedure and satisfaction with Essure insert wearing after the first year have been published previously (9). Through 5 years of follow-up, participant comfort with Essure insert wearing was rated as “good” to “excellent” by at least 99% of women at any visit. Similarly, overall satisfaction was rated as “somewhat” to “very satisfied” by at least 95% of women at all follow-up visits. At the 5-year follow-up visit, overall comfort with wearing was rated by 99.2% (382/385) of participants as either good (2.1%), very good (4.9%), or excellent (92.2%). At this same time point, overall satisfaction during this visit was rated by 97.9% (376/384) of participants as either somewhat (1.3%) or very (96.6%) satisfied.

Adverse Events

Data on adverse events occurring on the day of placement and during the first 15 months of wearing have been published previously (9). In the 4 years of subsequent follow-up, 15 adverse events were deemed to be “possibly” related to the Essure inserts, including heavy periods with or without pain, irregular periods (continuous, frequent, and varying) with or without pain, dyspareunia, and spotting when ovulating. Three severe adverse events were reported in 2 subjects during follow-up as being “possibly” related to the Essure inserts or procedure. One woman reported lower abdominal pain and very heavy periods at the 18-month follow-up visit and described her pain as sharp, aching, and continuous at her 24-month follow-up visit. She ultimately underwent hysterectomy at 34 months. The other severe event involved irregular menstrual bleeding, which resolved following dilation and curettage. In addition, as previously discussed, one woman underwent planned bilateral salpingectomy to remove the Essure inserts in an effort to become pregnant via in vitro fertilization.

During each follow-up visit, women were asked specifically about any unusual pain they experienced since the last study contact, and the results are summarized in Table 2. Irregular bleeding affected 5% to 12% of women over the 5 years of follow-up. Intermenstrual bleeding occurred frequently in the first 3 months following placement (23.6%). Post use of alternative contraception intermenstrual bleeding was reported in 6% to 9% of women. By year 5, no participants had persistent irregular or intermenstrual bleeding. At the 5-year follow-up visit, 20% of women reported heavier menses and 11% reported lighter menses. Table 3 describes changes in menstrual function at follow-up visits.

Fifteen women underwent hysterectomy during the 5 years of follow up. Details on the reason for hysterectomy and the investigator’s determination of relatedness to the Essure inserts were missing for 5 of these women. For the remaining women, the most common reasons cited (at least in part) for hysterectomy were menorrhagia/abnormal bleeding (n=7), pelvic pain (n=3), and dysmenorrhea (n=2). In only 2 instances did the respective investigator deem the hysterectomy to be possibly related to the Essure inserts (one woman as described above who reported heavy and irregular menstrual bleeding along with pelvic pain; the other a woman with continuous bleeding). None of the other hysterectomies were deemed by the investigators as being definitely or probably related to the Essure inserts.

DISCUSSION

The findings from the 5-year follow-up of the phase III trial confirm initial results that the Essure insert is an effective and well-tolerated nonhormonal, nonincisional, option for permanent contraception. With the exception of 1 intentional pregnancy (via in vitro fertilization), no pregnancies occurred among the 449 women with bilateral placement who relied on the Essure inserts for contraception over a total of 24,942 woman-months of follow-up. Bilateral placement was achieved in ~90% of all study participants, and among those achieving bilateral placement, 97% were able to rely on the Essure inserts for permanent contraception.

Both the hysteroscopic sterilization procedure and Essure insert wearing were generally safe and well tolerated. After 5 years of follow-up, more than 90% of participants rated the overall comfort with wearing as “excellent,” and more than 96% of participants were “very satisfied” with the Essure inserts at the end of the study. Adverse events during the first year of wearing were rated as either mild or moderate in severity, and occurred more commonly during the 3-month period following placement (9). Throughout 5 years of follow-up, relatively few adverse events were reported that were deemed “possibly” related to the Essure inserts.

The results described herein were included as part of a calculation of the long-term effectiveness rate for Essure inserts, which was reviewed by the US FDA for inclusion in the product labeling (14). The long-term effectiveness rate calculation for Essure inserts was determined using a Bayesian approach that allowed for the incorporation of data from a phase II trial into the phase III trial calculations. Additionally, a statistical age-adjustment was performed to make comparisons between failure rates in the Essure clinical trials and those in the Collaborative Review of Sterilization (CREST) study population (15). The distribution of the cumulative failure rate was calculated using an indirect age-adjustment method and Bayesian perspective, taking into account a beta (0.5,0.5) prior distribution, the number of observed pregnancies, and the number of observed women-months without pregnancy. The effectiveness rate calculations were restricted to cases of successful bilateral placement in women demonstrating bilateral tubal occlusion and appropriate device location on 3-month HSG. Overall, based on this approach, the calculated 5-year effectiveness rate for Essure inserts was 99.83% (14).

