1 Introduction and outline of thesis
Hysteroscopic Sterilization
Introduction

Female sterilization, by tubal ligation or tubal occlusion, is the most commonly used method of family planning in the world. Overall, in developed regions 8.1% of women between the ages of 15 and 49 years, married or in a union, currently use female sterilization for contraception, compared with 22.3% of those in less developed regions. More than 180 million couples rely on tubal sterilization for contraception (1). Approximately 75% of these people live in Asia (China and India). The majority of procedures are abdominal, by laparotomy or laparoscopy.

Approximately 50% of all female sterilizations are performed during Caesarean Section or in the puerperal period. The other 50%, which is called “interval sterilization”, is performed at least six weeks after the last pregnancy or delivery (2). Pomeroy in the 1930s made tubal sterilization well known but, because a laparotomy was needed, it was still considered a major procedure. The mini-laparotomy, an abdominal incision of 2-3 cm in length, was first described by Uchida and colleagues in 1961, offered a reduced recovery time and a better cosmetic result (3). Colpotomy, a technique that dates back to the early 19th century, began to attract new interest in the 1970s. Through a small incision in the anterior or posterior vaginal fault a modified Pomeroy technique or fimbriectomy was done. Surprisingly the complication rates in Europe and the US were much higher than those in India and the method was abandoned.

Laparoscopic sterilization

Techniques and settings of sterilization have progressively changed since the 1960s with the introduction of minimally invasive surgery. While in developing countries mini-laparotomy remains the most common approach, in developed countries nearly all interval sterilizations and an increasing proportion of postpartum sterilizations are performed by laparoscopy (4). Various laparoscopic methods have been introduced since 1936. Unipolar coagulation was the first method of laparoscopic tubal occlusion to achieve widespread use. Although highly effective, it was associated with early reports of thermal injuries, including thermal bowel lesions and deaths. In 1972 bipolar electrocoagulation of the tubal isthmus was first introduced, which eliminates the need for a ground plate and was safer for the patient (5). The first laparoscopic sterilization in the Netherlands was performed in Leiden in 1972 by Prof. van Hall (6). Several alternative laparoscopic techniques were introduced in the early 1970s. The elastic rubber band was developed by Yoon. The band is introduced with a specially designed laparoscopic applicator. The application of the band onto a tubal loop is associated with 2-3% incidence of haemorrhage from stretching the vessels underneath the tube or tearing the tube itself (7).
Approximately 3 cm of constricted tube undergoes necrosis. An advantage of the spring/Hulka clip was that it only compresses 3 mm of the mid-isthmus of the tube. As a result, anastomosis for reversal of sterilization is fairly successful. Another technique, described by Filshie and colleagues, uses a silicone rubber-lined titanium clip that is applied to the mid isthmus and must include the entire circumference of the tube (8). The Filshie Clip has been used around the world for the past 20 years and was approved by the Food and Drug Administration in the United States in 1996.

All methods currently in use are highly effective when performed properly, although pregnancy can occur in spite of optimal application. Such failures are often due to tuboperitoneal fistula formation. When pregnancies do occur they are much more likely to be ectopic than pregnancies during use of other methods or when no method is used. The risk of pregnancy persists during the fecund period and it is therefore important to consider the long-term cumulative probability of pregnancy with any contraceptive method -or methods- over time. Unfortunately there are no controlled trials comparing the different laparoscopic techniques with a follow-up period long enough to provide evidence on long term failure rates (1,9). Pregnancies can and do occur even many years after sterilization, as has been documented by the U.S. Collaborative Review of sterilization (CREST study) (10) in which pregnancies occurred in the 10 years after each of the four methods of laparoscopic sterilization studied (unipolar coagulation, bipolar coagulation, silicone rubber band application, and spring clip application). An analysis of the experience of 10,685 women followed prospectively for up to 8 to 14 years in the CREST study identified 143 sterilization failures (pregnancies other than luteal phase pregnancies) and found that the risk of pregnancy after sterilization varied by age at sterilization and method of tubal occlusion. The 10-year cumulative probability of pregnancy was low for most women aged 34-44 years at sterilization but was as high as 5% for women aged 18-27 years with two methods (bipolar coagulation and spring clip application). Another noteworthy finding from this analysis is that the risk of pregnancy accumulated over time. The timing of sterilization failures varied by method; for example, a high proportion of pregnancies after clip application occurred in the first three years after the procedure, whereas pregnancies after bipolar coagulation occurred at approximately the same rate year after year. A total of 47 (32.9%) of the 143 pregnancies identified were ectopic. The cumulative probability of ectopic pregnancy, like that for pregnancies overall, increased over time and varied by method of occlusion and age at sterilization (11).

