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ORIGINAL ARTICLE *Infertility*

Hysteroscopic proximal tubal occlusion versus laparoscopic salpingectomy as a treatment for hydrosalpinges prior to IVF or ICSI: an RCT

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STUDY QUESTION: Does hysteroscopic proximal tubal occlusion by intratubal devices as a treatment for hydrosalpinges result in comparable ongoing pregnancy rates following IVF/ICSI when compared with laparoscopic salpingectomy?

SUMMARY ANSWER: Hysteroscopic proximal tubal occlusion by intratubal devices is inferior to laparoscopic salpingectomy in the treatment of hydrosalpinges in women undergoing IVF/ICSI with respect to ongoing pregnancy rates.

WHAT IS KNOWN ALREADY: It is known that women with hydrosalpinges undergoing IVF have poorer pregnancy outcomes compared with women with other forms of tubal infertility. In these women, both laparoscopic salpingectomy and laparoscopic proximal tubal ligation are known to improve IVF outcomes. At present, it is unclear whether a less-invasive hysteroscopic treatment with intratubal devices leads to similar ongoing pregnancy rates following IVF when compared with laparoscopic salpingectomy.

STUDY DESIGN, SIZE, DURATION: A two-centre, randomized, controlled, non-inferiority trial. Between October 2009 and December 2014 a total of 85 women were included in this study; of whom, 42 were randomized to hysteroscopic proximal occlusion by intratubal device placement and 43 were randomized to laparoscopic salpingectomy. Randomization was based on a computer-generated randomization list. The study was unblinded. The primary outcome was ongoing pregnancy rate, defined as a fetal heartbeat on ultrasound beyond 10-week gestation following one IVF/ICSI treatment (fresh and frozen–thawed embryo transfers).

PARTICIPANTS/MATERIALS, SETTING, METHODS: We studied women aged 18–41 years, with uni- or bilateral ultrasound visible hydrosalpinges who were scheduled for an IVF/ICSI treatment.

MAIN RESULTS AND THE ROLE OF CHANCE: The ongoing pregnancy rates per patient according to the intention-to-treat principle were 11/42 (26.2%) after hysteroscopic proximal occlusion by intratubal devices (intervention group) versus 24/43 (55.8%) after laparoscopic salpingectomy (control group) ($P = 0.008$) [absolute difference: 26.1%; 95% confidence interval (CI): 0.5–51.7, relative risk (RR): 0.56; 95% CI: 0.31–1.03, $P = 0.01$]. In the per protocol analysis, the ongoing pregnancy rate per patient following hysteroscopic proximal occlusion by intratubal devices was 9/27 (33.3%) compared with 19/32 (59.4%) following laparoscopic salpingectomy ($P = 0.067$) (absolute difference: 29.6%; 95% CI: 7.1 to 49.1, RR: 0.47; 95% CI: 0.27–0.83, $P = 0.062$).

LIMITATIONS, REASONS FOR CAUTION: Masking participants and investigators would be difficult due to the nature of both interventions. Since we had objective outcome measurements, we withheld sham procedures, leaving the study unblinded. Furthermore, our low sample size resulted in wide CIs. A larger sample size would result in a more accurate treatment effect; however, this was non-feasible for recruitment and inclusion.

WIDER IMPLICATIONS OF THE FINDINGS: In the treatment of hydrosalpinges prior to IVF/ICSI, hysteroscopic proximal occlusion by intratubal devices is inferior to laparoscopic salpingectomy.

STUDY FUNDING/COMPETING INTEREST(S): The intratubal devices were received from Conceptus, Inc., San Carlos, CA, USA, which was acquired by Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ, USA in 2013. Conceptus, Inc./Bayer HealthCare Pharmaceuticals, Inc. had no role in the study design, data collection and analyses, decision to publish or preparation of the manuscript. The study as a whole was funded by the SWOG (foundation for scientific investigation in obstetrics and gynaecology of the VU University Medical Centre, Amsterdam, the Netherlands). P.G.A.H. has received non-financial support from Conceptus, Inc. during the conduct of this study. He has received grants from Ferring B.V., Merck Serono and Abbott outside the submitted work. M.H.E. has received personal fees from Smith and Nephew and IQ Medical Ventures outside the submitted work.

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TRIAL REGISTRATION DATE: October 21, 2009.

DATE OF FIRST PATIENT'S ENROLMENT: October 26, 2009.

Key words: hydrosalpinges / tubal infertility / salpingectomy / Essure® device / IVF / pregnancy outcome

Introduction

Approximately 15% of female subfertility is due to tubal pathology, thus being one of the major indications for IVF treatment (Hull *et al.*, 1985; Wilkes *et al.*, 2009). However, it is known that women with the most severe form of distal tubal pathology, hydrosalpinges, have poorer ongoing pregnancy rates following IVF treatment compared with women with other forms of tubal infertility [odds ratio (OR): 0.51; 95% confidence interval (CI): 0.417–0.613] (Zeyneloglu *et al.*, 1998). Especially the presence of hydrosalpinges large enough to be visible on ultrasound are associated with reduced implantation and pregnancy rates (OR: 0.38; 95% CI: 0.21–0.68 and OR: 0.37; 95% CI: 0.17–0.82, respectively) and increased miscarriage rates following IVF treatment (Andersen *et al.*, 1994; de Wit *et al.*, 1998; Strandell *et al.*, 1999).