The findings in the report herein are consistent with effectiveness results with Essure inserts in preventing pregnancy in the published literature. In a recent systematic review of hysteroscopic approaches to female sterilization (16), a total of 22 articles (published through March 2012)

involving Essure inserts provided information on whether pregnancies occurred following the procedure. No pregnancies were reported in 11 of these studies, which included sample sizes ranging from 36 to 4306 women and up to 7 years of follow-up. A total of 102 pregnancies were reported in the remaining 11 studies, with the majority of these pregnancies occurring as a result of not following up for imaging confirmation (X-ray, HSG, or ultrasound), misreading of imaging results, improper placement, or conception prior to placement or prior to imaging confirmation. Fifteen pregnancies were reported to occur after 3 months following the procedure in women with documented bilateral occlusion or placement (16). The authors of this analysis characterized the body of evidence as “fair” in quality, but with notable limitations, including: relatively short duration of follow-up for most studies (<5 years); the number of studies not reporting the duration of follow-up or duration of wearing; and lack of details regarding the timing of pregnancies during the follow-up period (16).

Subsequent to this systematic review, 3 additional articles have been published evaluating the effectiveness of the Essure inserts (17, 18, 19). The purpose of one analysis was to evaluate the available data from post-Essure pregnancies that have been reported from initial release of the device through December 2010 (19). From 2001 through 2010, 497,305 Essure kits were distributed worldwide. Of these, 133,000 were the original (ESS205) model, which is no longer commercially available, and 365,000 were the currently available model (ESS305). As of December 31, 2010, 748 pregnancies were identified, of which 508 could be sufficiently analyzed based on data availability. Of these, 355 pregnancies occurred >12 weeks after the Essure procedure, which corresponds with the time frame following the confirmation imaging test. Of the 508 evaluable pregnancies, 76.7% were attributed to misinterpreted confirmation test results (41.7%) or to noncompliance with the confirmation test (35.0%). The methods used for the analysis by Munro et al (19) likely underestimate the actual pregnancy rate; however, the estimated pregnancy rate based on distributed kits (0.15%) in this analysis corresponds with an estimated effectiveness of >99.7%. This is consistent with the labeled age-adjusted effectiveness for Essure inserts (based on phase II study results combined with phase III trial results (14)), with retrospective analyses of commercial data (12, 17, 18, 20), and with findings from other studies (21, 22, 23, 24). Given that a significant proportion of pregnancies following placement of Essure inserts occur as a result of misinterpretation of the confirmation test results or nonadherence with confirmation testing, an important distinction may be made between true human error (25).

Accordingly, the device should only be used by knowledgeable hysteroscopists who have read and understood the Instructions for Use and Physician Training Manual, and have successfully completed an Essure training program, typically including preceptoring in placement until competency is established (14). Nevertheless, the occurrence of pregnancies following Essure insert placement speak to the “functional effectiveness” of the procedure in real-world applications, and emphasizes the need for appropriate patient counseling and education on the factors that could potentially result in pregnancy. As such, the importance of confirmation testing should be stressed at both preprocedural counseling and at the time of the procedure. Some centers have established a system to remind patients when their confirmation test is due.

Relative to hysteroscopic approaches to sterilization, a much more robust data set exists regarding the long-term effectiveness of laparoscopic and abdominal approaches in preventing pregnancy (26), which begs a relevant clinical question of whether one particular approach is superior to another. To date, no prospective clinical studies have been conducted comparing hysteroscopic to laparoscopic approaches, and the 3 publications on this topic offer discordant conclusions. Two articles used evidence-based Markov modeling to estimate the probability of successful sterilization (27) or pregnancy (28). In the first analysis (27), the estimated proportion of women achieving successful sterilization at 1 year was 99% with laparoscopic sterilization versus 94% with hysteroscopic sterilization performed in an office setting. These results were obtained based on assumptions of 90% of women achieving successful insert placement on the first attempt and 69% returning after 3 months to confirm device location (27). In the second analysis (28), the expected cumulative risk of pregnancy was higher with hysteroscopic sterilization than with laparoscopic sterilization using silicone band application or bipolar coagulation. After 1 year, the expected pregnancy rates associated with each approach were 57, 7, and 3 per 1000 women, respectively. At 10 years, the cumulative pregnancy rates per 1000 women were 96, 24, and 30, respectively. This model was based on assumptions of 92% of women achieving successful insert placement on the first attempt and 79% returning after 3 months to confirm device location (28).

