

ESSURE®

**Obstetrics and Gynecology Devices
FDA Advisory Committee Meeting**

September 24, 2015



ESSURE®

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FDA Advisory Committee Meeting**

September 24, 2015



CN-1

Sponsor Presentation

Clinical Need

Essure Overview

FDA Topics of Interest

Edio Zampaglione, MD, FACOG

VP, US Medical Affairs,
Women's Healthcare + Neurology
Bayer HealthCare

Real World Clinical Experience

Cindy Basinski, MD, FACOG, FPMRS

Private Practitioner,
Educator, Researcher

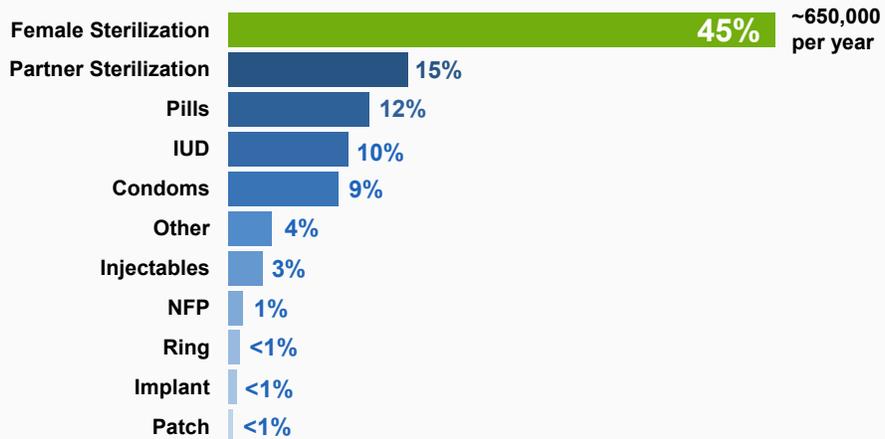
Benefit / Risk Summary

Patricia Carney, MD, FACOG

Director, US Medical Affairs,
Women's Healthcare
Bayer HealthCare

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Completion of Childbearing and Current Contraceptive Method (N=20.6M)



Secondary analysis adapted from the 2011-2013 National Survey of Family Growth, Centers for Disease Control and Prevention.

CN-3

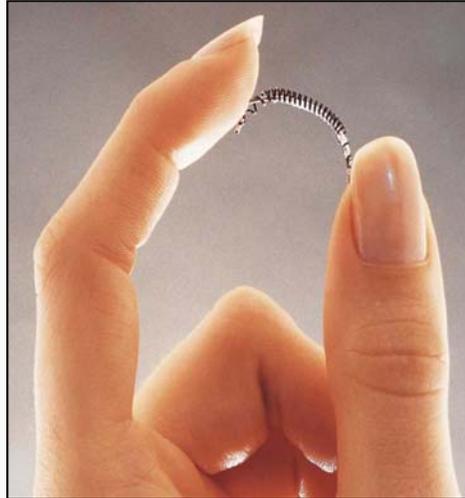
Essure®

- Essure System is a Class III, PMA device, in US
 - FDA approval on November 4, 2002 (P020014)
- Commercially available in US, Canada, Europe, Australia and several Latin American and Asian countries
- Approximately 1 million Essure Systems* distributed worldwide

*Each system contains two inserts and two delivery catheters

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Essure Insert



CN-5

Essure Procedure

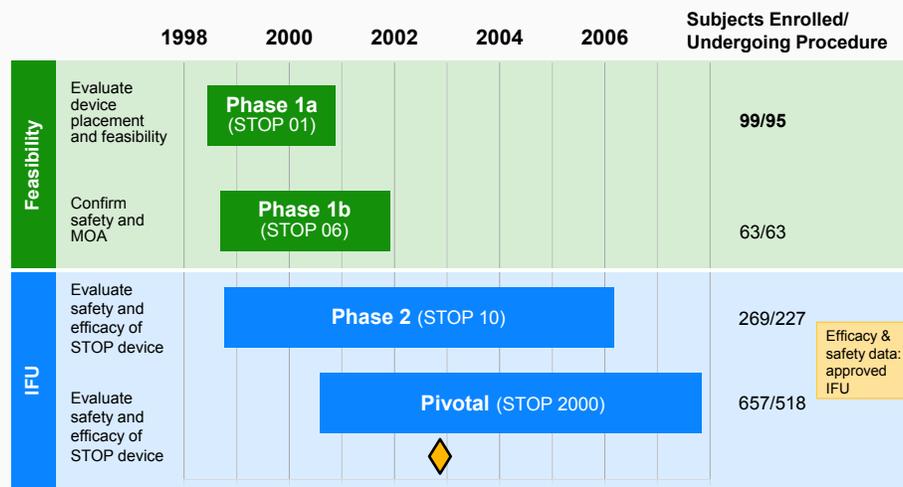


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Essure Clinical Development Program

CN-7

Clinical Studies Supporting Original PMA



STOP = Selective Tubal Occlusion Procedure

CN-8

Essure Design Refinements

STOP/
ESS205

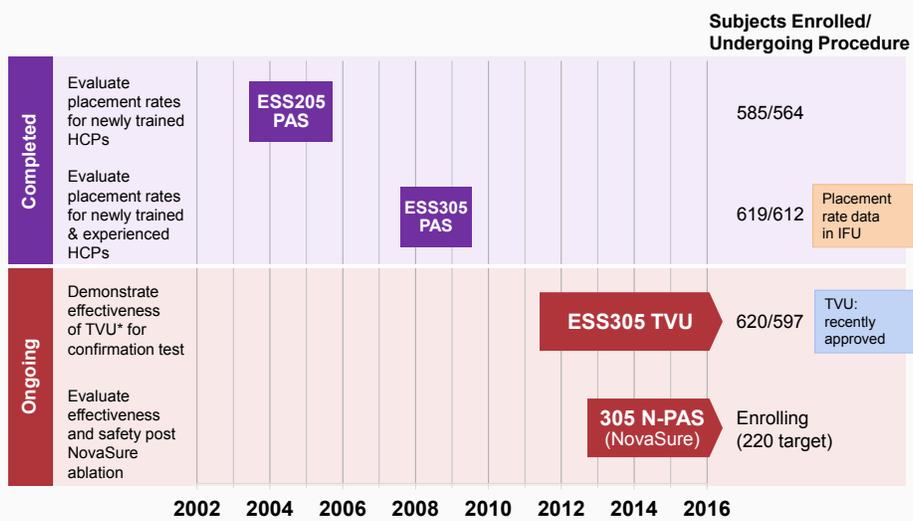


ESS305



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Post Approval Studies



*Transvaginal ultrasound study being followed for ten years

CN-10

SUCCES II: Survey on Use and Characteristics of Definitive Contraception with ESsure (N=2600)