Various surgical treatments, such as salpingectomy, salpingostomy, proximal tubal ligation and transvaginal aspiration of hydrosalpingeal fluid, have been studied. However, only salpingectomy, proximal tubal ligation and transvaginal aspiration of hydrosalpingeal fluid have been evaluated in randomized controlled trials (RCTs) (Dechaud *et al.*, 1998; Goldstein *et al.*, 1998; Strandell *et al.*, 1999; Kontoravdis *et al.*, 2006; Moshin and Hotineanu, 2006; Hammadieh *et al.*, 2008). Laparoscopic salpingectomy in women with hydrosalpinges increases ongoing pregnancy rates following IVF by ~50% compared with no intervention and is, therefore, the current standard treatment (Johnson *et al.*, 2010). Laparoscopic proximal tubal ligation as an alternative treatment to laparoscopic salpingectomy results in similar improvement in the IVF outcome (OR: 1.7; 95% CI: 0.7–3.7) (Kontoravdis *et al.*, 2006; Johnson *et al.*, 2010). The effectiveness of aspiration of hydrosalpingeal fluid could not be demonstrated (Hammadieh *et al.*, 2008). Although laparoscopic salpingectomy and laparoscopic proximal ligation increase ongoing pregnancy rates in women with hydrosalpinges, those interventions are invasive and carry anaesthesiological and surgical risks, especially in the presence of extensive adhesions, often seen in women with hydrosalpinges. In view of the possible adverse effects of laparoscopic surgery, an alternative less-invasive treatment for hydrosalpinges prior to IVF would be useful.

Similar to laparoscopic proximal tubal ligation, hysteroscopic placement of Essure® intratubal devices occludes the tube and thus prevents leakage of hydrosalpingeal fluid into the uterine cavity. The safety and effectiveness of Essure® in minimally invasive permanent tubal sterilization is apparent from the thousands of procedures in which it is applied (Hurskainen *et al.*, 2010; Ouzounelli and Reaven, 2015). Since 2005 several case reports and observational studies have been published which describe the treatment of hydrosalpinges by Essure® devices prior to IVF or ICSI (Rosenfield *et al.*, 2005; Hitkari *et al.*, 2007; Omurtag *et al.*, 2009; Mijatovic *et al.*, 2010, 2012; Galen *et al.*, 2011; Thebault *et al.*, 2012; Inocencio *et al.*, 2013; Matorras *et al.*, 2013; Ozgur *et al.*, 2014). A meta-analysis, including almost all of these studies, demonstrated that this non-incisional Essure® treatment is feasible in women with hydrosalpinges prior to IVF (Arora *et al.*, 2014). However, the effectiveness of Essure® devices when compared with salpingectomy has not been established, as randomized clinical trials comparing the proximal occlusion of hydrosalpinges prior to IVF with Essure® devices or laparoscopic salpingectomy are lacking.

The present study was designed to compare Essure® devices and laparoscopic salpingectomy in the treatment of hydrosalpinges prior to IVF. We hypothesized that in women scheduled for IVF/ICSI proximal occlusion of hydrosalpinges with Essure® devices would be non-inferior to laparoscopic salpingectomy in terms of ongoing pregnancy rates following IVF/ICSI.

Materials and Methods

We undertook a two-centre, open-label, RCT in one academic hospital (VU University Medical Centre, Amsterdam, the Netherlands) and one teaching hospital (Spaarne Gasthuis, Hoofddorp, the Netherlands) that collaborate in a nationwide consortium for women's health research (www.studies-obsgyn.nl). The study was approved by the Institutional Review Board of the VU University Medical Centre in Amsterdam (2008-337) and by the board of directors of the participating hospital. The study was registered as the DESH trial (Dutch Essure® versus salpingectomy for hydrosalpinges) in the Dutch Trial Registry (NTR2073). All participants provided informed consent prior to participation.

Inclusion criteria

We studied infertile women scheduled for IVF/ICSI, who were diagnosed with uni- or bilateral hydrosalpinges visible at ultrasound. The diagnosis of hydrosalpinges had to be confirmed at hysterosalpingography (HSG) or laparoscopy. A hydrosalpinx was defined as a distally occluded Fallopian tube, which became pathologically dilated during tubal patency testing. Furthermore, women needed to be between 18 and 41 years old. Indications for IVF were bilateral tubal pathology, severe endometriosis, male

factor with a total motile sperm count (TMSC) $<3 \times 10^6$ spermatozoa/ml or following intrauterine insemination (IUI) in women with an idiopathic subfertility while ICSI was indicated when the TMSC was $<1 \times 10^6$ spermatozoa/ml.

Women with a recent history of pelvic inflammatory disease (PID within previous 6 months), women with hydrosalpinges that were already blocked proximally, women who could not undergo laparoscopic salpingectomy because of a frozen pelvis seen during a previous laparoscopy, women diagnosed with fibroids (Type 0 or 1) interfering with Essure® insertion and women declining Essure® insertion were excluded. Women fulfilling the inclusion criteria and who had no exclusion criteria were asked to participate in this study and randomized after informed consent was given.

Randomization and allocation

We randomly assigned women (1:1) to Essure® treatment (intervention group) or laparoscopic salpingectomy (control group), using a computer-generated randomization list with block sizes of four. The order of treatments within the blocks was randomly permuted. This randomization list was rendered by an independent data-manager (J.W.R.T.). Masking participants and investigators would be difficult due to the nature of both interventions and since we had objective outcome measurements we witheld sham procedures, leaving the study unblinded.

Surgical procedures

Hysteroscopic proximal tubal occlusion with Essure® intratubal devices

All Essure® devices (Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ, USA) were inserted in an ambulatory setting under antibiotic prophylaxis (Doxycycline 200 mg, 5 days). Local cervical anaesthetics may be used if necessary during hysteroscopy. Introduction of the hysteroscope (Rigid hysteroscope 5.5 mm with 5-Fr working channel, Olympus Netherlands B.V.) was performed according to the method of Bettocchi (1996). The Essure® micro-inserts were placed into the proximal end of the Fallopian tube (uni- or bilateral depending on whether one or two hydrosalpinges were present) using a special delivery system. The Essure® devices were placed with a maximum of three coils protruding into the uterine cavity. Twelve weeks after placement a HSG was carried out to check proximal occlusion of the hydrosalpinges by the Essure® devices.