Markov analysis is an interesting way of comparing these two procedures and correctly points out that unlike with laparoscopic procedures, where 99% of procedures will be completed, only 95% of hysteroscopic procedures will be completed. Assuming that 95% of hysteroscopic procedures will be completed may also overestimate the sterilization rate, which cannot be achieved until occlusion is demonstrated. Using this analysis, it is obvious that there would be more expected pregnancies with hysteroscopic procedures, especially if no birth control or

inferior alternatives are chosen. What the Markov analysis does not take into account is how many women never consider sterilization laparoscopically because of the need to go to the operating room, undergo general anesthesia, and miss work. Many women who desire permanent contraception choose inferior methods because of these concerns, which are obviated by the hysteroscopic approach. Furthermore, these analyses are only comparing projected pregnancy rates; other factors such as complications (rate and severity) for laparoscopic versus hysteroscopic are also important considerations. It is also noteworthy that the models accentuate poor HSG follow-up with hysteroscopic sterilization (disproportionate weighting), and the pregnancy rate in those who undergo HSG is lower than with laparoscopic bilateral tubal ligation. The third publication involved a retrospective analysis of procedure codes from 109,277 French women undergoing permanent tubal sterilization procedures (39,169 Essure procedures and 70,108 tubal ligations) between 2006 and 2009, and followed through the end of 2010 (12). From this analysis, the rate of spontaneous (eg, unintended) and assisted (eg, in vitro fertilization) pregnancies was significantly lower in patients undergoing the Essure procedure (0.36%) compared with tubal ligation (0.46%). Compared with the Markov Analysis, which relies on predictive statistical models, this analysis by Fernandez et al (12) describes actual reported pregnancies with the 2 procedures. Despite a lack of head-to-head studies comparing the effectiveness of these 2 sterilization approaches, hysteroscopic sterilization may offer advantages with respect to less morbidity, faster recovery, and lower costs relative to laparoscopic sterilization (7, 12, 29, 30, 31, 32, 33). The observation that hysteroscopic approaches to sterilization are increasingly being chosen over laparoscopic approaches also speaks to these perceived advantages (12, 34, 35).

The potential complications associated with Essure inserts have been reviewed elsewhere (25); however, a benefit of increased acceptance and use of the Essure inserts in a postmarketing setting is that it allows an opportunity to evaluate the safety and tolerability in real-world practice. A recent search of the Manufacturer and User Facility Device Experience (MAUDE) database for events related to hysteroscopic sterilization with Essure (November 2002 to February 2012) revealed 457 reported adverse events (36). The first 5 events were reported in 2004 and increased over subsequent years to 114 in 2010, reflecting greater overall use of the Essure inserts for hysteroscopic sterilization. Of all adverse events, pain was the most frequently reported event (217/457 events; 47.5%), followed by delivery catheter malfunction (121/457 events; 26.4%); perforation (90/457 events; 19.7%); poststerilization pregnancy

(61/457 events; 13.3%); abnormal bleeding (44/457 events; 9.6%); and malposition (33/457 events; 7.2%).

Pelvic pain associated with Essure insert placement has been a recent topic of interest (37-38). Throughout 5 years of follow-up in the phase III trial described herein, pelvic pain (dysmenorrhea, dyspareunia, ovulatory, or other) was reported in no more than 7% of study participants at any visit. No subjects reported persistent pelvic pain of any kind at the 3-, 4-, and 5-year follow-up visits. Furthermore, at the completion of follow-up, overall comfort with wearing was rated as excellent by more than 90% of women, and overall satisfaction was rated as very satisfied by more than 96% of women. However, an important caveat is that women with preexisting chronic pain were excluded from participation (9). Nevertheless, these results are consistent with a recent analysis of 458 women who underwent the Essure procedure between January 1, 2005, and June 30, 2012 (39). In this analysis, the incidence of acute pelvic pain following the hysteroscopic sterilization procedure and ≥ 3 months after the procedure was 8.1% and 4.2%, respectively. Women with a preexisting diagnosis of any chronic pain (pelvic, low back, headache, fibromyalgia) were more than 6-fold more likely (vs women without preexisting diagnosis of chronic pain) to report either acute or chronic pain after the Essure procedure. Most women with documented pelvic pain reported their symptoms within 130 days of the procedure, and pain resolved in 50% of women by 3 months after the procedure. In a case series of 4274 patients undergoing the Essure procedure from January 2005 to December 2011, chronic pelvic pain was reported in 7 (0.16%) women, and the symptoms resolved in each individual after the Essure inserts were removed (40).