- Prospective, non-interventional, multi-center and observational single arm study (procedure, month 3 and years 1,2 and 5)
- Recruitment 2008-2011, 5 years observational period, ongoing
- Primary objective: assessment of patient satisfaction at 5 years
- Secondary objectives includes assessment of complications

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SUCCES II Interim Analysis Bleeding and Pain (Including 3 Month Visit)

	Cases Reported n/N (%)
3 Month Post-procedure Visit	
Question: "Postoperative pain/cramps" Y/N? at <u>3-months</u> follow-up	542/2281 (22.8)
Question: "Postoperative bleeding" Y/N? at <u>3-months</u> follow up	382/2281 (16.7)
2 Year Contact	
Abdominal/pelvic pain reported at later time point as an AE at <u>2-year</u> follow-up	59/1219 (4.8)
Bleeding reported at later time point as an AE at <u>2-year</u> follow-up	165/1219 (13.5)

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Adverse Events of Interest Pivotal Study vs SUCCES II (Interim Results)

Adverse Event of Interest	Pivotal Study %	Women Reaching 2-year Follow-up N=1219 %
Unintended pregnancy	None	0.41
Perforation/migration	1.1	2.5
Expulsion	2.9	0.7
Infectious complications	1.0	0.6
Allergic reactions	0	0.16

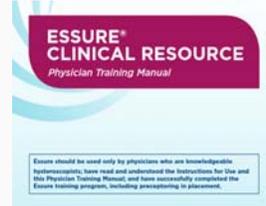
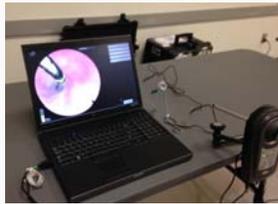
CN-13

Summary of Clinical Data

- 2,676 women have undergone placement procedures in clinical development studies
 - 557 women completed 5 years of follow-up
 - Pivotal and Phase 2 studies
 - 493 women in ongoing 10-year TVU follow-up study
- In addition, SUCCES II enrolled 2600 women with a 5-year planned follow-up
- Efficacy and safety profile consistent across the clinical data

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Essure Physician Training Program “Clinical Pathway”



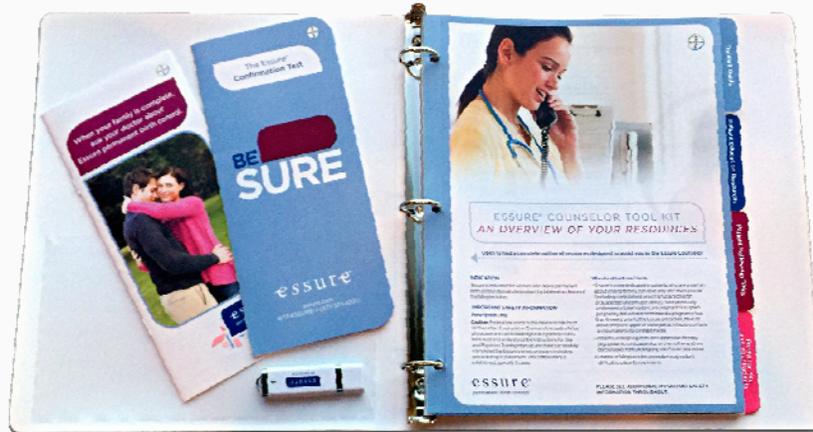
CN-15

“Clinical Pathway” Three Steps

1. Didactic Portion:
 - Essure overview:
 - Appropriate patient selection (per IFU) and counseling
 - Indications, contraindications, warnings and precautions
 - Placement steps and the Confirmation Test
 - Clinical trial data
 - Provide comprehensive training manual: “Clinical Resource”
 - Demonstration video of Essure procedure
2. Computer simulator and/or silicone uterine model
3. Perform ≥ 5 supervised Essure procedures prior to completion of Clinical Pathway and Certification of Completion

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Additional Training: Office Staff



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Additional Training: Advanced Workshop



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Additional Training: Radiology Training



THE ESSURE® CONFIRMATION TEST

A GUIDE FOR
RADIOLOGISTS &
OB/GYNs

INDICATION
Essure is indicated for women who desire permanent birth control (female sterilization) by bilateral occlusion of the fallopian tubes.

IMPORTANT SAFETY INFORMATION
Prescription Only

Caution: Federal law restricts this device to sale by or on the order of a physician. Device to be used only by physicians who are knowledgeable hysteroscopists have read and understood the Instructions for Use and Physician Training manual, and have successfully completed the Essure training program, including preoperating requirement until competency is established, typically 9 cases.

Who should not use Essure

- Essure is contraindicated in patients who are uncertain about ending fertility, can have only one insert placed (including contralateral proximal tubal occlusion or surgical unilaterally absent), have previously undergone a tubal ligation, are pregnant or suspect pregnancy, delivered or terminated a pregnancy less than 6 weeks prior to the Essure procedure, have an active or recent upper or lower pelvic infection, or have a known allergy to contrast media.
- Patients undergoing immunosuppressive therapy (e.g. systemic corticosteroids) or chemotherapy are discouraged from undergoing the Essure procedure.
- Uterine or fallopian tube anomalies may make it difficult to place Essure inserts.

PLEASE SEE ADDITIONAL IMPORTANT SAFETY INFORMATION ABOUT ESSURE ON NEXT PAGE.

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Evaluating Insert Location

Distance from the filled uterine cornua to the proximal end of the inner coil can be measured in several ways:

- Using the inner coil as a point of reference. The inner coil measures 30 mm in length (most commonly used method)
- Calipers
- Using the distal 2 markers as a measuring reference point. The distance between the 2 distal markers measures 5 mm

Note the 4 radiopaque markers and inner coil length. The inserts are symmetrical with a normal curvature. Ideal insert location is when the inner coil crosses the uterotubal junction. Note that the distal markers are fixed in relation to one another, but the proximal markers may move or seem stretched because of the flexibility of the outer coil.

