10 General discussion and future perspectives
Preceding experience with hysteroscopic sterilization

For more than 100 years, physicians have searched for a transcervical way to occlude the fallopian tubes at their uterotubal junction to avoid the complications that are associated with general anesthesia and abdominal instrumentation. Methods using electrocoagulation, cryocoagulation or other techniques of heating the tubal openings by access through the uterine cavity were unsuccessful. Many designs of intratubal mechanical devices (screws, plugs and formed-in-place intratubal devices) have been tried out over the past 60 years, with limited success (1,2).

Only three methods were released on the European Market (Ovabloc Intratubal Device System (1980), Essure System (2002) en Adiana Permanent Contraception System (2009), while the FDA only approved the Adiana (3) en Essure (4,5,6). The Ovabloc and the Adiana were both withdrawn from the market. The Ovabloc in 1988 after reports of disappointing results, technical problems with the cold storage of the silicon and the fact that the claim to be a reversible sterilization technique could not be confirmed by a histological study. The Adiana was withdrawn as part of a deal to settle ongoing patent infringement litigation in March 2012. Currently, the Essure method is the only available hysteroscopic sterilization method.

Placement rates, efficacy and safety of current hysteroscopic sterilization devices.

The latest Cochrane Review of techniques for the interruption of tubal patency for female sterilization concluded in 2011 that data on rare and long-term outcomes are available from cohort studies, rather than from randomised controlled trials (8). Despite the different clinical settings (office or theatre; in-patient or out-patient) and differences in pre-medication and the use of different kind of anaesthetics (none, paracervical block, sedation or general anesthesia,) during the procedures all authors claimed high patient tolerance and satisfaction and a high effectiveness and safety of the methods.

Since the introduction of Essure in 2002 only gynecologists with experience in hysteroscopy were trained to perform this new method of sterilization, but studies have been shown that the learning curve for successful bilateral placement is steep (9). According to Levie the procedure can be recommended to be carried out by general obstetrician/gynecologists after an appropriate training course and supervision for the first several procedures. No differences were found in patient age, nulliparity, and BMI between successful and incorrect placement procedures (10,11). However, second half of menstrual cycle at the time of surgery and an enlarged uterus are predictors of unsuccessful placement. Difficulty to visualize
the tubal ostia, was significantly associated with failure. A longer procedure time was also associated with failure (12), likely due to procedure difficulty rather than as a direct cause of placement failure. In most of the published studies the procedures were scheduled in the proliferative phase of the menstrual cycle or oral contraceptives were prescribed, starting one month before the procedure to induce endometrial suppression.

In chapter 2 we conducted a systematic review to examine the placement rate, efficacy, safety and risk factors for failure of hysteroscopic sterilization techniques. In total, 45 studies were included. Feasibility was expressed as successful bilateral placement rate in one attempt (A, table 1). For Ovabloc, Essure and Adiana, these placement rates were respectively: 80% (95% CI: 76-83%), 92% (95% CI: 91-94%) and 94.7%. The percentages of women that could rely on successful bilateral placement confirmed at three months follow-up (B, table 1) were respectively: 0.96% (95% CI: 0.93-0.96), 0.97 (0.95%-0.98) and 0.91. Because of unspecified follow-up data and variation in sample size we were not able to pool the data and calculate cumulative pregnancy rates for Ovabloc and Adiana methods. Twelve pregnancies occurred in 1212 patients who relied on Ovabloc sterilization (1.2%), while 8 pregnancies occurred in 7,706 women after successful Essure sterilization (0.1%). The 36 months cumulative pregnancy rate of Adiana was 1.5%.

Complications during the hysteroscopic procedures were incidentally reported. During the Ovabloc procedures, perforation of the uterine wall occurred in five out of 438 cases (13). The most important risk factors for placement failure of Ovabloc were bad visualization, tubal spasm or inability to obtain linear axis between obturator tip of the catheter and tubal ostium (14) In the Essure studies, two perforations during the procedure were reported (15), while 42 expulsions, 45 perforations and 9 migrations of devices were notified at the three-month control in a total of 10,124 cases. Hyponatremia (sodium 129 mEq/L) occurred in one case of sterilization with Adiana.

Table 1: Feasibility and efficacy of three methods of hysteroscopic sterilization.