Laparoscopic salpingectomy

A uni- or bilateral salpingectomy was performed, depending on whether one or two hydrosalpinges were present. In women with unexpected extensive pelvic adhesions during laparoscopy, denying salpingectomy, proximal tubal ligation was performed as an alternative procedure to salpingectomy. Proximal tubal ligation was performed by bipolar diathermy applied at two separate sites on the isthmic segment of the hydrosalpinges, ~1 and 1.5 cm from the corneal section of the Fallopian tube. The treated hydrosalpinges were left *in situ*. Conversion to laparotomy to perform the salpingectomy was not allowed. All women who underwent a laparoscopic treatment of their hydrosalpinges (salpingectomy or proximal tubal ligation) received perioperative antibiotic prophylaxis (cefuroxime 1500 mg/metronidazole 500 mg).

To evaluate ovarian function pre- and post-treatment all women underwent an ultrasound before and 12 weeks after treatment. During this ultrasound, the antral follicle count (AFC) was measured. Furthermore, blood samples were collected in the follicular phase (cycle day 2–4), before and 12 weeks after treatment, to measure FSH, estradiol (E_2) and anti-Mullerian hormone (AMH). FSH concentrations were determined by immunometric assay (Delfia, PerkinElmer, Waltham, MA, USA), with a lower detection limit of 0.5 U/l and an inter-assay coefficient of variation (CV) of <7%. E_2 was determined by competitive immunoassay (Delfia, PerkinElmer), with a lower detection limit of 20 pmol/l and an inter-assay CV of <10%, while AMH was determined by AMH Gen II ELISA (Beckman Coulter Nederland B.V, Woerden, the Netherlands), with a lower detection limit of 0.2 mg/l and an intra-assay CV 7–10%.

IVF

Patients started their IVF/ICSI treatment 12 weeks after the treatment of their hydrosalpinges. IVF/ICSI was performed according to the local protocols of each centre. Pituitary down-regulation could be achieved by administration of GnRH agonists or GnRH antagonists. Doses of administered FSH were noted, as well as the number of retrieved oocytes, fertilization method and quality of transferred embryos.

If women had undergone an IVF/ICSI treatment before inclusion in this study, the remaining frozen-thawed embryos that were transferred after the treatment of the hydrosalpinges were included in the analysis. Their next IVF/ICSI cycle was not included in the primary analysis. If a fresh embryo transfer was cancelled and there were no cryopreserved embryos, the first subsequent cycle ending in a transfer was included in the analysis.

Outcome measurements

The primary outcome was ongoing pregnancy following one IVF/ICSI treatment. Ongoing pregnancy was defined as a fetal heartbeat on ultrasound beyond 10-week gestation. Implantation rate, defined as the number of gestational sacs on ultrasound divided by the number of embryos transferred, was a secondary outcome measure. An ectopic pregnancy, at any extra-uterine site, was considered as an implanted embryo. Other secondary outcome measures were miscarriage rate, ectopic pregnancy rate, live birth rate, proximal tubal occlusion rate after Essure® device placement and differences in ovarian reserve before and 3 months after the treatment of hydrosalpinges. We also assessed time to ongoing pregnancy.

Sample size calculation

To calculate the required sample size, we used the standard power calculation for non-inferiority trials (equivalence trials) (Piaggio *et al.*, 2012). We assumed a 35% pregnancy rate following one treatment cycle in each group with a non-inferiority margin of 10% (Strandell *et al.*, 1999). The calculated sample size would result in 426 patients in each group (α: 0.025 and β: 0.80) which we regard as a non-feasible target for recruitment and inclusion. Therefore, we decided to study only women with hydrosalpinges large enough to be visible on ultrasound as those hydrosalpinges have the poorest prognosis for getting pregnant during IVF and showed the largest benefit from salpingectomy prior to IVF (Strandell *et al.*, 1999). Based on this subgroup analysis of Strandell et al. (1999), we decided to reduce our sample size to 40 patients in each group. The estimated 95% CI around a given Δ of 5% (with an α of 0.05 and a power of 80%) ranges from −15 to 25%. Although this will not provide a definitive proof of non-inferiority, this is the best (and probably the only) approach feasible to test this new treatment (Essure®) versus the current standard (laparoscopic salpingectomy). We analysed the data according to the intention-to-treat (ITT) as well as to the per protocol (PP) principle.

Statistical analyses

Women who were randomized, but never started IVF/ICSI treatment were included for the ITT analyses. However, those women were excluded for the PP analysis. Furthermore, women who underwent both interventions (e.g. unilateral salpingectomy and unilateral Essure® placement), women who were treated with proximal tubal ligation and women who showed leakage along the Essure® device on HSG were also excluded for the PP analysis. We analysed the first IVF/ICSI cycle (including fresh and all frozen-thawed embryo transfers) following the treatment of the hydrosalpinges.

Categorical baseline data were reported as absolute numbers and percentages. Normally distributed continuous variables were summarized as means with standard deviations (SDs) and non-normally distributed continuous variables were reported as medians with 25th–75th percentiles. For binary outcomes, absolute differences in proportions and relative risks (RRs) were calculated and χ^2 tests were used to obtain *P*-values. For normally distributed continuous outcomes, mean differences were calculated and independent *t*-tests were used. For non-normally distributed continuous outcomes Mann–Whitney *U*-tests were used. A Kaplan–Meier analysis was performed to evaluate the time to ongoing pregnancy. A value of $P < 0.05$ was considered significant. The Statistical Package for the Social Sciences version 22.0 (IBM Corp., NY, USA) was used for statistical analyses.

Results

Between October 2009 and December 2014, a total of 99 women were screened for eligibility to take part in the DESH trial, of whom 7 did not meet the inclusion criteria and 7 declined to participate, while 85 women provided informed consent. These women were randomized to Essure® treatment ($n = 42$) or laparoscopic salpingectomy ($n = 43$) before IVF/ICSI. Figure 1 shows the patient flowchart.

Baseline characteristics

There were no differences in baseline characteristics between the two groups (see Table I).

All 42 women randomized to Essure® treatment underwent an (attempt at) Essure® insertion after a median of 1.3 months following randomization. Five women randomized to Essure® treatment had a cross-over to laparoscopic salpingectomy because of unsuccessful Essure® device insertions. Six women randomized to Essure® treatment did not start IVF/ICSI treatment because of personal reasons. Two women were lost to the follow-up.