The findings from this review of sterilization techniques should be interpreted with some precaution, keeping in mind that they were based on procedures performed more than 20 years ago and that a substantial number of the procedures were performed shortly after the introduction of laparoscopic sterilizations in the USA.
A subgroup analysis of women undergoing bipolar tubal coagulation showed that the cumulative failure rate during the period 1978 – 1982 (19.5 per 1,000) was three times higher than during the period 1985 – 1987 (6.3 per 1,000). In addition, those women who had three or more sites coagulated had a very low probability of pregnancy (3.2 per 1,000) compared to women with fewer sites coagulated (12.9 per 1,000).

The Filshie Clip was not available in the United States until 1996 and was not included in the U.S. Collaborative Review of sterilization. However, published data suggest that the clip is, like the other methods of tubal occlusion, highly effective. Four studies from the Family Health International (FHI) were designated pivotal evaluations: all were prospective, randomised and multicenter investigations of interval sterilizations. A 12-month cumulative pregnancy rate of 0.1-0.2 per 100 women for the Filshie Clip were reported (12). Long-term follow-up data for the Filshie Clip such as those obtained by CREST are limited. A five-year follow-up study from Kovac and Krins involving 30,000 women revealed a failure rate of 73 per 30,000 (2.4 per 1,000) (13).

**Hysteroscopic sterilization**

The idea of utilising hysteroscopy for tubal occlusion goes back for more than a century. In the last 100 years transcervical approaches were studied and promoted during four separate periods, beginning in the early 1920s. During World War II, in 1942, Clauberg started his criminal research in Auschwitz on thousands of imprisoned Jewish and Gypsy women, looking for a cheap and efficient method to sterilise women. He injected acid liquids into their uterus without the use of anaesthetics. After the war Lindemann continued sterilization experiments with the Claubergs technique of coagulating the fallopian tubes (14). The fourth period started at the beginning of this century (15). Hysteroscopic sterilization techniques have been sought because they avoid the risks of the laparoscopic route, they allow women a quicker return to normal activities and are especially useful in women for whom laparoscopy is contraindicated. The methods for tubal closures include chemical applications, mechanical devices and thermal methods where electrosurgery, cryocoagulation, radiofrequency and laser are used.

**Thermal**

In 1934 the first hysteroscopic sterilization with electrocoagulation was performed in two patients. Both procedures were unsuccessful. In the 1970s an overall bilateral tubal occlusion rate of 83% was achieved, but pregnancies including ectopics were reported (16). Finally the method did not prove to be reliable and suffered from serious complications due to bowel injury (17). Other methods with cauterization of the tubal openings have not been developed further (18,19,20).
**Chemical**

Quinacrine sterilization is used in many developing countries because of good results and low costs. The technique requires two insertions of quinacrine into the uterine cavity. This can be done “blind” or by hysteroscopic guidance and direct tubal instillation by a specially developed catheter (21). The procedure is reported to have a 1-2% failure rate, although the rates for ectopic pregnancy and serious complications are equal to or less than those for transabdominal sterilization (22,23,24). Drawbacks from the procedure include the need for multiple applications and the problem of reliably confirming tubal occlusion. An HSG is not recommended, because of the risk to blow out the delicate occluding scars (25). The need to make this procedure simple, safe, inexpensive and thereby more acceptable, even in countries with limited surgical facilities is well recognized. Use of quinacrine pellets has become the most widely adopted method of non-surgical female sterilization (26). The Family Health International has recently decided not to pursue further research on quinacrine, partly because of the relatively high pregnancy rates after quinacrine compared to other contraceptive methods (27). The 10-year pregnancy probability is approximately four times higher than after laparoscopic tubal sterilization (bipolar coagulation) as reported by CREST.