Note: The insert may shift in response to fallopian tube movement following placement.

Satisfactory location
A satisfactory location is defined as the distal end of the inner coil being within the fallopian tube with <math>< 50\%</math> of the inner coil trailing into the uterine cavity. Of the proximal end of the inner coil being <math>< 30</math> mm into the tube from where contrast fills the uterine cornua.



Satisfactory bilateral insert location and fallopian tube

Figure 10 **Figure 11** **Figure 12**



Note the normal curvature and symmetrical appearance of both inserts

PLEASE SEE IMPORTANT SAFETY INFORMATION ABOUT ESSURE® ON PAGE 31.

<http://www.hcp.essure-us.com/resources/you/> CN-19

Additional Training: Residency Training Programs

- Module 1: Sterilization
- Module 2: Hysteroscopy
- Module 3: Clinical Data
- Module 4: Device and Procedure
- Module 5: Essure® Confirmation Test
- Module 6: Patient Identification and Counseling

Patient Identification: Contraindications

Essure® is contraindicated in women who:

- Are uncertain about ending fertility
- Can have only one insert placed (including contralateral proximal tubal occlusion or unilateral unilaterally absent)
- Have previously undergone a tubal ligation
- Are pregnant
- Delivered or have an ectopic pregnancy
- Have a history of pelvic infection

Visualization of the Tubal Ostia With a 30° Hysteroscope



Radiographic Markers



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Physician Support Services

- Proctor Program
 - Peer to peer training with experienced Essure physicians
- National Consultancy Network
 - Peer to peer consulting with Essure experts
 - Case-specific questions or advice sought
- Physician Inquiry Requests (PIRs)
 - Medical information department
 - Recorded and tracked

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Topics of Interest

CS-22

Postmarketing Monitoring

- Amount of postmarketing reporting has increased over time
- Disproportionate increase in non-medically confirmed cases
 - Coincides with acquisition of Conceptus by Bayer
 - Attention in social and traditional media
 - Bayer “active listening” and “outreach” programs

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Topics

- Efficacy
- Unsatisfactory location
- Pain (persistent/chronic)
- Allergic reaction/hypersensitivity (to nickel)
- Device removal
- Death
- Pregnancy outcomes

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Contraceptive Efficacy of Essure Clinical Trials

Cumulative Failure Rates

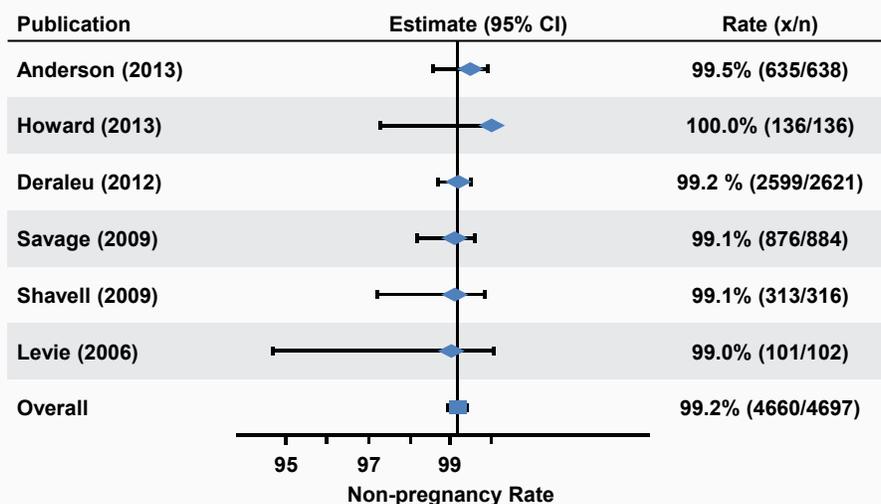
	Phase 2	Pivotal	Combined	ESSTVU
	0%	0%	0%	0.67%*
1 year	N=193	N=441	N=634	N=547
(CI)	(0-0.35%)	(0-0.19%)	(0-0.12%)	(0.16-1.53%)

*Four pregnancies occurred in the TVU study:

- 2 due to perforation
- 2 due to unsatisfactory device location

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Contraceptive Efficacy of Essure Literature (US Studies)



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Contraceptive Efficacy of Essure

Postmarketing Monitoring

- Postmarketing reporting frequency of pregnancy is 0.21%
 - Includes pregnancies occurring within the first 3 months after placement and in women without, or with unsatisfactory, confirmation tests

Conclusion

- No method of contraception is 100% effective
- Pregnancies with Essure in place have been reported in the commercial setting and literature
- Patient compliance with 3-month alternate contraception as well as obtaining the confirmation test, are important factors to prevent unintended pregnancies*
- Data are consistent and confirm an efficacy >99% when in proper location

*Essure Instructions for Use, Bayer HealthCare Pharmaceuticals, 2012

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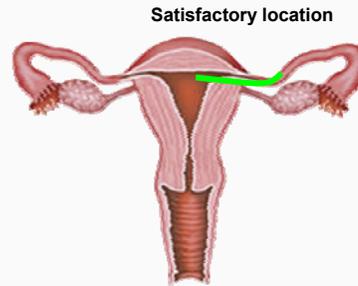
Topics

- Efficacy
- Unsatisfactory location
- Pain (persistent/chronic)
- Allergic reaction/hypersensitivity (to nickel)
- Device removal
- Death
- Pregnancy outcomes

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Satisfactory Location

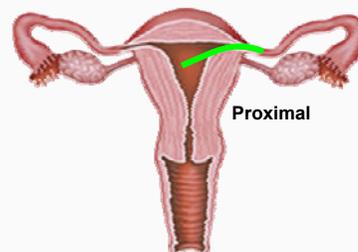
- Satisfactory location spans the interstitial segment of the fallopian tube



CS-29

Unsatisfactory Location: Proximal

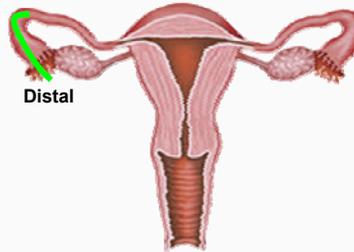
- Satisfactory location spans the interstitial segment of the fallopian tube
- Unsatisfactory locations:
 - Insert not sufficiently far into the tube (e.g. too much of insert is in uterine cavity)
 - Could lead to expulsion