Women randomized for laparoscopic salpingectomy underwent this intervention after a median of 1.1 month following randomization. Two of these women did not undergo this intervention. One had a spontaneous pregnancy that resulted in a live birth, before laparoscopy was performed. The other woman had no salpingectomy, as at laparoscopy her tube was found to be patent after adhesiolysis. Also, five women randomized to laparoscopic salpingectomy needed a cross-over to Essure® device treatment because of the inability to treat the hydrosalpinges laparoscopically. Four women randomized to salpingectomy did not start IVF/ICSI treatment, two because of personal reasons, one because of a spontaneous pregnancy before salpingectomy and another woman because she no longer had an IVF indication following laparoscopic adhesiolysis. This woman became pregnant after her first IUI treatment and gave birth to a healthy child. Two women were lost to the follow-up.

Surgical procedures

In the 42 women randomized for Essure® treatment a total of 63 Essure® devices were inserted (median of 2 devices per woman, range 0–2) with a median of 1 coil (range, 0–3 coils) visible in the uterine cavity immediately after insertion. In 13 women (31%) local cervical anaesthetic (10 cc lidocaine 1%) was given before hysteroscopy. In two women (both with bilateral hydrosalpinges) the Essure® device insertions were too painful in an ambulatory setting therefore the devices were placed under general anaesthesia in a second attempt. Two women (both with an unilateral Essure® device) declined to undergo an ultrasound, to check the position of the devices, and a HSG, to check proximal occlusion of the hydrosalpinges, 12 weeks after Essure® device placement. In the 40 women with a total of 61 Essure® devices who did have a conformational ultrasound and HSG examination 12 weeks after treatment, ultrasound examination showed a correct position of all 61 devices. However, HSG showed leakage of contrast medium along four (6.6%) of the devices. Despite these findings these women started with IVF at their own request, but none of them became pregnant during the study period.

In 3 of the 43 women (7.0%) randomized for laparoscopic salpingectomy a proximal tubal ligation was performed due to extensive intra-abdominal adhesions and the inability to perform a salpingectomy.

Cross-overs

Five women (11.9%) randomized for Essure® treatment (two with unilateral and three with bilateral hydrosalpinges) had a cross-over to laparoscopic salpingectomy. In four women, it was impossible to insert the devices deep enough into the proximal part of the tube. Three of them had a salpingectomy, and one woman had a proximal tubal ligation. The other woman had a bilateral Essure® placement. HSG showed leakage of contrast along one device. Despite these findings she had an embryo transfer following Essure® treatment, but did not became pregnant. She had a unilateral laparoscopic salpingectomy before a next embryo transfer.

Also five women (11.6%) randomized for laparoscopic salpingectomy had a cross-over to Essure® treatment (three with unilateral and two with bilateral hydrosalpinges). In four women (two with unilateral and two with bilateral hydrosalpinges), the treatment of one of the hydrosalpinges was laparoscopically impossible due to extensive intra-abdominal adhesions. An Essure® device was inserted in the untreated hydrosalpinges in a second attempt. One women, who had a laparoscopic bilateral proximal tubal occlusion, showed fluid in the uterine cavity during the subsequent IVF treatment. An HSG following IVF showed recanalization of one of the treated hydrosalpinges and she subsequently underwent unilateral Essure® device insertion.

The median procedure time was significantly shorter for women who underwent Essure® treatment [7.0 min (25th–75th percentiles 5.0–12.0)] compared with women who underwent laparoscopic salpingectomy [41.0 min (35.0–55.0)] ($P = 0.000$). Furthermore, women who underwent Essure® treatment were not hospitalized. Women undergoing salpingectomy had a median duration of hospitalization of 11.0 h (9.3–13.9) ($P = 0.000$). The mean pain scores at the moment of discharge, measured using a visual analogue scale (0.0–10.0 cm), were significantly lower following laparoscopic salpingectomy 4.0 cm (± 1.4) than following Essure® treatment 5.4 cm (± 2.6) ($P = 0.02$).

Complications

Three of the women randomized for Essure® treatment had a complication. One woman had a PID after insertion of the devices despite antibiotic prophylaxis. She was successfully treated with additional antibiotics. Two women, with bilateral Essure® devices, had a second-look hysteroscopy after one or two failed IVF cycles. During this hysteroscopy the tip of one of the devices was visible and, therefore, those visible Essure® devices were removed hysteroscopically. Both women had a