<table>
<thead>
<tr>
<th></th>
<th>Successful bilateral placement 1st attempt (A)</th>
<th>Satisfactory confirmation after total bilateral placements (B)</th>
<th>Satisfactory confirmation after successful placement 1st attempt (A x B)</th>
<th>Pregnancies after confirmation</th>
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<tbody>
<tr>
<td>Ovabloc</td>
<td>0.80</td>
<td>0.96</td>
<td>0.77</td>
<td>12 / 1212</td>
</tr>
<tr>
<td>Essure</td>
<td>92</td>
<td>0.97</td>
<td>0.89</td>
<td>8 / 7706</td>
</tr>
<tr>
<td>Adiana</td>
<td>0.95</td>
<td>0.91</td>
<td>0.86</td>
<td>9 / 570</td>
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Based on this systematic review it seems that the Essure method has the highest successful placement rate at first attempt with proper position at confirmation and the highest efficacy.

**Confirmation of correct bilateral placement and bilateral tubal occlusion.**

As the primary objective of sterilization is occlusion of both tubes, the obvious ‘gold standard’ reference test is testing tubal patency. Other, less invasive tests such as transvaginal ultrasound and X-ray aim to confirm the appropriate position of the devices in both tubes, but are constructs for tubal patency. If tubal patency can be predicted accurately by the position of the devices, better tolerated confirmation tests may become the professional standard.

It is remarkable that in the United States of America an hysterosalpinography (HSG) is obligatory after successful bilateral placement, while the European Health Office approved the Essure method requiring only an X-ray or transvaginal ultrasound three months after the procedure accepting the lack of information of tubal occlusion. A review of the clinical data from studies by Kerin et al. and Cooper et al. of more than 700 patients showed that an HSG seems not always necessary (6,16,17). During these phase II and III multicenter clinical trials, satisfactory bilateral insertions were ultimately achieved in 664 of 734 patients (90%). The original protocol required that an HSG has to be performed three months after placement to confirm tubal occlusion. However, in patients in whom a satisfactory bilateral insertion had been achieved, a 100% bilateral occlusion rate was found (18).

A three-month confirmation test is not uncommon after hysteroscopic sterilization methods. Also for the Adiana Permanent Contraception System and Ovabloc Intratubal Device Method, a three months confirmation was indicated. In the late 1970’s the three-month HSG was abandoned as a routine follow-up after laparoscopic sterilization because of discordance between tubal patency and pregnancy rates (19). In a pre-hysterectomy study of Valle, with the STOP microcoil device (an earlier type of the Essure ESS 105 with a stainless steel inner coil, an outer coil of nitinol and PET fibres) hysteroscopic placement was performed in women who required hysterectomy. Histology data of the tubes demonstrated that tissue in-growth reaction was predictable, occurred in all fibered specimens collected and was localised to the device. More than 80% occlusion was noted more often in specimens in which the device had been in place for more than four weeks. Histological confirmation of complete occlusion of the tube histologically was difficult, as artefacts may have been introduced during processing. Other studies have demonstrated that an inflammatory response peaks between two and three weeks,
after which the inflammatory response slowly resolves during a 10-week period (20). In the study of Valle (21), tubal occlusion was also evaluated by HSG just prior to hysterectomy. It is remarkable that occlusion was noted in all tubes, even in those cases with device placement less than two weeks before hysterectomy.

In chapter 3, we evaluated the diagnostic characteristics of pelvic X-ray of the pelvis and a transvaginal ultrasound after Essure sterilization with HSG as a reference test. In 9 of 150 patients with successful bilateral placement it was not possible to identify both devices in correct position with ultrasound. In one of these nine patients one microinsert was missing on pelvic X-ray; this patient seemed to have had an expulsion. In the other 149 patients the pelvic X-ray was determined to be satisfactory with both microinserts in situ. In one of these 149 women there was evidence of dye passage (patency) past the microinsert into the distal tubal lumen upon HSG. The sensitivity of transvaginal ultrasound with the HSG as reference test for correct position of the devices and tubal occlusion was 50% (one true positivea, one false negativeb), and the specificity was 94.6% (Table 2). If compared with X-ray as reference test sensitivity and specificity were respectively 100% (one true positivea) and 94.6% (table 3).