**Mechanical**

To avoid the risk of complications many different device were developed and have been tried during the second half of the last century. Most of the devices were unsuccessful (24). Three devices became commercially available and were introduced on the European Market.

**Ovabloc Intra-Tubal Device**

The concept of blocking the fallopian tubes with silicone was first introduced by Crofman (28). The first studies performed on rabbits, proved an efficacy of 100% if the silicone material was applied up to the isthmic part of the tubes. Erb developed a technique for hysteroscopic intratubal administration of liquid silicone, mixed with a catalyst and cure-in-place to form rubbery implants, with the aim of producing a non-incisional, non-scarring method for permanent contraception with minimal discomfort for the patient (29).

This Ovabloc method has been in use since 1978. Phase II and III studies were performed in the late 1970s and early 1980s in Belgium and the USA (30). These FDA trials were stopped when the initially assumed reversibility was poor (31,32). In 1985 the Ovabloc procedure became commercially available in the Netherlands (Ovabloc Europe BV, Alphatron Medical Systems, Rotterdam, later Advanced Medical Grade Silicons BV, Beverwijk, the Netherlands), where its use has mainly been confined to a few centers (33). A CE Mark for the European market is achieved in 2001.
The insertion is an outpatient procedure. The procedure involves high pressure injection of viscous silicone into the ostium with a catheter placed in the tubal ostium through a hysteroscope with a 7 French working channel. The silicone conforms to the shape of the ampoule of the tube and solidifies in approximately five minutes. The silicone contains radio-opaque silver powder, which enables a radiological check for correct placement at completion of the procedure. Bilateral placement takes around 30 minutes. The woman is asked to use contraception for three months, at which point a second plain X-ray is performed to exclude migration and expulsion. Published data report a high failure rate, expulsion to the abdominal cavity and complete expulsions. The method never became very popular, probably because it was too complicated. It was stopped in 2009. In 2012 CE approval was obtained for Ovalastic (Urogyn BV, Nijmegen, the Netherlands), which is the result of a technical upgrade of Ovabloc. With this upgrade the manufactory claims a less time consuming, more reliable and safe procedure.

**Essure**

In November 2002 the Food And Drug Administration approved the Essure sterilization while it has been available on the European market since 2001 (Conceptus Inc. Mountain view, CA, USA). The device is a dynamically expanding insert that consists of a stainless steel innercoil, a nickel titanium (nitinol) expanding outercoil and Polyethylene Teraphtelate (PET) fibres. The device, with a length of 4 cm, is placed into the fallopian tube using a modern standard hysteroscope with a 5 French working channel. After placement the device will be anchored in the tubo-cornual junction by the expanded nitinol coil. The PET fibres induce an inflammatory reaction that causes scarring and occlusion of the tubes. The exact time that it takes for tubal occlusion of the tubes to allow the patient to rely on the devices as permanent contraception is unknown (34). Obliteration of the tubal lumen was demonstrated histologically in four of nine tubes removed within four weeks after device placement and five of five tubes removed within four to eight weeks after placement. Functional occlusion confirmed by hysterosalpingography (HSG) was already confirmed one week after placement (35). Patients are instructed to use alternative contraception until a three months confirmation test has shown adequate bilateral localization and tubal occlusion. In the US a HSG is required for confirmation according to the FDA approval while in other countries, scout X-ray or transvaginal ultrasound is used for confirmation. The ESS205, a modification of the former ESS105 device, with higher insertion rates was introduced in 2004. In 2007 the ESS305 with automatic release mechanism of the introducer catheter and a special introducer was introduced.
Successful placement is achieved in 95-99% of the cases in an office setting (36,37). Worldwide more than 500,000 women rely on Essure sterilization. The cumulative nine years failure rate is 0.2% on the basis of follow-up data from 449 women included in the phase II and pivotal trials (34). More than 700 unintended pregnancies are reported (38). Data analysis of patient files shows that 44% of the pregnancies are attributed to patient non-adherence to the protocol or misreading of the confirmation test. Shavell reported a 12.7% compliance with the three months HSG in a general clinic population in an urban environment, despite both preoperative and postoperative counselling and a follow-up rate of 70% for the one-week postoperative control (39).

