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V. D. 8. CONCLUSIONS

10. DISCUSSION AND OVERALL CONCLUSIONS

Female sterilization is one of the safest, most effective, and most cost-effective contraceptive methods, providing permanent contraception in a one time procedure involving mechanical or surgical intervention to block the tube fallopian. Prior to the mid 1970's, female sterilization was only available to women undergoing laparotomy and carried significant surgical risk. The introduction of new, safer surgical approaches to access the tubes (minilaparotomy and laparoscopy for interval sterilization) dramatically influenced the uptake of sterilization as a popular contraceptive option. For the past 20 years, the most common methods of female sterilization in the United States have been interval tubal sterilization using a laparoscopic approach or post-partum tubal sterilization using a subumbilical minilaparotomy approach. An estimated 50% of the 700,000 female sterilizations performed annually in the US are interval sterilization procedures.

Although both minilaparotomy and laparoscopy can be provided under local anesthesia, general or regional anesthesia is used in the majority of cases in the US today. Minilaparotomy requires a 2-5 cm subumbilical (post-partum) or suprapubic abdominal incision. Laparoscopic abdominal entry requires a blind insertion of the Verres needle for insufflation with inert gas followed by blind insertion of a sharp trocar. General anesthesia risks are exacerbated by its use post-partum and during laparoscopy. Major laparoscopic sterilization complication rates vary by study but range from 0.9% to 1.6% and include life threatening hemorrhage and viscus perforation.⁶⁸

Due to the attendant risks and limitations of surgical sterilization methods, various non-incisional methods have been developed. In 2002, the U.S. FDA approved the Essure[®] microinsert device for interval tubal sterilization. This device is placed transcervically through a hysteroscope, and may be placed in the office under local anesthesia. The approval of this product represented a significant change in the array of sterilization options available to women, and was a positive change in providing a less invasive choice. For many otherwise healthy women of reproductive age, the risks associated with the traditional surgical sterilization procedures were too high. Also, this less invasive transcervical method is highly effective and so the combination of improved safety coupled with high efficacy makes it an attractive alternative for risk averse women.

This first generation transcervical device does, however, carry some more indirect risk associated with use. The Essure[®] coil contains nickel. Nickel allergy is more common in women and appears to be increasing in the general population.^{69,70} The Essure[®] coil is also permanent and removal for uncommon, but reported, complaints of pain following successful cornual placement requires a significant surgical procedure. The Essure[®] coil has a reported perforation rate of 1.1%, and often requires surgical intervention for removal. In addition, the risk of post sterilization regret is known to range from 6-20% in women of reproductive

⁶⁸ Peterson, H., Pollack, A., Warshaw, J.S. 2006. Tubal Sterilization. In Rock, J.A., Jones, H.W. (eds), TeLinde's Operative Gynecology, tenth edition. Philadelphia: Lippincott Williams & Wilkins Publishers

⁶⁹ <http://www.mayoclinic.com/health/nickel-allergy/DS00826/DSECTION=4>

⁷⁰ Kerusuo H, Kullaa A, kerusuo E, et al. Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears. Am J Orthod Dontotac orthap 1996; 109: 148-54

age.⁷¹ The tail coils of the Essure[®] device leave a foreign body extending into the uterus and represent unknown risk to the patient desiring fertility treatment following a life-change and subsequent regret. The significance of this unknown risk should not be underestimated.

To provide patients with an alternative, highly safe, effective, accessible, and widely acceptable female sterilization option, the Adiana System was developed as the next generation transcervical device. The intention was to further improve the safety profile of the transcervical device such that barriers were decreased for use in the general population. The Adiana System can be placed in the office setting without the use of general or regional anesthesia. There have been no reported complications including aberrant burns or uterine or tubal perforations related to the delivery of the low-level RF energy or placement of the Matrix.

The EASE study was undertaken to evaluate the safety and demonstrate the efficacy of the Adiana System in the prevention of pregnancy. The specific objectives of this study were: 1) to assess the safety and demonstrate the efficacy of the Adiana System for transcervical sterilization over a 12-month wearing period; and 2) to describe the device placement rates, safety of device placement and wearing, and patient satisfaction and comfort with device placement and wearing.

Seven hundred-seventy (770) patients were enrolled in the study and treatment was attempted in 645 patients. Of those patients, bilateral placement success was achieved in 611 (94.7%). Six hundred-four (604) of the 611 patients were evaluated for occlusion by HSG and 570 patients demonstrated bilateral occlusion. Thus, 88.4% of the patients in whom treatment was attempted achieved final treatment success and were able to begin reliance on the Adiana System.