The positive predictive value of ultrasound to diagnose a correctly positioned microinsert was 99%, while the negative predictive value was only 11%. This means that when a microinsert is not clearly visible by ultrasound one should not conclude that it is an unsatisfactory sterilization but that further evaluation is indicated. In our second study, described in chapter 4, we analyzed the interobserver agreement of X-ray without contrast after Essure sterilization and concluded that interobserver agreement was low. Even gynecologists with extensive experience in reading radiographs after Essure, were not able to recognise suspicious or unsatisfactory X-rays of patients with abnormal positions of the devices. In scoring reliability of the Essure sterilization there was a large difference in the agreement between radiologists (moderate, $\kappa$-value: 0.52) and gynecologists (slight, $\kappa$-value: 0.09).

<table>
<thead>
<tr>
<th>TVU</th>
<th>HSG</th>
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<th>satisfactory</th>
<th>total</th>
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</tr>
<tr>
<td>satisfactory</td>
<td>1b</td>
<td>140</td>
<td></td>
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</tr>
<tr>
<td>total</td>
<td>2</td>
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<td></td>
<td>150</td>
</tr>
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Table 2: Counts of position of Essure microinsert, diagnosed by transvaginal ultrasound with HSG as reference test.
while for a high number of cases (27/47) at least one of the radiologists advised additional HSG to confirm a reliable sterilization.

In chapter 5, three cases with different types of incorrect position of Essure microinserts at three-months follow-up and their appearance on X-ray and by ultrasound were discussed (one case of complete expulsion with a missing device, one case of perforation and one case of proximal position of a device, which was located in the uterine cavity). In the cases of the perforation and the proximal position, pelvic X-ray demonstrated an abnormal position of one microinsert and abnormal configuration with a deviation of the fourth marker (proximal end of outer coil). In chapter 6 we analyzed data collected from 10 patients with unintended pregnancies after Essure sterilization in the Netherlands and identified one case of luteal pregnancy (pregnancy already occurred before the procedure). In three cases single placement was followed by a three months HSG and bilateral tubal occlusion was concluded. In the other six cases an abnormal position of a microinsert was recognized after termination of pregnancy.
Based on our own findings, conclusion from other studies (18,22,23) and analysis of unintended pregnancies cases we developed a new follow-up protocol for Essure sterilization with transvaginal ultrasound as first-line investigation after an uncomplicated bilateral placement (Addendum Fig. 1):

- No unintended pregnancies occurred after proper demonstration of bilateral occlusion following device placement (24).
- Improper placement of devices was usually preceded by difficult or complicated procedures (25).
- Procedure time of failed procedures was longer than procedure time of bilateral successful placements (26).
- Unilateral device placement in patients with bilateral tubal occlusion on HSG, without a history of salpingectomy was related to unintended pregnancy (24).
- Transvaginal ultrasound (TVU) has proved to be an adequate alternative method for confirmation of the microinsert placement at follow-up (18,23,25,27).

This revised Dutch protocol was validated in a center study, as described in chapter 7. With a reduction of the number of HSG’s to less than 15%, the effectiveness of hysteroscopic sterilization was not reduced. The two-years cumulative pregnancy rate was 3.86 per 1,000, while two of four pregnancies occurred after violation of the protocol (VOP). In one case, placement was complicated, and a third device was placed after a spontaneous expulsion of the first device. Ultrasound examination was performed at three months instead of HSG. In the second patient, device placement was unsuccessful on one side, and only one device was placed. At HSG, the contralateral tube seemed to be occluded, and the patient was instructed to cease alternative contraception. This suggests that strict following of the protocol could further reduce the already low pregnancy rate. The extra four-weeks ultrasound examination as suggested by others (27) to detect perforations before the 3 months control, did not cause any deviations from the protocol and should be reserved for specific indications (difficult procedure with high risk for perforation or patient with post-procedure abdominal pain). The results of our study supported the submission to receive the CE mark for transvaginal ultrasound as first-line confirmation test after Essure sterilization, which was assigned in 2011. Others studies (23,28,29,30) confirmed the validity of ultrasound as first-line confirmation test. In 2011 a clinical trial was initiated to obtain FDA approval for transvaginal ultrasound confirmation in the United States.