CS-30

Unsatisfactory Location: Distal

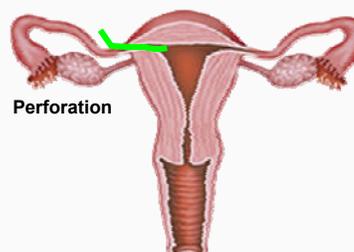
- Satisfactory location spans the interstitial segment of the fallopian tube
- Unsatisfactory locations:
 - Insert advanced too far into tube



CS-31

Unsatisfactory Location: Perforation

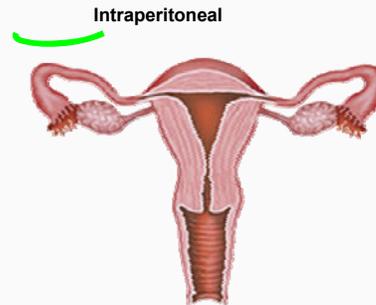
- Satisfactory location spans the interstitial segment of the fallopian tube
- Unsatisfactory locations:
 - Perforation



CS-32

Migration

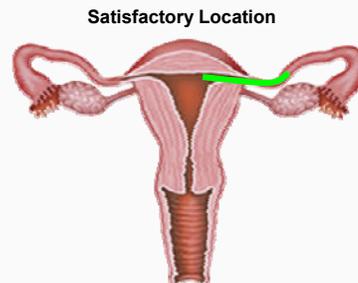
- Satisfactory location spans the interstitial segment of the fallopian tube
- Unsatisfactory locations:
 - Distal
 - Perforation



CS-33

Satisfactory Location

- Satisfactory location spans the interstitial segment of the fallopian tube
- Migration after confirmation of satisfactory location is unlikely



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Reasons for Unsatisfactory Location Clinical Trials

Study	Women with Placement Attempt n	Women with Perforation n/N (%)	Women with Expulsion n/N (%)	Unsatisfactory Device Location n/N (%)	Total Unsatisfactory Location n (%)
Phase 2	227	7 ^a /206 (3.4)	1/206 (0.5)	1/206 (0.5)	9 (4.4)
Pivotal	507	5/476 (1.1)	14/476 (2.9)	12/476 (2.5)	31 (6.5)
ESSTVU	594	2/587 (0.3)	3/587 (0.5)	7/587 (1.2)	12 ^b (2.0)

^a Support wire that has since discontinued was used in 5 of 7 cases

^b Does not include 25 subjects lost to follow-up and did not undergo confirmation testing. May include patency seen on HSG

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Unsatisfactory Location

Literature

- Abdominal pain was most commonly reported symptom of perforation, though most are asymptomatic
- Range of perforation rates
 - Retrospective study of 4,306 women in Spain reported 0.02%¹
 - Retrospective study of 610 women in Canada reported 3.6%²

¹Povedono, et al 2012

²Thiel et al, 2011

CS-36

Unsatisfactory Location

Postmarketing monitoring

- Majority of cases are medically confirmed
- Reporting for all unsatisfactory locations ~ 0.4%

Conclusion

- Unsatisfactory location is a known complication and described in the IFU and PIB
- Postmarketing data and analyses support a low incidence as found in the clinical trials
- Recognition and management are a focus of the physician training program

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Topics

- Efficacy
- Unsatisfactory location
- Pain (persistent/chronic)
- Allergic reaction/hypersensitivity (to nickel)
- Device removal
- Death
- Pregnancy outcomes

CS-38

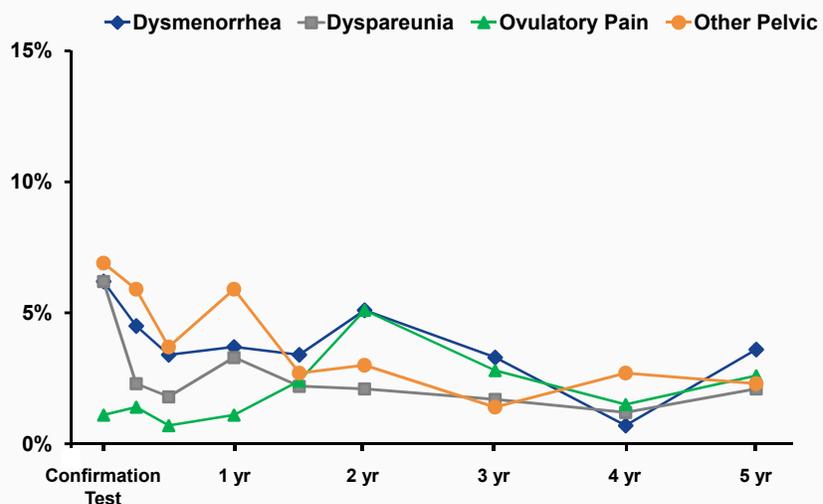
Pain (Persistent/Chronic)

- Chronic pelvic pain is a common gynecologic problem
 - Estimated prevalence ranges from 3.5% - 26.6%^{1,2}
- Short-term pain/discomfort is expected with Essure placement procedure
 - Any patient with unexpected or prolonged pain must be evaluated

¹Myers, DL, 2007
²Ahangari 2014

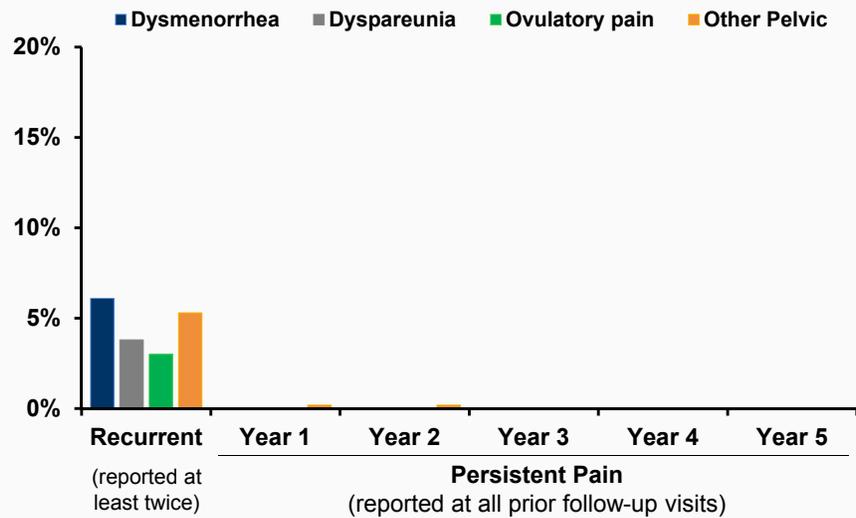
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Pelvic Pain During Follow-up Pivotal Trial