During the one-year follow-up period, there were six pregnancies: three were attributable to physician error (misinterpretation of HSG results) and the remaining three were due to method failure. Excluding failures attributed to known HSG misinterpretations, the one-year pregnancy prevention rate (derived from life-table methods) is 99.5%, with a single-sided, lower confidence bound of 99.0%. The one-year pregnancy prevention rate including all pregnancies for the Adiana System is 98.9% with a single-sided, lower confidence bound of 98.2%. Both of these outcomes exceed the pre-planned threshold set for demonstration of efficacy in the primary endpoint.

In order to further evaluate the pregnancy prevention rates observed for the Adiana System, a comparison to the six alternative methods reported in the CREST study was conducted. The results of the comparison showed that the Adiana System is statistically comparable at one, two, and three years to the combined results from all methods as well as to the combined results from all 'comparable methods' reported in the CREST study (excluding post-partum salpingectomy and unipolar coagulation procedures). Separately, the Adiana System also was shown to be comparable to methods reported after the publication of the CREST study. These methods specifically included the Filshie Clip and the Essure[®] method.

⁷¹ Hillis SD. Marchbanks PA. Tylor LR. Peterson HB. Poststerilization regret: findings from the United States Collaborative Review of Sterilization. *Obstetrics & Gynecology*.1999; 93(6):889-95.

There were no uterine or tubal perforations reported during the Adiana treatment procedures. There were also no reports of aberrant burns, nor other injuries related to the delivery of RF energy and matrix placement within the fallopian tubes. Additionally, there were no reports of excessive pain or bleeding due to the device. There have been no reported allergic or adverse reactions to the implants, no signs of infection related to the implants, and no need for implant removals.

Over the course of the trial thus far, 49 serious adverse events have been reported in 41 patients; no patients have died. In addition to one case of procedure-related hyponatremia, three additional events were considered device-related (two ectopic pregnancies and one endometrial polyp resection). Of these four procedure- or device-related serious adverse events, two were resolved with medication (hyponatremia with Lasix, and one ectopic pregnancy with Methotrexate), and the remaining two required surgical intervention (an ectopic pregnancy salpingectomy and the endometrial polyp resection). It should be noted that fluid overload (i.e. hyponatremia) and ectopic pregnancy events are known complications of hysteroscopic and sterilization procedures. Thus, these events were not unexpected, had a low incidence rate, and did not represent an unknown or unreasonable risk to the patient. Also, the observed ectopic pregnancy rate was within the range expected for a post-sterilization population. Sterilization remains protective against ectopic pregnancy compared with the non-contracepting population.

In this study, patients overwhelmingly reported satisfaction with the Adiana System throughout short and long-term follow-up including more than 16,000 patient-months of device wearing. The simplicity of the procedure with rare reported complications, the rapid return of the patient to daily activity, low incidence of patient reported symptoms, along with the mild severity of the majority of these symptoms, indicates that the Adiana Procedure and the wearing of the devices are exceptionally well-tolerated and accepted by patients.

No contraceptive method is perfect and in most cases individuals are required to weigh the range of safety risks against the range of efficacy for different methods. Personal preference and risk aversion often dictate this choice within a general range of safety and efficacy. Many women choose user-dependent hormonal methods despite lower typical-use efficacy rates because of the impact on their menstrual cycle, while many other women are averse to hormone use because of safety concerns. To many, the Levonorgestral IUD seems a perfect long acting reversible contraceptive option with non-contraceptive benefits; however, many women do not want a foreign body in the uterus. For many women, barrier methods are a necessity, while for others that is not an option unless paired with a more highly effective contraceptive method. Surgical procedures have long been a recognized barrier to wider use of both female and male sterilization. In all of this, the notion that there can be a "perfect" contraceptive method is flawed because all women juggle different needs at different times in their own lives.

The Adiana System, a second generation transcervical sterilization device will provide an alternative choice for women who seek a minimally invasive, highly safe and effective single procedure to terminate their fertility -- one that does not require abdominal surgery, carries no associated user risk, and will leave the intrauterine cavity device free. These advances

warrant access for women seeking new and improved alternatives to currently available contraceptive options.

In conclusion, the results of this study demonstrate that the Adiana System is highly safe and effective for pregnancy prevention. Further, the required treatment procedure has a high degree of placement success; patients overwhelmingly reported satisfaction with the Adiana Procedure; and remained satisfied with the Adiana System throughout short and long-term follow-up including more than 16,000 patient-months of device wearing.

**V. D. 9. TABLES REFERRED TO BUT NOT
INCLUDED IN THE TEXT**

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