Adiana

Adiana’s complete transcervical sterilization procedure (Adiana Inc., Redwood City, CA purchased by Hologic, USA) is a two-stage procedure. First, a superficial lesion of the epithelium of the intramural part of the tube is created with bipolar radiofrequency energy. The second step is placement of a 3.5 mm porous, silicone, non-biodegradable implant (matrix) into the tubal lumen. The implant provokes a fibrous reaction that occludes the tube over a period of weeks. Patients must use alternative contraception for three months until an HSG is performed. A CE Mark for the European market was obtained in December 2008 and the FDA approved the application in July 2009. The Evaluation of Adiana System (EASE trial) was completed in 2005 (40). It was stated that 611 women were treated, with a 95% bilateral insertion rate. Almost half of the patients (47%) received conscious sedation with an intravenous agent. The HSG confirmation test after three months showed tubal patency of one or both tubes in 8.8% of the patients. During the first four years of this trial, 15 pregnancies have been reported. Five of the pregnancies occurred while subjects were instructed to rely on an alternate contraceptive: two pregnancies following placement failure, and three pregnancies after successful placement, but during the waiting period (patient non-compliance). Ten pregnancies occurred following successful placement and HSG showing tubal occlusion. Six of these pregnancies occurred in the first year of rely. Retrospective review of HSGs for three of these subjects suggests that the diagnosis of tubal occlusion was in error (misread). The six pregnancies contributed to a one-year failure rate of 1.1%. In March 2012, the manufactory decided Adiana was not generating the expected revenue and the manufacturing of Adiana was stopped. At that moment a long-standing battle over patent infringement between the two companies was going on.
Hysteroscopy

Between the 1970s and 1980s modern hysteroscopy was introduced. Procedures for distending the uterine cavity were introduced, with carbon dioxide and high-molecular weight fluids to allow visualization of the uterine cavity and tubal ostia (15). The Ovabloc ITD procedure was performed with a single flow hysteroscope with an Alberan deflexion bridge, initially with Hyskon (32% Dextran 70 in 10% glucose) or carbon dioxide as distension medium. From 1991, a continuous flow 8.0 mm hysteroscope with a 2.2 mm (7 French) working channel and an Alberan deflexion bridge, fitted with a 4.0 mm 300 fore-oblique telescope was used with sorbitol for uterine distension (33).

At the beginning of the 1990s, scopes were used with operative sheats with a diameter equal or less than 5.5 mm with a working channel of 1.7 mm (5 French) and telescopes with a diameter ranging between 1.2 and 3.0 mm. With the use of these smaller instruments the use of a speculum and tenaculum and dilatation of the cervix was no longer necessary: the vaginal cavity can be distended with a distension medium to facilitate location of the cervical canal. The anatomy can be followed by gentle movements of the hands that correctly drive the hysteroscope into the cervix and through the internal cervical os (41). This method has been defined as the “vaginoscopic approach”, the patient discomfort associated with the traditional approach to the uterus has been eliminated (42).

As anesthesia and analgesia are not required for hysteroscopy, women now have the option of permanent contraception while avoiding the risk associated with laparoscopy and general anesthesia. Some physicians are still hesitant to perform the procedure in an office setting, most commonly citing patient discomfort as the major concern, but several studies support high tolerability and satisfaction with an office approach (43).

One study indicates that patients undergoing hysteroscopic sterilization experience significantly less pain than those undergoing laparoscopic sterilization (44).

Paracervical block with 1% lidocaine provides effective pain relief for cervical manipulations during office hysteroscopic sterilization, but does not reduce the pain associated with upper uterine/tubal manipulation when placing the devices (45).