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Recurrent/Persistent Pelvic Pain Pivotal Study



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Pain (Persistent/Chronic) Incidence Literature (US Studies)

Author & Study Design	n	Pain	%
Retrospective cohort study (2005-2012), US ¹	458	Chronic pain (lasting >3 months) after procedure	4.2%
Retrospective review – MarketScan database (2005-2012), US ²	26,927	2 diagnoses of pelvic pain on separate days, and ≥2 opioid Rx filled on separate days	0.88%*

*No significant difference between laparoscopic tubal ligation (0.93%) and hysteroscopic sterilization

¹Yunker et al, 2014

²Conover et al, 2015

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Pain (Persistent/Chronic) Postmarketing Monitoring

- Reporting frequency for abdominal, pelvic and back pain is 0.3%
- Medically confirmed cases more frequently reported additional events such as perforation, expulsion or improper placement

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Pain: Conclusions

- Post-procedural pain after Essure placement is expected
- The only published comparative study between BTL and hysteroscopic sterilization reported no difference in pain rates post-procedure
- Improper placement of Essure has been identified as a potential factor for persistent or chronic pain
- Postmarketing data supports the low incidence of chronic or persistent pain noted in the clinical trials

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Topics

- Efficacy
- Unsatisfactory location
- Pain (persistent/chronic)
- Allergic reaction/hypersensitivity (to nickel)
- Device removal
- Death
- Pregnancy outcomes

CS-45

Allergic Reactions/Hypersensitivity: Nickel

- Essure insert consists of a Nitinol (nickel titanium alloy) outer coil and stainless steel inner coil wrapped in PET (polyethylene terephthalate) fibers
- Nitinol has been widely used in medical and dental applications since mid 80's
 - Heart valves, stents, guide wires, orthodontic archwire
- Maximum Essure in vitro nickel leaching rate = 0.14 µg/day¹
 - Other implant devices range from 0.42 – 8.4 µg/day²
 - Normal daily exposure to nickel from food & water: 300 µg/day³
- All biocompatibility testing requirements were met

¹Zurawin RK, Zurawin JL. Adverse Events Due to Suspected Nickel Hypersensitivity in Patients with Essure Micro-Inserts, Journal of Minimally Invasive Gynecology, 2011; 18 (4) p. 475-482.

²<http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM296980.pdf>

³Medical and Biological Effects of Environmental Pollutants, published by the National Academy of Sciences, Washington, D.C., 1975

CS-46

Allergic Reaction/Hypersensitivity: Nickel

Company Sponsored Clinical Trials

- Three of >5000 women reported symptoms consistent with an allergic reaction

External Literature

- Reports of hypersensitivity reactions to nitinol (both for Essure and other devices) are rare^{1,2}
- 2 cases out of 4306 women (0.05%) revealed nickel allergy in a large independent, retrospective Spanish study³
- No correlation between skin patch test results and hypersensitivity outcome has been reported⁴

¹ Peter et al (2011) Thomas P, Thomas M, Sumner B, Dietrich K, Zauzig M, Steinhauser E, Krenn V, Arnholdt H, Flaig MJ. Impaired wound-healing, local eczema, and chronic inflammation following titanium osteosynthesis in a nickel and cobalt-allergic patient: a case report and review of the literature. J Bone Joint Surg Am. 2011 Jun 1;93(11).

² Schram SE, Warshaw EM, Laumann A. Nickel hypersensitivity: a clinical review and call to action. Int J Dermatol. 2010 Feb;49(2):115-25.

³ Povedano B, Arjona JE, Velasco E, Monserrat JA, Lorente J, Castelo-Branco C. Complications of hysteroscopic Essure® sterilisation: report on 4306 procedures performed in a single centre. BJOG. 2012 Jun;119(7):795-9.

⁴ Zurawin RK, Zurawin JL. Adverse Events Due to Suspected Nickel Hypersensitivity in Patients with Essure Micro-Inserts. Journal of Minimally Invasive Gynecology, 2011; 18 (4) p. 475-482.

CS-47

Allergic Reaction/Hypersensitivity: Nickel

Postmarketing monitoring

- Reporting frequency of suspected allergy is approximately 0.06%
- 15% of these reported cases were test or specialist confirmed allergies

Conclusions

- The amount of nickel released from Essure *in vitro* is minimal
- Hypersensitivity to nitinol is rare
 - Less than 0.1% in sponsored and non-sponsored trials
- Despite the rarity, counseling regarding nickel sensitivity is important prior to implanting Essure

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Topics

- Efficacy
- Unsatisfactory location
- Pain (persistent/chronic)
- Allergic reaction/hypersensitivity (to nickel)
- **Device removal**
- Death
- Pregnancy outcomes

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Device Removal

- Inserts are intended to be left in place permanently
- The IFU states: “Do not remove insert(s) unless patient is experiencing an adverse event(s) associated with its presence, or if removal is demanded”¹
- IFU section on removal updated to reflect recent published literature² and case reports³
- Clinical judgment and surgical expertise must be used

1. Essure Instructions for Use, Bayer HealthCare Pharmaceuticals, 2012
2. Brito et al. J Minim Invasive Gynecol. 2015 Jul-Aug;22(5):910-3
3. Arjona et al. J Obstet Gynaecol. 2014 Nov;34(8):712-3.

CS-50

Device Removal Clinical Trials

Essure Device Removal in Clinical Trials

	Phase 2 Study (STOP 10)	Pivotal Study (STOP 2000)	ESS305 TVU (16974)
Total device removals (%)	11/206 (5.3)	20/476 (4.2)	11/587 (2.0)
Number attempted placement	227	507	594
Laparoscopic removal	4	5 ^a	7
Other removal (including cornual resection)	2 ^b	-	-
Removal with hysterectomy	5 3 bleeding and/or pain 2 prolapse	15 ^c 9 bleeding and/or pain 1 Asherman's Syndrome, 1 fibroids, 4 missing	4 1 pain 1 fibroid 1 endometriosis 1 bleeding

Executive summary table 7-17

^a Inserts removed hysteroscopically prior to in vitro fertilization in woman desiring pregnancy, and one removed laparoscopically.