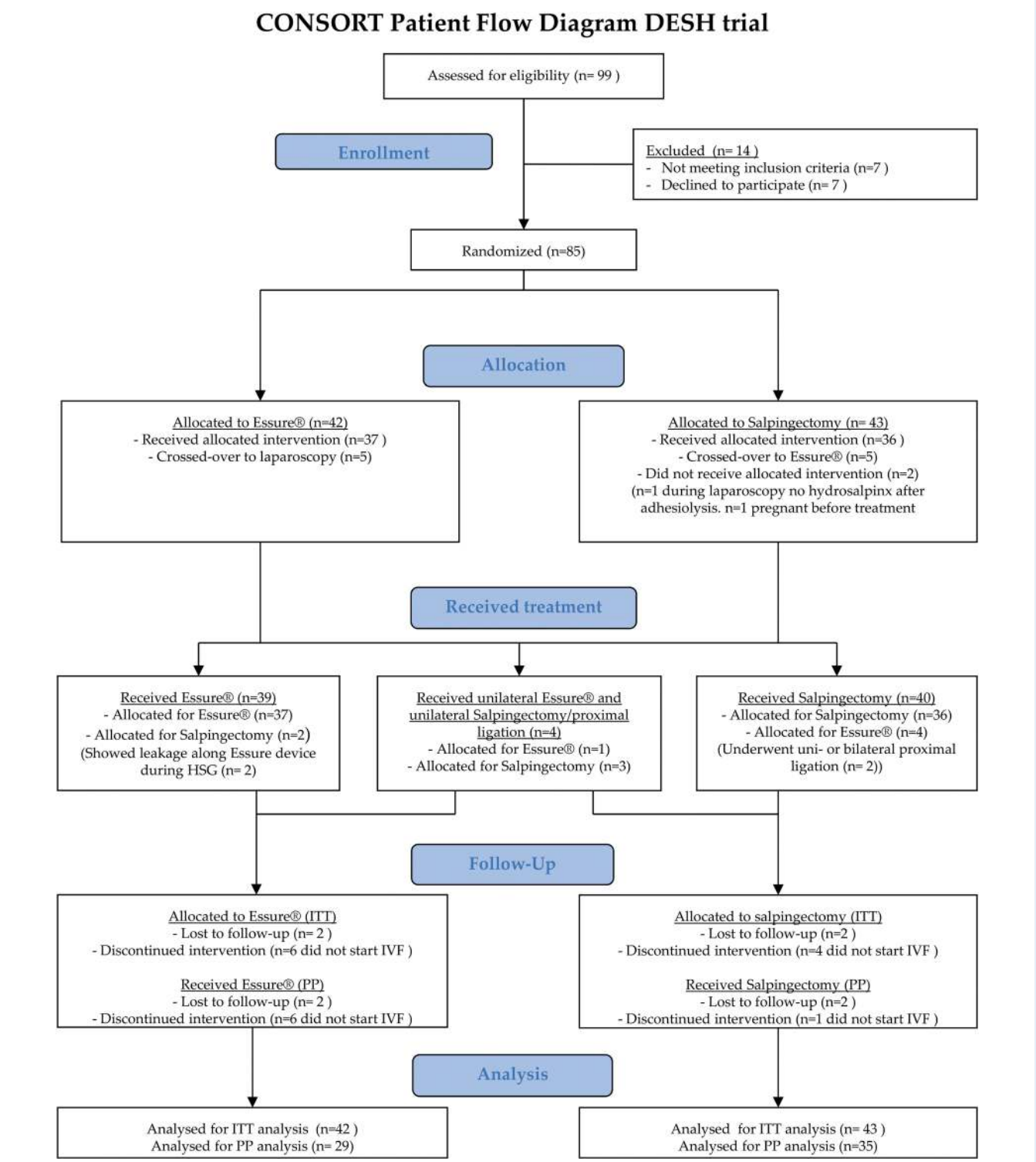

Figure 1 CONSORT patient flow diagram for DESH trial. ITT, intention-to-treat; PP, per protocol; DESH, Dutch Essure® versus salpingectomy for hydrosalpinges; HSG, hysterosalpingography.

subsequent IVF treatment, and one of them became pregnant, which resulted in a live birth. One woman randomized for laparoscopic salpingectomy had a post-operative infection of the umbilical incision, which resolved without treatment.

IVF/ICSI treatment characteristics

Of all randomized women, 71 started with IVF/ICSI after a median of 3.0 months following the treatment of the hydrosalpinges. For the IVF/ICSI treatment characteristics see Table II.

Table I Baseline characteristics of women randomized to Essure® or laparoscopic salpingectomy treatment before IVF/ICSI.

	Intention-to-treat		Per protocol	
	Essure® (*n* = 42)	Salpingectomy (*n* = 43)	Essure® (*n* = 27)	Salpingectomy (*n* = 32)
Age (years) (mean with SD)	32.6 (±4.5)	32.0 (±4.5)	32.8 (±4.5)	32.0 (±4.8)
Duration of subfertility (months) (median with 25th–75th percentile)	32.4 (18.4–50.9)	25.4 (16.1–38.9)	30.7 (20.1–40.4)	26.5 (20.8–37.2)
Subfertility				
Primary	27/42 (64.3%)	23/43 (53.5%)	16/27 (59.3%)	17/32 (53.1%)
Secondary	15/42 (35.7%)	20/43 (46.5%)	11/27 (40.7%)	15/32 (46.9%)
Hydrosalpinx				
Unilateral	18/42 (42.9%)	16/43 (37.2%)	15/27 (55.6%)	11/32 (34.4%)
Bilateral	24/42 (57.1%)	27/43 (62.8%)	12/27 (44.4%)	21/32 (65.6%)
BMI (kg/m^2) (median with 25th–75th percentile)	24.5 (22.0–27.2) (*n* = 41)	23.5 (21.0–25.3) (*n* = 41)	25.8 (22.1–27.4)	23.5 (21.2–25.4) (*n* = 30)
Cycle duration (days) (median with 25th–75th percentile)	28.0 (28.0–29.0) (*n* = 39)	28.0 (27.0–29.0) (*n* = 43)	28.0 (28.0–32.0)	28.0 (26.3–28.0)
Semen (TMSC) (×106/ml) (median with 25th–75th percentile)	29.0 (10.5–59.3) (*n* = 28)	33.0 (12.0–48.0) (*n* = 31)	30.0 (12.1–64.3) (*n* = 22)	36.0 (16.3–52.5) (*n* = 28)

TMSC, total motile sperm count; SD: standard deviation.

Pregnancy outcomes

ITT analysis

The primary outcome ongoing pregnancy rate following one IVF/ICSI cycle was 11/42 (26.2%) in the Essure® group compared with 24/43 (55.8%) in the laparoscopy group (χ^2 $P = 0.008$) (absolute difference: 29.6%; 95% CI: 7.1–49.1) (RR: 0.47; 95% CI: 0.27–0.83; $P = 0.01$). Our secondary outcome measures are listed in Table III. Adjustment for the baseline characteristics: age, duration of subfertility, primary or secondary subfertility and BMI, had negligible impact on trial results and hence are unreported. The median time to ongoing pregnancy was 12.0 months (7.9–19.5) for women randomized for Essure® treatment compared with 6.7 months (5.3–9.5) for women randomized for laparoscopy ($P = 0.000$).