Pain scores were associated with procedural time. A likely explanation for this is that procedural time is a marker for difficulty of the procedure or skills of the hysteroscopist. In general, the more difficult the Essure placement is, the longer it will take to achieve correct placement, and frequently additional manipulations are needed to assist in appropriate placement, the more cramping of the fallopian tubes will be induced. An important finding is that the largest difference in observed pain scores was 2.3 on the VAS. Even though for the purposes of this study a relatively conservative difference of 0.9 on the VAS was used to be clinically relevant to prevent
under powering, some studies indicate that the clinically relevant VAS difference is around 2.5. Therefore, although a difference was observed and found to be statistically significant, this may not represent a clinically relevant difference. When examining the placebo group, we observed that pain was not significantly greater than reported menstrual pain. This is critical when counselling patients regarding the pain from the Essure procedure, as well as likely other office hysteroscopy procedures that require less manipulation than Essure. Because pain is one of the most common patient concerns when choosing to undergo an office procedure, the ability to tell a patient that the pain will be similar or less than a typical menstrual period can be very reassuring for many patients (45).

According to a Cochrane review from 2012 the available literature is insufficient to determine the appropriate pain regimen for outpatient sterilization by hysteroscopy. Neither paracervical block with lidocaine nor conscious sedation significantly reduced overall pain scores during sterilization by hysteroscopy with Essure. Although paracervical block with lidocaine did not reduce overall patient-reported pain, it did reduce pain during some portions of the procedure, particularly with injection into, or manipulation, of the cervix. Since paracervical anesthesia is safe and inexpensive it may be a reasonable option. The provision of intravenous conscious sedation did not reduce the total pain score but did significantly reduce pain at the time of insertion of the second tubal insert; this is one of the most painful parts of the procedure. Thus, it may have some benefit (46).

**Confirmation test**

In the late 1970s the hysterosalpingography (HSG) was abandoned as a routine follow-up after laparoscopic sterilization because of discordance between tubal patency and pregnancy rate. In a study of 250 women with laparoscopic tubal fulguration the patency rate with HSG was 3.6% while the pregnancy was only 0.62%. A review of additional contemporary studies confirmed discordant patency and pregnancy rates (47).

The results of the CREST review did not change the policy of confirmation of laparoscopic sterilization. The CREST review reported an overall cumulative failure rate of 1.9%. This was more than double what has been accepted as the standard failure rate for tubal sterilization. This failure rate contrasted sharply with previous studies of common tubal occlusion techniques that cited figures lower than 1%. Until then, comparisons of contraceptive failure rates had reported the probability of failure during the first year after sterilization ranging between 0% and 0.4% (48). These failure rates, however, were based on investigations having only one or two years of follow-up. Alternative diagnostic tests for confirmation of laparoscopic sterilization have not been described.
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An HSG is also not recommended after transcervical sterilization with quinacrine, because of the risk to blow out the delicate scars (25). No other tests have been evaluated.

For all hysteroscopic techniques initially a HSG was recommended. For the Ovabloc method finally two X-rays images were required to evaluate the effectiveness of the device: one X-ray immediately following instillation to check the integrity and shape of the plug and a second X-ray at three months post-instillation to check the proper location of the Ovabloc devices. This decision that patients could not rely on the sterilization for three months was an arbitrary point in time (49).

In the US, according to the FDA, an HSG is required after hysteroscopic sterilization with Essure, while in Europe and other countries initially X-ray was an accepted alternative. In February 2011 the Conformité Européene Mark approved to use Transvaginal Ultrasound (TVU) to confirm proper placement of the microinsert, three months following the procedure. Available data confirm that proper location of the microinserts correlates very well with tubal occlusion and high effectiveness (50). Evaluation of data from 745 patients with unintended pregnancies showed a high incidence of misreading of the HSGs and patient non-compliance to the HSG confirmation test (38). In an urban clinic population in Michigan the compliance to a protocol with HSG revealed only 12.7%, despite correct counselling and a 70% follow-up rate for the post-operative visit (39). Studies with confirmation tests other than HSG report higher patient compliance (36,37,43, 50).