^b Includes one woman with devices removed via cornual resection and one woman with devices removed via laparotomy due to pain

^c 6 with device fragments remaining in situ.

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Device Removal Literature

Mostly case reports

- Hysteroscopic removal up to 7 weeks post-placement
- Linear salpingostomy or salpingectomy
- Laparoscopic salpingectomy up to 4 years post-placement
- Cornual resection (carries higher risk of hysterectomy)
- Localization should be confirmed prior to removal procedure

Lannon, et al, *Fertility and Sterility*, 2007
Langenveld et al, *Fertility and Sterility*, 2008
Albright et al, *Contraception*, 2012
Adelman et al JMIg, 2014

CS-52

Device Removal Postmarketing Monitoring

- Principal reasons for removal
 - Unsatisfactory location
 - Pain and bleeding disturbances
- Reported at a frequency of 0.11%

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Device Removal Conclusion

- The need for Essure removal is infrequent
- When removal is indicated, the least invasive method that can safely be conducted should be performed
 - Clinical studies and literature demonstrate that removal can be accomplished without hysterectomy
 - Removal method depends on anatomical location of insert, symptoms, and other gynecologic pathology
 - Removal is guided by general gynecologic surgical principles
- The specific removal procedure selected involves a discussion between the patient and their physician

Essure Instructions for Use, Bayer HealthCare Pharmaceuticals, 2012

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Topics

- Efficacy
- Unsatisfactory location
- Pain (persistent/chronic)
- Allergic reaction/hypersensitivity (to nickel)
- Device removal
- **Death**
- Pregnancy outcomes

CS-55

Death

	Clinical Trials	Literature	Postmarketing Monitoring
Number	2	0	7
Related	0		Associated with the procedure only
Cause	Leukemia, Myocardial Infarction post bypass surgery		<ul style="list-style-type: none"> • Three anesthetic complications which includes the case of suspected air embolism during placement procedure • One case each of cardiac arrest, sleep apnea, Group A strep, pulmonary embolism during a hysterectomy

Conclusion

- Deaths specifically due to the inserts have not been reported
- The risk associated with Essure procedure is low and is in line with laparoscopic tubal ligation fatality risk

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Topics

- Efficacy
- Unsatisfactory location
- Pain (persistent/chronic)
- Allergic reaction/hypersensitivity (to nickel)
- Device removal
- Death
- Pregnancy outcomes

CS-57

Pregnancy Outcomes

Literature

- Limited reporting in the literature on unintended pregnancies

Postmarketing monitoring

- Frequency of reporting of events within the expected range for the population of similar age

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Pregnancy Outcomes

IVF Literature

- Desired pregnancies are carefully followed and outcomes well documented in IVF procedures
- Large systematic review¹ identified 11 studies of 115 women using Essure off-label during IVF
 - 54 pregnancies
 - Pregnancy rate of 39% per embryo transfer
 - Live birth rate per embryo transfer 29%
- Comparisons to salpingectomy in the same setting, have shown comparable pregnancy rates and outcomes²

Conclusion

- No evidence that Essure increases the risk of adverse fetal outcomes (e.g.: miscarriage, stillbirth, PPRM, preterm delivery, fetal anomalies)

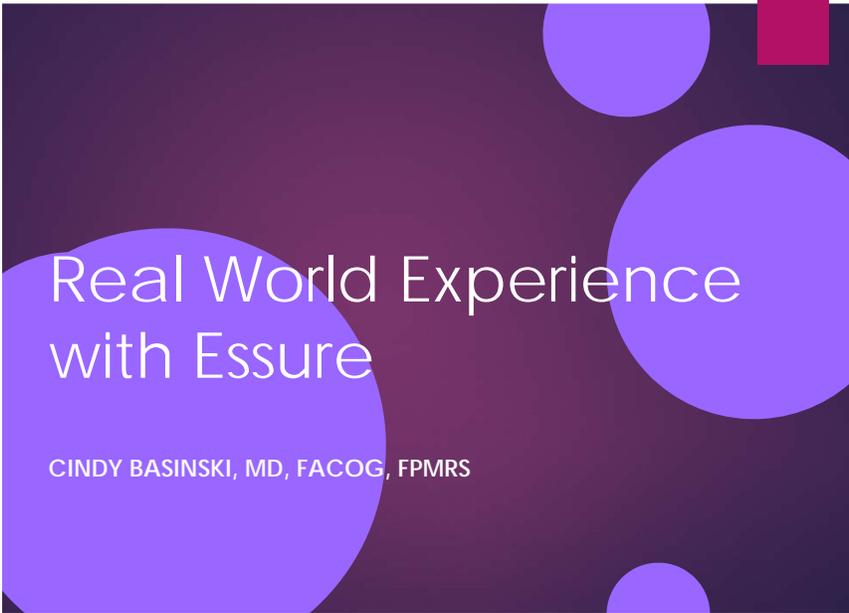
¹Aurora et al, 2014
²Ozgun et al, 2014

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ESSURE Research

- Over a decade of research
- Over 10,000 women
- Safety and efficacy of ESSURE consistent across:
 - Clinical development
 - Independent literature
 - Postmarketing surveillance
- Ongoing studies continue to follow >3000 women

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Real World Experience with Essure

CINDY BASINSKI, MD, FACOG, FPMRS

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Financial Disclosures

- ▶ Paid consultant for: Bayer, Inc.; Hologic, Inc.; Channel Medical Systems
- ▶ Primary Investigator for FDA premarket and post market trials for: Bayer, Hologic, Minerva Surgical, AEGEA, Gynesonics

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My Experience

- ▶ Private practice physician in a small community since 1999
- ▶ Urogynecology/minimally invasive procedures with a focus on in-office procedures
- ▶ Performing in-office procedures for the past 9 years since 2006
- ▶ 1100 Essure procedures
- ▶ Educating physicians, allied health personnel, students since 2007
- ▶ Involved with American Medical Association and hysteroscopic sterilization procedures