Thiel et al. (23) and Legendre et al. (32,33) assessed the position of the microinsert with 3D ultrasound. The use of volume-contrast 3D imaging improved the visualization of the microinserts within the uterine cornua and proximal fallopian tube. A classification with four different positions of the microinsert (perfect, proximal, distal...
and very distal) was proposed. 3D-US showed a sensitivity of 100% and a Specificity of 58.2% with HSG as reference test and inadequate evaluation of 3D-US was regarded as a positive test result (indicative of sterilization failure), whereas a satisfactory evaluation was regarded as a negative test result (indicative of successful sterilization). The Negative Predictive Value (NPV) of 3D-US was 100% (95% CI: 100–100%) (i.e. proportion of patients with negative results, i.e. satisfactory position and successful sterilization on 3D-US, with actual negative results) and the Positive Predictive Value (PPV) of 3D-US was 23.3% i.e. proportion of women with at least an unsatisfactory position on 3D-US whose sterilization was correctly found to have failed (33). Advantage of the 3D ultrasound compared to 2D is that the volume 3D data can be preserved for a later assessment. As far as we know the performance of 2D and 3D ultrasound to confirm hysteroscopic sterilization has not yet been compared. Connor evaluated Contrast Infusion Sonography (CIS) as a first-line Essure confirmation test (34). The contrast solution infused consists of 1 mL of a perflutren microsphere contrast agent (Bristol Myers-Squibb Medical Imaging, North Billerica, MA) mixed with 20 mL of normal saline. Preliminary data suggested that CIS is a feasible, safe and accurate confirmation test, which is well accepted by patients.

Outcome of unintended pregnancies and IVF pregnancies after regret or pre-procedure closure of hydrosalpinges.

Finally we started a prospective study to investigate the success rate of proximal tubal occlusion with Essure devices in subfertile women with hydrosalpinges and to observe the results of subsequent treatment with IVF. Our case series in chapter 9, shows good pregnancy rates with IVF-ET following Essure placement, and is consistent with rates found after tubal obstruction with microinserts or laparoscopic salpingectomy (35-38).

A significant concern for women with unintended pregnancies and subfertile women wishing to conceive with microinserts in situ, is the trailing of Essure coils into the uterine cavity and its possible effects on implantation as well as on pregnancy.

Although two out of 50 pregnancies in our case series ended with a stillbirth we concluded that it was unlikely that these events were induced by the presence of the microinsert. In a recent review on the efficacy and safety of Essure in the management of hydrosalpinges prior to IVF, data of 115 women in 11 studies were pooled. Successful placement of Essure was achieved in 96.5% (95% CI: 91.1-98.9%) of women and tubal occlusion in 98.1% (95% CI: 93.1-99.9%). Subsequent IVF resulted in 38.6% pregnancy rate (95% CI: 30.9-46.8%).
27.9% live birth rate (95% CI: 21.1-35.8%) and 28.6% combined ongoing pregnancy and live birth rate (95% CI: 21.7-36.6%) per embryo transfer (39).

The strength of this thesis is the high clinical relevance. The outcomes of our studies were used to revise the Dutch follow-up protocol of hysteroscopic sterilization, which was validated in a large multicenter study. The major limitation of the studies is that they were not comparative and based on single-arm prospective cohort studies and case series.

The effectiveness of hysteroscopic sterilization methods is based on correct intra-tubal position of devices confirmed by a diagnostic test after three months. The predictive value of a diagnostic test for recognizing an abnormal position of a device depends on the incidence of these improper placed devices. Because of the low incidence of abnormal positioned devices we found a low negative predictive value. However confirmation of the proper position of the devices makes effective sterilization very likely. To evaluate the diagnostics characteristics of a confirmation test, a larger cohort of patients would have been preferable. Although we studied the interobserver agreement for X-ray we could not study this for transvaginal ultrasound examination. The biggest disadvantage of using ultrasound as a diagnostic test is that it is a real-time examination, while capturing the diagnosis on a hardcopy. We did not succeed in capturing videos of all our ultrasound examinations. 3D ultrasound volumes that can be stored and reviewed, may solve the problem of retrospective analysis of diagnostic data.