Chronic pelvic pain is a common problem in women and its etiology is varied. It is important to consider that the monthly incidence of chronic pelvic pain in the general population is ~1.6%, and the annual prevalence is 3.8%. Furthermore, prevalence rates for chronic pelvic pain in women increase with age (41). Similarly, abnormal uterine bleeding has an annual prevalence of 5.3% in the US (42). Therefore, a thorough evaluation as to the etiology of these symptoms must be undertaken, as symptoms may be unrelated and incidental to hysteroscopic sterilization.

History of abnormal and intermenstrual bleeding was elicited from patients post Essure insert placement (see Table 3). The incidence was highest immediately post hysteroscopic sterilization as would be expected after any intrauterine instrumentation. A historical complaint of abnormal bleeding was elicited from 5-12% of women after stopping use of alternative

contraception. This is consistent with data reported in the literature where abnormal uterine bleeding has been noted to occur in 9 to 14 percent of women between menarche and menopause (43). The complaint of intermenstrual bleeding was elicited in 6% to 9% of women. Once again this falls well within the parameters of what has been reported in the general population. In a study by Shapely et al(44), the 2-year cumulative incidence of intermenstrual bleeding was 24%. Twenty percent of women at 5 years of follow up in the study described herein noted heavier menses, whereas 11% reported lighter periods with the large majority noting no change in menstrual bleeding. Changes in the amount of bleeding as well as bleeding intervals are quite variable over a woman's lifetime and can be affected by many factors including age, weight and contraceptive use. It is estimated that 30% of all women report having had menorrhagia at some point in their lives (45) and approximately 9% to 30% of reproductive-age women have menstrual irregularities requiring medical evaluation (46). Lastly it is important to note that 43% of participants were using oral contraceptives prior to the Essure procedure as their birth control modality, underlying abnormal and heavy bleeding as well as pelvic pain may have been masked with the use of hormonal contraception.

Fifteen hysterectomies were reported in this cohort over 5 years of follow-up, which translates to 3.8% (15/397) of evaluable participants. The estimated annual hysterectomy rate in the general population of women 40-50 years of age is approximately 9.6 per 1,000 (47). Therefore we would expect approximately 4 women each year for a total of 20 hysterectomies over a 5 year study. One might expect an even higher incidence of hysterectomies in this study population as many were using hormonal contraceptives, which may mask bleeding and pain symptoms prior to changing to a non-hormonal contraceptive. Furthermore, there is some limited data showing that women after tubal sterilization have a higher rate of hysterectomy (48). Even so, the hysterectomy rate seems to be in accordance with expectations.

The strength of this study is that it was a prospective study following the initial cohort of women in the trials leading to FDA approval who underwent hysteroscopic sterilization. A limitation of this trial is that ~30% of the intention-to-treat population did not complete the full 5 years of follow-up, either because of study termination or loss to follow-up. While loss to follow-up is not uncommon in these types of studies, this may represent a different group that was lost due to pregnancy or other complications. Lastly, a final limitation is that adverse event rates may not be known with a great deal of certainty as bias may have been introduced as a result of the nature of data collection (self-reported).

CONCLUSION

In conclusion, the results from 5 years of follow-up of the phase III trial extend the findings from previous studies supporting the effectiveness and safety of the Essure procedure and inserts. In addition, high rates of comfort (with wearing) and satisfaction were reported throughout follow-up.

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FIGURE LEGEND

Figure. Disposition of study participants through 5 years of follow-up.