CR-63

My Experience

- ▶ Research
 - ▶ FDA Trials for new in-office technologies
 - ▶ Review of patient outcomes
 - ▶ Publishing data
- ▶ Comprehensive review of 1024 patients over 8 years
 - ▶ 1732 women years of follow-up with average 1.7 years (0-8 years)
 - ▶ 94.4% intent-to-treat reliance rate
 - ▶ 9 perforations/6 expulsions
 - ▶ 1 patient request removal due to pain
 - ▶ No allergic reactions or autoimmune symptoms reported
 - ▶ 2 luteal phase pregnancies

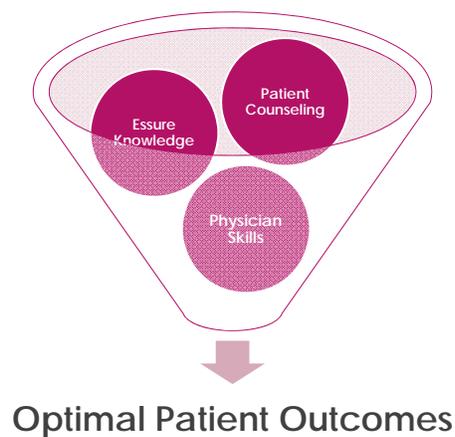
CR-64

Need for Contraceptive Options

- ▶ **Other options unacceptable**
 - ▶ Hormonal methods
 - ▶ IUD
 - ▶ Operative tubal ligation
- ▶ **Essure offers an important option**
 - ▶ Many women have chosen this option worldwide
 - ▶ Non-hormonal and permanent
 - ▶ No general anesthesia, no incisions
 - ▶ Private, in-office setting

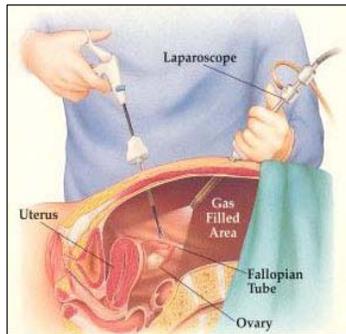
CR-65

Real World Use

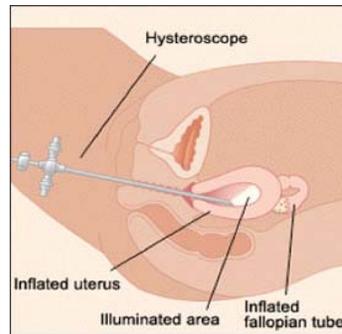


CR-66

How is laparoscopy different from hysteroscopy?



Laparoscopy



Hysteroscopy

CR-67

Physician Education



CR-68

Physician Education Industry Contribution

- ▶ **Basic hysteroscopic skills**
 - ▶ Residency
 - ▶ Experienced partners
 - ▶ Courses through OBGYN organizations
 - ▶ ACOG, AAGL, SLS, etc.
 - ▶ **Industry sponsored opportunities**
 - ▶ Seminars co-sponsored by hysteroscopic companies and Conceptus Bayer by expert physicians knowledgeable in operative hysteroscopy
 - ▶ **Bayer Clinical Pathway**

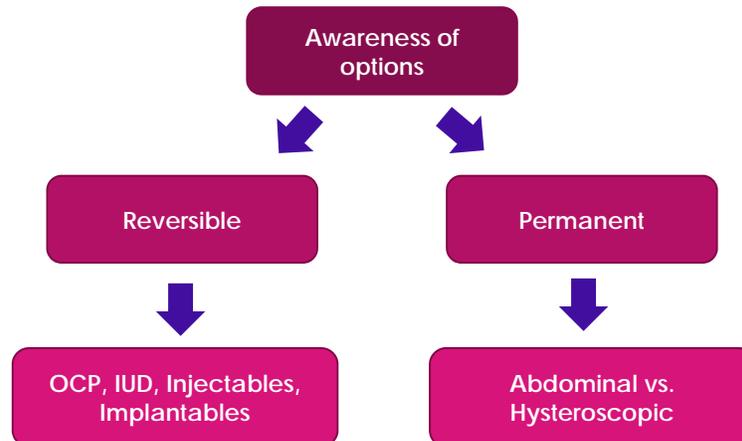
CR-69

Physician Education

- ▶ **Additional peer-to-peer education**
 - ▶ Bayer Consultancy Network
 - ▶ Proctoring Program
 - ▶ Patient Counseling

CR-70

Patient Counseling



CR-71

Patient Counseling

- ▶ Reliable and accurate data
 - ▶ Benefits
 - ▶ Placement rate
 - ▶ Confirmation testing
 - ▶ Risks/complications
 - ▶ Management options
- ▶ Informed consent

CR-72

Understanding Patient Outcomes

- ▶ Responsibility to continue obtaining data
 - ▶ Industry
 - ▶ Oversight agencies
 - ▶ Organized medicine
 - ▶ Physicians

CR-73

Thank You

CR-74

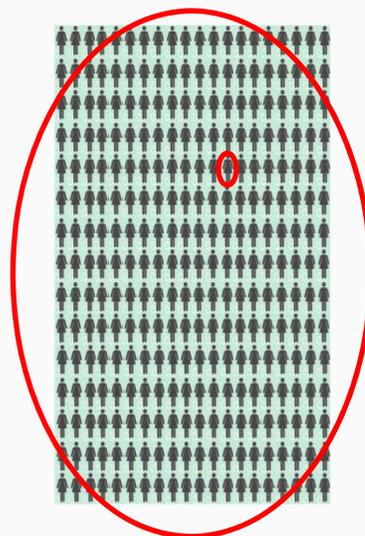
Benefit/Risk Summary

Patricia Carney, MD, FACOG
Director, US Medical Affairs
Women's Health
Bayer HealthCare Pharmaceuticals

CB-75

Translating Population-wide Risks into Individual Risks

- Low rate for a population
- Low rate to an individual
- When an untoward outcome happens, the rate for the affected individual is high