PP analysis

The difference in the ongoing pregnancy rate according to the PP analysis implies that statistical comparisons showed an effect in favour of laparoscopic salpingectomy, but there is no demonstrated statistical significance. The ongoing pregnancy rate following Essure® treatment was 9/27 (33.3%) compared with 19/32 (59.4%) following salpingectomy (χ^2 $P = 0.067$); absolute difference: 26.1% (0.5–51.7) [RR: 0.56 (95% CI: 0.31–1.03; $P = 0.062$)]. For the secondary outcome measures of the PP analysis see Table IV. The median time to ongoing pregnancy was 8.9 months (7.6–15.3) for women treated with Essure® devices compared with 6.6 months (5.3–8.6) for women treated with a laparoscopic salpingectomy ($P = 0.000$) (Fig. 2).

Ovarian reserve

There was no difference in FSH before and after the treatment of the hydrosalpinges in both study groups. The AMH significantly decreased following treatment with Essure® devices compared with the pre-treatment values in both ITT and PP analyses. The AFC significantly increased following Essure® treatment in the ITT analysis, while in the PP analysis there was no difference in values before and after treatment.

In the salpingectomy group, the AMH significantly increased following treatment in the ITT analysis, while in the PP analysis there was no difference between before and after treatment values. There was no difference in AFC before and after salpingectomy in both ITT and PP analyses. However, the observed differences are small and the CIs are wide due to the small sample sizes. Therefore, it is not possible to draw firm conclusions with respect to the impact of both interventions on ovarian function with our study (see Table V).

Discussion

In this RCT, we evaluated the effectiveness of hysteroscopic proximal tubal occlusion by Essure® devices in comparison to laparoscopic salpingectomy for the treatment of hydrosalpinges in women planned for IVF/ICSI. Our study showed an ongoing pregnancy rate following one IVF/ICSI cycle of 11/42 (26.2%) in women randomized for Essure® treatment compared with 24/43 (55.8%) in women randomized for laparoscopic salpingectomy, which is a significant difference in favour of laparoscopic salpingectomy (absolute difference: 29.6%; 95% CI: 7.1–49.1, RR: 0.47; 95% CI: 0.27–0.83). The difference in the ongoing pregnancy rate according to the PP analysis implies an effect in favour of laparoscopic salpingectomy, but there is no demonstrated statistical significance: 9/27 (33.3%) following Essure® versus 19/32 (59.4%) following salpingectomy (absolute difference 26.1%; 95% CI: 0.5–51.7, RR: 0.56; 95% CI: 0.31–1.03). This difference did not reach statistical significance, due to the smaller sample size in the PP analysis. However, the ongoing pregnancy rate per embryo transferred

Table II IVF/ICSI treatment characteristics.

	Intention-to-treat			Per protocol		
	Essure® (*n* = 42)	Salpingectomy (*n* = 43)	*P*-values	Essure® (*n* = 27)	Salpingectomy (*n* = 32)	*P*-values
Started with ART			0.82			n/a
Yes	34/42 (81.0%)	37/43 (86.0%)		27/27 (100%)	32/32 (100%)	
No	6/42 (14.3%)	4/43 (9.3%)		0/27 (0%)	0/32 (0%)	
Missing	2/42 (4.8%)	2/43 (4.7%)				
Time interval between treatment and embryo transfer (months) (median with 25th–75th percentile)	5.3 (4.5–6.4) (*n* = 34)	4.1 (3.3–5.7) (*n* = 36)	0.008	5.2 (4.5–6.2)	3.9 (3.1–5.3) (*n* = 31)	0.001
Units of gonadotrophins (median with 25th–75th percentile)	2475.0 (1643.8–3450.0) (*n* = 26)	2043.8 (1687.5–3112.5) (*n* = 28)	0.59	2550 (1700–3788) (*n* = 21)	2138 (1725–3075) (*n* = 25)	0.331
Duration of ovarian stimulation (days) (median with 25th–75th percentile)	13.0 (11.3–14.0) (*n* = 28)	12.0 (11.0–12.3) (*n* = 30)	0.06	13.0 (12.0–14.3) (*n* = 22)	12.0 (11.0–12.0) (*n* = 27)	0.009
No. of retrieved oocytes (median with 25th–75th percentile)	11.0 (6.0–16.0) (*n* = 29)	12.0 (5.0–15.0)(*n* = 31)	0.87	10.0 (5.0–15.0) (*n* = 23)	12.5 (6.3–16.5) (*n* = 28)	0.525
No. of fertilized oocytes (mean with SD)	7.3 (±4.2) (*n* = 29)	7.2 (±4.6) (*n* = 31)	0.90	6.0 (4.0–10.0)	8.0 (3.3–11.0)	0.471
Fertilization method			0.81			0.774
IVF	27/42 (64.3%)	30/43 (69.8%)		21/27 (77.8%)	27/32 (84.4%)	
ICSI	2/42 (4.8%)	1/43 (2.3%)		2/27 (7.4%)	1/32 (3.1%)	
No fresh treatment	11/42 (26.2%)	9/43 (20.9%)		4/27 (14.8%)	4/32 (12.5%)	
Missing	2/42 (4.8%)	3/43 (7.0%)				
Transferred embryos						
Fresh	30	30	0.92	24	27	0.743
Frozen-thawed	48	30	0.03	37	21	0.017
Embryo transfer						
SET	68	56	0.13	53	44	0.021
DET	5	2	0.37	4	2	0.488
Embryo quality	(missing *n* = 9)	(missing *n* = 7)		(missing *n* = 7)	(missing *n* = 7)	
TQE	44	33	0.25	31	29	0.204
MQE	16	15	0.41	15	7	0.326
PQE	9	5	0.30	8	5	0.772

ART, assisted reproductive technology; SET, single-embryo transfer; DET, double-embryo transfer; TQE, top-quality embryo; MQE, medium-quality embryo; PQE, poor-quality embryo.

showed, even in the PP analysis, a significant difference between Essure® treatment 9/61 (14.8%) and laparoscopic salpingectomy 19/48 (39.6%) (absolute difference: 24.8%; 95% CI: 6.9–41.8, RR: 0.37; 95% CI 0.19–0.75).