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TABLES

Table 1. Patient Demographics

| Characteristic | n | Mean (SD) |
|------------------|------------------|--------------|
| Age | 518 | 31.9 (4.6) |
| Weight (lb) | 511 ^a | 159.9 (37.3) |
| Height (in) | 508 ^a | 64.5 (2.6) |
| Cycle length (d) | 512 ^a | 28.1 (2.6) |
| Gravidity | 518 | 3.0 (1.5) |
| Parity | 518 | 2.3 (1.0) |

SD=standard deviation.

^aObservations missing for some women.

Table 2. Pelvic Pain Results

| Visit | Pelvic pain | | | |
|--------------------------------|-----------------------|----------------------|-------------------------|----------------------------------|
| | Dysmenorrhea n (%) | Dyspareunia n (%) | Ovulatory pain n (%) | Other pain ^a n (%) |
| Baseline (N=518) | 183 (35) | 22 (4.2) | NA | NA |
| 3 Month (n=440) | 20 (4.5) | 10 (2.3) | 6 (1.4) | 26 (5.9) |
| 6 Month (n=436) | 15 (3.4) | 8 (1.8) | 3 (0.7) | 16 (3.7) |
| 12 Month (n=460) | 17 (3.7) | 15 (3.3) | 5 (1.1) | 27 (5.9) |
| 18 Month (n=410) | 14 (3.4) | 9 (2.2) | 10 (2.4) | 11 (2.7) |
| 24 Month (n=435) | 22 (5.1) | 9 (2.1) | 22 (5.1) | 13 (3.0) |
| 36 Month (n=422) ^b | 14 (3.3) | 7 (1.7) | 12 (2.8) | 6 (1.4) |
| 48 Month (n=402) | 3 (0.7) | 5 (1.2) | 6 (1.5) | 11 (2.7) |
| 60 Month (n=386) | 14 (3.6) | 8 (2.1) | 10 (2.6) | 9 (2.3) |
| Recurrent (n=473) ^c | 29 (6.1) | 18 (3.8) | 14 (3.0) | 25 (5.3) |
| Persistent ^d | | | | |
| Year 1 (n=460) | 0 | 0 | 0 | 1 (0.2) |
| Year 2 (n=435) | 0 | 0 | 0 | 1 (0.2) |
| Year 3 (n=422) | 0 | 0 | 0 | 0 |
| Year 4 (n=402) | 0 | 0 | 0 | 0 |
| Year 5 (n=386) | 0 | 0 | 0 | 0 |

^aDefined as pelvic pain that was not reported to be dysmenorrhea, dyspareunia, or ovulatory pain.

^bData missing on 1 participant.

^cDefined as symptoms reported at more than 1 visit.

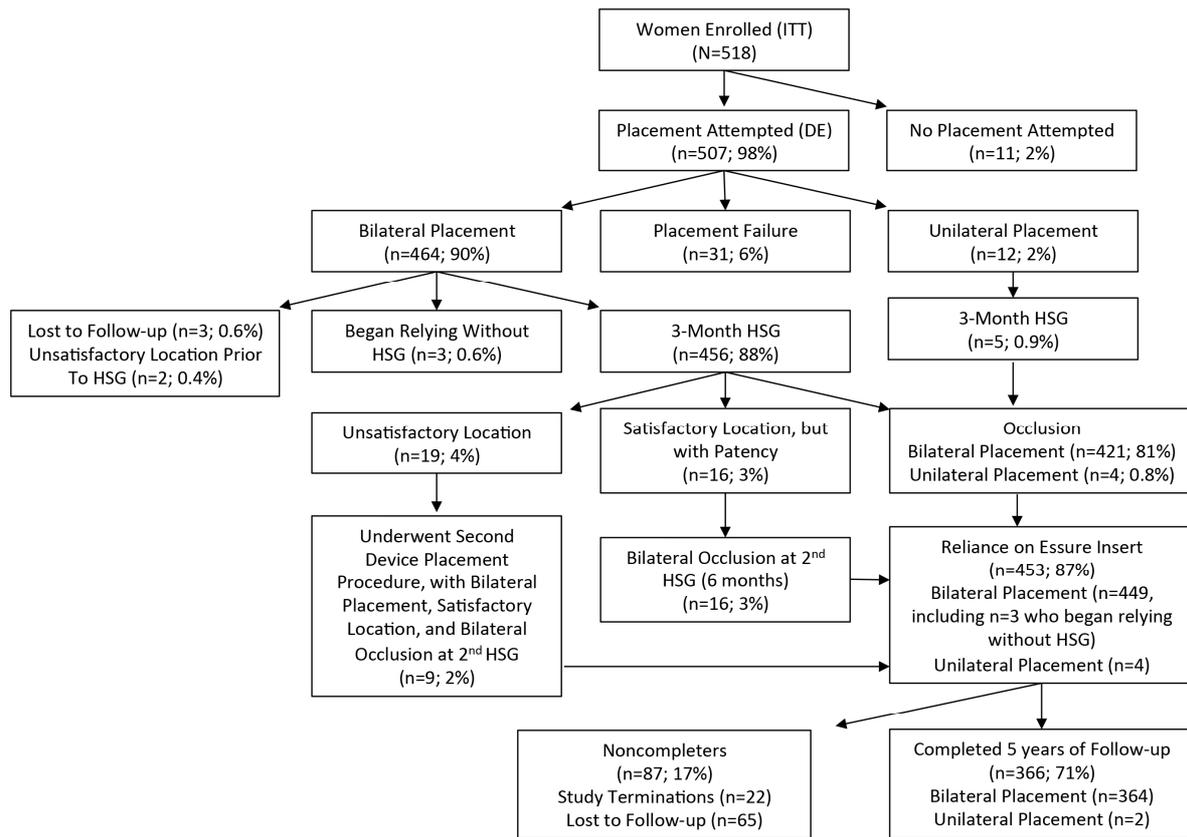
^dDefined as symptoms reported at all prior visits.