CB-76

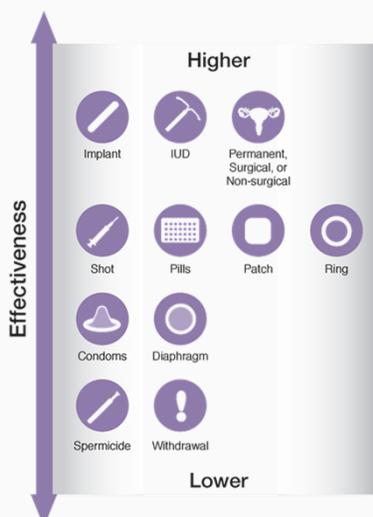
Determining Benefit/Risk Profile

- It is important to take into account all available data when assessing the Benefit/Risk profile
- Must understand the limitations of different data sources
- Must put Benefits/Risk into context with alternative options and/or general population
- Need to assess whether or not particular risks can be appropriately mitigated

ACOG Practice Bulletin 133: Benefits and Risks of Sterilization, 2013

CB-77

Typical Effectiveness of Contraception



Adapted from: WHO. Family Planning: A Global Handbook

CB-78

Once Permanent Contraception is Selected

- Type of procedure selected
 - Factors that may influence selection
 - Patient interests and selection
 - Provider assessment of medical issues if any

CB-79

Patient Selection and Counseling IFU, 2015

XI. Patient Selection and Counseling

Consider risks and benefits as described in Sections VIII and IX

A. Patient selection factors should include:

- Certainty about desire to end fertility
- Evaluation for pelvic infection, cervicitis, undiagnosed vaginal bleeding, anatomical variants and/or uterine pathology that may make patient unsuitable for procedure
- The decision to undergo treatment is at patient discretion, following physician counseling and informed consent
- **IMPORTANT: Counsel patients that this product does not protect against either HIV infection or other sexually transmitted infections**

CB-80

Essure Benefits

- Clinical trials demonstrate high efficacy when properly placed and confirmation test obtained
 - Postmarketing data provides support
- Safety profile was established in the clinical trial program
 - Postmarketing data provides support
- Does not require general anesthesia in most cases
- Does not require entry into peritoneal cavity

CB-81

Essure Risks

- Placement is not always achieved
- Essure inserts contain nickel and potential for allergic reaction
- Essure requires a patient to be compliant with a number of specific steps before she can rely for contraception
- Adverse events include pain, perforation or unsatisfactory device location, menstrual changes, infection, lack of efficacy due to improper placement
- Pregnancy

CB-82

Laparoscopic Tubal Ligation Benefits

- High efficacy
- Immediate effectiveness
- No patient compliance needed

CB-83

Laparoscopic Tubal Ligation Risks

- Bowel injury
- Vascular injury
- Failures (especially ectopic pregnancy)
- Anesthesia complications (aspiration, respiratory dysfunction, cardiovascular dysfunction)

Llarena et al. Am Obstet Gynecol 2015 June; 125(6):1407-17, Escobedo et al. Am J Obstet Gynecol, 1989 Jan;160(1):147-50
Ulker, et al World J Clin Cases. 2014 Dec 16;2(12):846-51, Jamieson, et al Obstet Gynecol. 2000;96:997-1002
Fuller J, Scott W, Ashar B. 2003. Laparoscopic Trocar Injuries: A report from a FDA-CDRH Systematic Technology Assessment of Medical Products (STAMP) Committee: FDA Safety Communication.

CB-84

Laparoscopic Tubal Ligation Risks

Adverse Experiences Reported from Surgical Procedures

Adverse Events (multiple events may be reported per woman)	Filshie Clip N=5454	Hulka Clip, Falope Ring N=3845
Pelvic pain	35.7%	43%
Clip migration or expulsion	0.13%	N/A
Musculoskeletal pain	6.0%	6.1%
Adnexal pain/enlargement/infection	5.0%	6.6%
Incisional inflammation, bleeding, abscess or pain	4.9%	6.3%
Nausea/vomiting	4.3%	4.0%
Keloids	3.9%	5.1%
Headache	3.0%	2.3%
Serious discharge (skin)	2.8%	3.1%
Hematoma	1.0%	0.9%
Misapplication to ovarian ligament, broad or cornual ligament, omentum, bowel, tubal serosa	0.5%	N/A

Filshie Tubal Ligation System. IFU Cooper Surgical 2011

CB-85

Essure Risks

Adverse Events Day of Placement Procedure - Pivotal Trial

Adverse Event/Side Effect	Procedures N=544
Cramping	29.6%
Pain	12.9%
Nausea/vomiting	10.8%
Dizziness/light headed	8.8%
Bleeding/spotting	6.8%
Other	2.9%
Vaso-vagal response	1.3%
Hypervolemia	0.4%
Band detachment	0.4%

Pivotal trial: 657 women initially enrolled; 518 underwent the procedure; 99 changed their minds about participating; 23 did not meet the inclusion criteria and were terminated from study; 17 failed screening tests

CB-86

AEs by Body System, First Year of Reliance* Pivotal Trial: Patients Implanted With at Least One Insert

Adverse Events by Body System	Total=476
Abdominal	
Abdominal pain/abdominal cramps	3.8%
Gas/bloating	1.3%
Musculo-skeletal	
Back pain/low back pain	9.0%
Arm/leg pain	0.8%
Nervous/Psychiatric	
Headache	2.5%
Premenstrual Syndrome	0.8%
Genitourinary	
Dyspareunia	3.6%
Dysmenorrhea/menstrual cramps (severe)	2.9%
Pelvic/lower abdominal pain (severe)	2.5%
Persistent increase in menstrual flow	1.9%**
Abnormal bleeding - timing not specified (severe)	1.9%
Vaginal discharge/vaginal infection	1.5%
Menorrhagia/prolonged menses (severe)	1.1%
Pain/discomfort - uncharacterized:	2.9%

* Only events occurring in $\geq 0.5\%$ are reported

** Eight women reported persistent *decrease* in menstrual flow

In the Phase II trial, 12/206 (5.8%) women with at least one insert reported episodes of period pain, ovulatory pain, or changes in menstrual function.

CI-87

Benefit/Risk Summary

- All permanent birth control procedures carry risk
- Essure's safety profile is well characterized and compares favorably with the risk profile of BTL
- The risks of Essure are appropriately mitigated through:
 - IFU and Patient Information Booklet
 - Educational materials
 - Physician training
 - Support programs
- The assessment concludes that the Benefit/Risk profile of Essure remains positive

CB-88

Thank You

CB-89