**Conclusion**

At this moment there is only one hysteroscopic sterilization method available. The Essure method can be performed in an office setting without anesthetics during the procedure. Patient satisfaction and tolerance are high. Hysteroscopic sterilization with a strict follow-up protocol with transvaginal ultrasound as first-line test for confirmation is highly effective and reduces the need for radiologic examination. The risk of complications (perforation, expulsion and pregnancy) is low. Radiologic confirmation is only needed for strict indications. The use of microinserts to obstruct hydrosalpinges in an IVF program to improve the “take home baby” rates is promising and related to less burden (in contrast to laparoscopic treatment, hysteroscopic treatment can be performed in an outpatient setting, without use of general anesthesia, with shorter procedure times and a quicker recovery) and possibly also less interventional and/or anesthesiologic risk for the patient. It is unlikely that the presence of Essure microinserts interferes with implantation and the developing amniotic sac and fetus.
Future perspectives

The need for a confirmation test after sterilization is questionable. Because the contraceptive principle of hysteroscopic sterilization methods such as Essure System and Adiana Permanent Contraception System is based on tubal occlusion by tissue in-growth and not by direct tubal occlusion by the device itself, it makes sense to use a tubal patency test for confirmation after the procedure. On the other hand, persisting anatomical tubal patency does not necessarily imply sterilization failure and a negative dye spill post-procedure sterilization HSG does not completely exclude the possibility of pregnancy at a later stage (40). HSG is an ionizing radiation technique inconvenience for the patient and risk of anaphylactic reaction. In the United States it is an obligatory test although the patient-compliance is very low (41). A theoretical risk of flushing the fallopian tube with contrast medium and wash-out of scarred tissue has not been described (21).

One of the outcomes of this thesis is that the chance of an abnormal position of Essure microinserts after bilateral placement (one or more attempts) is less than 3%. Perforation or expulsion happened after complicated procedures. Pregnancies were described after violation of protocol or in patients who were non-compliant to the protocol. None of the cases of pregnancy were a method failure but all were related to improper position of a device. Our hypothesis is that a standard confirmation test is not necessary and can be removed from the flow chart. It will not reduce the effectiveness of Essure sterilization. In case of an “abnormal” procedure, with a procedure time of more than 12 minutes, to deep or to proximal placement (more than eight coils visible) or the need for a second attempt, confirmation by transvaginal ultrasound or X-ray is indicated X-ray. In these scenarios X-ray and transvaginal ultrasound are complementary. X-ray verifies devices presence, the position, symmetry and distance between the microinserts and the configuration of the devices with its four markers, while ultrasound visualizes the relation of the microinserts to soft tissue, and the tubocornual junction in particular.

If the first-line test is unsatisfactory, the complementary test has to be performed. If both tests have an unsatisfactory result (meaning: there is doubt in the efficacy of the sterilization), additional HSG should confirm proper position of the device and tubal occlusion. This renewed Dutch protocol has to be validated in a prospective multicenter study (Addendum Fig. 2, page 215).

The “ideal” hysteroscopic sterilization device, with 100% effectiveness and 100% safety and no need for confirmation, has not been developed yet. There is still a need to improve the available intratubal devices.
Three new hysteroscopic sterilization devices will be launched in the near future. One is a redesigned Ovabloc Intratubal Device System. Challenges related to the design included the storage of material under room temperature conditions achieving reliable curing times and incorporating a contrast agent to facilitate visibility for evaluation. A study with a new model of the Essure System has recently been completed. The investigational device offers immediate, permanent contraception without a three-month confirmation test. A multicenter pivotal study for safety and efficacy of Altaseal will be started this year. The Altaseal (42) is a hysteroscopically placed mechanical occlusion implant for immediate contraception.

In case that in the future confirmation tests are still indicated after hysteroscopic sterilization, a new diagnostic test like 3D ultrasound has to be evaluated to confirm proper placement. Results from earlier studies (32,33,43-45) are promising. If tubal occlusion still has to be confirmed new non-radiation techniques like Contrast Infusion Sonography or Hysterosalpingo Contrast Sonography (HyCoSy) as suggested by Connor in 2008 (34) or the newer Hysterosalpingo-Foaminfusion Sonography (HyFoSy) could be considered to be evaluated as confirmation test for tubal occlusion (46-48).

Patient Outcome Measurement Tool (POMT) is a surgical registry that has recently been introduced in the Netherlands for the collection, analysis and reporting of patient clinical data for gynecological patients undergoing surgical interventions. Procedures and adverse events or complications will be related to patients unique Citizen Service Number (BSN), independent of where the procedure was performed. Registration of sterilization procedures and complication, gives the opportunity for long-term follow-up of all methods of sterilization and life-table mathematics to calculate 2-year, 5-year or 10-year cumulative pregnancy rates. Therefore, we strongly recommend that all data of patients seeking for sterilization will be registered in this module.
References