Table 3. Changes in Menstrual Function During Follow-up

| Follow-up visit | Irregular menses | Bleeding between menses | Heavier than usual menstrual flow | Less than usual menstrual flow |
|-------------------------|---------------------|-------------------------|-----------------------------------|--------------------------------|
| Baseline (N=518) | 9 (1.7%) | 12 (2.3%) | NA | NA |
| 3 Month | 36 (8.2%) N=440 | 40 (9.1%) N=440 | 96 (21.9%) N=439 | 55 (12.5%) N=439 |
| 6 Month | 36 (8.2%) N=437 | 29 (6.6%) N=437 | 94 (21.6%) N=435 | 57 (13.1%) N=435 |
| 12 Month | 35 (7.7%) N=455 | 31 (6.7%) N=460 | 77 (16.8%) N=458 | 67 (14.6%) N=458 |
| 18 Month | 19 (4.6%) N=410 | 42 (10.2%) N=411 | 70 (17.0%) N=411 | 63 (15.3%) N=411 |
| 24 Month | 20 (4.6%) N=435 | 32 (7.4%) N=435 | 89 (20.6%) N=432 | 53 (12.3%) N=432 |
| 36 Month | 31 (7.4%) N=420 | 25 (6.0%) N=420 | 83 (20.0%) N=411 | 47 (11.4%) N=411 |
| 48 Month | 33 (8.4%) N=393 | 33 (8.3%) N=396 | 69 (17.9%) N=386 | 52 (13.5%) N=386 |
| 60 Month | 45 (11.7%) N=386 | 29 (7.5%) N=386 | 74 (19.6%) N=377 | 40 (10.6%) N=377 |
| Recurrent ^a | 70 (14.8%) N=473 | 89 (18.8%) N=473 | 177 (37.5%) N=472 | 110 (23.3%) N=472 |
| Persistent ^b | | | | |
| 12 Month | 3 (0.7%) N=455 | 2 (0.4%) N=460 | 7 (1.5%) N=458 | 12 (2.6%) N=458 |
| 24 Month | 0 (0.0%) N=435 | 1 (0.2%) N=435 | 4 (0.9%) N=432 | 3 (0.7%) N=432 |
| 36 Month | 0 (0.0%) N=420 | 1 (0.2%) N=420 | 4 (1.0%) N=411 | 2 (0.5%) N=411 |
| 48 Month | 0 (0.0%) N=393 | 0 (0.0%) N=396 | 3 (0.8%) N=386 | 1 (0.3%) N=386 |
| 60 Month | 0 (0.0%) N=380 | 0 (0.0%) N=386 | 2 (0.5%) N=377 | 0 (0.0%) N=377 |

^aSymptom reported at more than one visit during the follow-up period. The denominator ("N") is the sum of all unique patients who responded over the course of their follow-up period. Not all women responded at all follow-up visits.

^bSymptom reported at all visits during the follow-up period. The denominator ("N") is the total number of unique women responding at the latest follow-up visit.



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