The first and only study available data for the Adiana method reports 53 of 604 patients with unilateral or bilateral tubal patency with the three months HSG. By six months post-procedure, 26 still showed at least unilateral patency. With TVU, 598/604 subjects had devices visualized bilaterally. There have been a total of 10 pregnancies among 553 women who were told to rely on Adiana for contraception based on the three-months HSG, two pregnancies of which were ectopic. It is unclear how the TVU imaging correlates with these unintended pregnancies. The devices are not radiopaque, therefore pelvic X-ray is not useful for the confirmation (40).

There is a need for other tests to confirm proper position and tubal occlusion after sterilization. HSG is still the gold standard. The procedure is invasive and uncomfortable for the patient. In addition it is associated with infection, vasovagal reaction and anaphylactic shock. Also uterine bleeding and perforation may occur.
Alternative ideas are suggested and are subject of research:

- **Contrast Infusion Sonography (CIS) or Saline Infusion Sonography (SIS).** NaCl infusion in the uterine cavity while inspecting for real time flow within the tube or unequivocal dye spill in the adnexa (51).

- **Hysterosalpingo Contrast Sonography (HyCoSY)** with the use of an ultrasound contrast agent to examine tubal patency.

- **Volume Contrast 3D Ultrasound** produces a 5 mm thick volume image in the C-plane (VCI-C) similar to HSG. The images yield more detail with regard to the relationship of the device to the uterine cavity than conventional (2D) ultrasound or HSG. Like 2D US it gives information about the position of the microinsert but not about the integrity of the fallopian tubes. A Classification has been developed to assess the position of the microinsert. Four positions are described: perfect, proximal, distal and very distal. Only the last one is associated with a higher chance of tubal patency on HSG (52,53).

**Tubal occlusion prior to IVF**

Hydrosalpinx is associated with poor in-vitro fertilization outcome but the actual mechanism is not yet fully understood. The passage of hydrosalpingeal fluid into the endometrial cavity might create an unfavourable environment for embryo implantation or development (54). Laparoscopic salpingectomy prior to IVF in patients with ultrasound-visible hydrosalpinges is recommended. Hysteroscopic sterilization techniques offer the possibility of an alternative for salpingectomy by proximal tubal occlusion prior to IVF. Previous reports estimated the efficacy of proximal tubal occlusion in patients with hydrosalpinges and shows excellent reproductive outcomes after Artificial Reproduction Techniques (ART). The presence of nickel in the Essure device is cause of concern related to embryologic development, but Nitinol showed no cytotoxic, allergic or genotoxic activity in animal studies (55). Second look hysteroscopy after Essure placement showed that the devices are encapsulated and the devices may therefore be compatible with implantation and successful pregnancies outcomes after IVF (56).
Aims of this thesis

- To review the history and current practice of hysteroscopic sterilization.

- To review placement rates, effectiveness and safety of current hysteroscopic sterilization methods.

- To validate different diagnostic tests for the three months confirmation after hysteroscopic sterilization.

- To evaluate the outcome of unintended pregnancies and IVF pregnancies after regret or pre-procedure closure of hydrosalpinges.
Outline of the thesis

Chapter 2 determines the placement rate, efficacy and safety of hysteroscopic sterilization methods that are currently available or has been available.

Chapter 3 determines the diagnostic characteristics of X-ray and transvaginal ultrasound to localize Essure microinserts after successful bilateral placement.

Chapter 4 determines the reproducibility and inter-observer agreement of pelvic X-ray 3 months after hysteroscopic sterilization with microinserts.

Chapter 5 describes different types of incorrect position of microinserts after successful bilateral placement.

Chapter 6 estimates the causes of unintended pregnancies after hysteroscopic sterilization and determines whether this can be prevented.

Chapter 7 evaluates the protocol for confirmation of satisfied position of microinserts after hysteroscopic placement based on first-line examination with transvaginal ultrasound.

Chapter 8 determines the success rate of proximal tubal occlusion with microinserts in subfertile women with hydrosalpinges.

Chapter 9 evaluates the obstetrical outcome of intended and unintended pregnancies after Essure hysteroscopic sterilization.

Chapter 10 summarizes the results of the studies presented in this thesis and gives clinical implications and implications for future research.
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References


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