Our previous pilot study, in which we treated women with hydrosalpinges with Essure® devices who were laparoscopically inaccessible, showed an ongoing pregnancy rate of 7/20 (35%) after the first IVF cycle (Mijatovic *et al.*, 2010, 2012). This is comparable with the results of our PP analysis, which showed an ongoing pregnancy rate following Essure® treatment of 9/27 (33.3%), but much higher than the results of the ITT analysis (ongoing pregnancy rate 26.2%).

Theories about the negative influence of hydrosalpinges on IVF outcomes suggest that any surgical intervention interrupting the communication between hydrosalpinges and the uterine cavity should improve pregnancy outcomes (Mukherjee *et al.*, 1996; Daftary *et al.*, 2007; Donaghay and Lessey, 2007; Johnson *et al.*, 2010; Lu *et al.*, 2013). The differences in the ongoing pregnancy rate between our pilot study and PP analysis on the one hand and the ITT analysis on the other side could be explained by a difference in the proximal occlusion rate of the hydrosalpinges following Essure® insertion. In the pilot study, 1 of the 27 (3.7%) treated hydrosalpinges showed leakage of contrast along the Essure® device during HSG compared with 4/61 (6.6%) in the ITT analysis in the current trial. In the PP analysis, none of the devices showed leakage of the contrast medium along the devices during HSG.

However, even if we exclude the women whose hydrosalpinges were not proximal occluded by the Essure® devices, the PP analysis resulted in

Table III Primary and secondary outcome measures: pregnancy outcomes following one IVF/ICSI treatment cycle (ITT analyses).

	Essure® ($n = 42$)	Salpingectomy ($n = 43$)	Absolute difference (95% CI)	*P*-values (χ^2)	Relative risks (RR)	95% CI for the RR
Primary outcome						
Ongoing pregnancy						
Per included patient	11/42 (26.2%)	24*/43 (55.8%)	29.6% (7.1–49.1)	0.008	0.47	0.27–0.83
Per embryo transferred	11/78 (14.1%)	22*/60 (36.7%)	22.6% (7.1–37.7)	0.003	0.38	0.20–0.73
Secondary outcome						
Implantation rate						
Per embryo transferred	13/78 (16.7%)	23/60 (38.3%)	21.6% (5.7–37.0)	0.006	0.43	0.24–0.79
Clinical pregnancy rate						
Per included patient	13/42 (31.0%)	25/43 (58.1%)	27.1% (4.4–47.0)	0.016	0.53	0.32–0.89
Miscarriage rate						
Per included patient	2/42 (4.8%)	1/43 (2.3%)	2.5% (−8.3–14.1)	0.616	2.05	0.19–21.74
Per embryo transferred	2/78 (2.6%)	1/60 (1.7%)	0.9% (−6.7–7.5)	1.000	1.54	0.14–16.57
Ectopic pregnancy rate						
Per included patient	0/42 (0%)	0/43 (0%)	n/a	n/a	n/a	n/a
Per embryo transferred	0/78 (0%)	0/60 (0%)	n/a	n/a	n/a	n/a
Live birth rate						
Per included patient	9/42 (21.4%)	20*/43 (46.5%)	25.1% (3.4–44.5)	0.022	0.46	0.24–0.89
Per embryo transferred	9/78 (11.5%)	18*/60 (30.0%)	18.5% (4.0–33.1)	0.009	0.38	0.19–0.80

ITT, intention-to-treat analyses; CI, confidence interval; n/a, not applicable.
*One twin pregnancy following SET, calculated as one pregnancy and one live birth.

Table IV Primary and secondary outcome measures: pregnancy outcomes following one IVF/ICSI treatment cycle (PP analyses).

	Essure® ($n = 27$)	Salpingectomy ($n = 32$)	Absolute difference (95% CI)	*P*-values (χ^2)	Relative risks (RR)	95% CI for the RR
Primary outcome						
Ongoing pregnancy						
Per included patient	9/27 (33.3%)	19/32 (59.4%)	26.1% (0.5–51.7)	0.067	0.56	0.31–1.03
Per embryo transferred	9/61 (14.8%)	19/48 (39.6%)	24.8% (6.9–41.8)	0.004	0.37	0.19–0.75
Secondary outcome						
Implantation rate						
Per embryo transferred	11/61 (18.0%)	20/48 (41.7%)	23.7% (5.3–41.1)	0.01	0.43	0.23–0.81
Clinical pregnancy rate						
Per included patient	11/27 (40.7%)	20/32 (62.5%)	21.8 (−6.0–46.4)	0.121	0.65	0.38–1.11
Miscarriage rate						
Per included patient	2/27 (7.4%)	1/32 (3.1%)	4.3% (−10.3–21.4)	0.588	2.37	0.23–27.74
Per embryo transferred	2/61 (3.3%)	1/48 (2.1%)	1.2% (−8.3–9.5)	1.000	1.60	0.15–17.12
Ectopic pregnancy rate						
Per included patient	0/27 (0.0%)	0/32 (0.0%)	n/a	n/a	n/a	n/a
Per embryo transferred	0/61 (0.0%)	0/48 (0.0%)	n/a	n/a	n/a	n/a
Live birth rate						
Per included patient	8/27 (29.6%)	16/32 (50.0%)	20.4% (−7.0–44.5)	0.143	0.59	0.30–1.17
Per embryo transferred	8/61 (13.1%)	16/48 (33.3%)	20.2% (3.2–36.9)	0.007	0.39	0.18–0.84

PP, per protocol analyses.

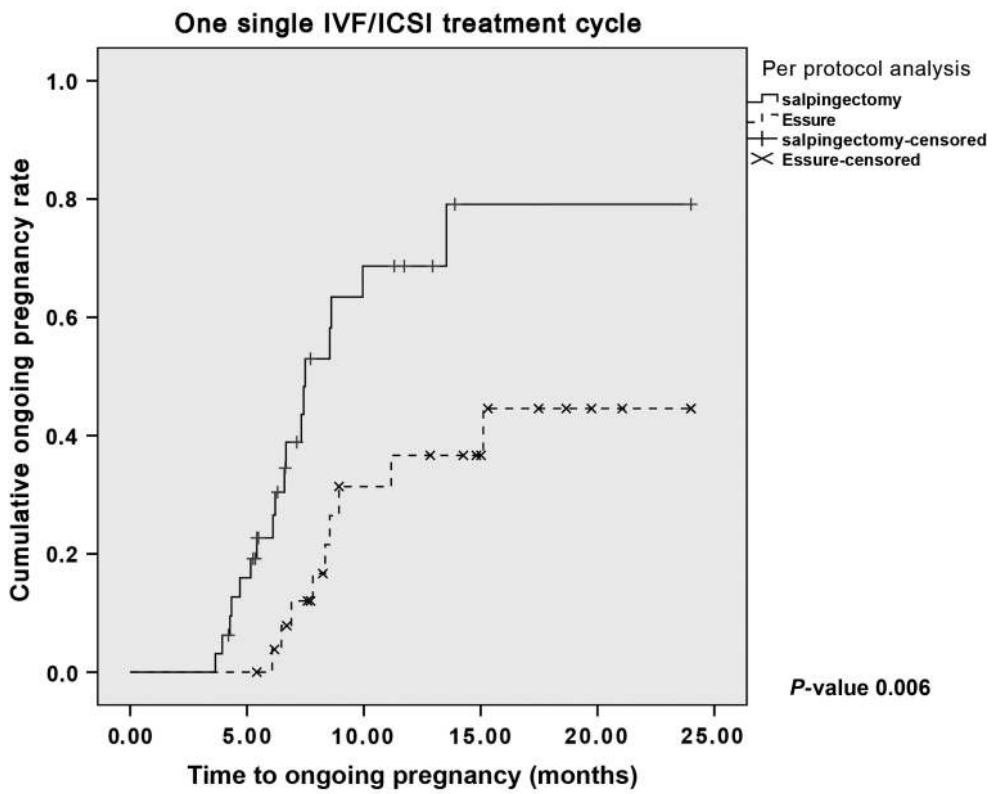

Figure 2 Kaplan–Meier curve: time to ongoing pregnancy (from randomization).

Table V Ovarian reserve tests: before and 12 weeks after treatment of the hydrosalpinges.

	Intention-to-treat			Per protocol		
	Ovarian reserve before treatment	Ovarian reserve 12 weeks after treatment	*P*-values	Ovarian reserve before treatment	Ovarian reserve 12 weeks after treatment	*P*-values
Essure®						
FSH (U/l)	6.2 (5.2–7.0) ($n = 33$)	6.7 (5.3–8.4) ($n = 28$)	0.53	6.3 (5.3–7.2) ($n = 23$)	6.4 (4.8–8.8) ($n = 20$)	0.17
AMH (μg/l)	2.9 (1.5–5.9) ($n = 32$)	2.1 (0.9–5.7) ($n = 31$)	0.02	3.6 (1.4–5.9) ($n = 22$)	2.1 (1.0–6.1) ($n = 22$)	0.02
AFC	13.0 (9.0–20.0) ($n = 41$)	14.0 (8.0–16.0) ($n = 39$)	0.04	14.0 (10.3–19.3) ($n = 26$)	14.0 (10.0–16.0) ($n = 26$)	0.58
Salpingectomy						
FSH (U/l)	6.0 (5.4–7.2) ($n = 38$)	6.6 (4.9–7.6) ($n = 26$)	0.28	6.0 (5.4–7.4) ($n = 29$)	6.7 (5.5–7.9) ($n = 25$)	0.39
AMH (μg/l)	2.7 (1.5–8.0) ($n = 34$)	2.8 (1.1–4.6) ($n = 26$)	0.005	2.2 (1.3–5.7) ($n = 26$)	2.7 (1.0–5.0) ($n = 25$)	0.07
AFC	14.0 (10.0–16.0) ($n = 41$)	14.0 (9.0–18.5) ($n = 38$)	0.11	14.0 (10.0–16.0) ($n = 31$)	13.5 (8.8–18.5) ($n = 30$)	0.06

AMH, anti-Mullerian hormone; AFC, antral follicle count.
Median with 25th–75th percentile.

an ongoing pregnancy rate of 9/27 (33.3%), which is still much lower than the ongoing pregnancy rate following salpingectomy 19/32 (59.4%). The difference in ongoing pregnancy following Essure® treatment versus laparoscopic salpingectomy can be explained by a difference in the implantation rate. The implantation rate following Essure® treatment is 11/61 (18.0%) compared with 20/48 (41.7%) following laparoscopic salpingectomy (0.43; 95% CI: 0.23–0.81). This difference in the implantation rate may be caused by the presence of the Essure® device itself. The Essure® device may have a negative influence on the endometrial environment leading to lower endometrial receptivity thereby lowering the

implantation rate and thus resulting in lower ongoing pregnancy rates. We will address this issue in an endometrial receptivity study, in a selection of women who participated in the DESH trial, which is now in progress by our group.

One of our secondary outcome measures was the influence of both interventions on ovarian function, as some studies suggested that salpingectomy may affect ovarian function by interfering with ovarian blood flow (Lass *et al.*, 1998; Gelbaya *et al.*, 2006; Ye *et al.*, 2015). However, there are also studies that showed no differences in the response to ovarian hyperstimulation before and after salpingectomy (Strandell *et al.*, 2001; Ni *et al.*, 2013). Our study showed no, or only small clinically unimportant, differences between the FSH and AFC measurements before and after the treatment of the hydrosalpinges in both study groups. However, AMH significantly decreased following Essure® treatment in both analyses in our study. It may be that the presence of the device itself has an influence on the premature ovarian follicles, which produce AMH. On the other hand, the individual intra-cycle variation of AMH may be up to 13% (van Disseldorp *et al.*, 2010). Furthermore, the CIs of the differences are wide, therefore, it is questionable if AMH really decreases following Essure® treatment. Further research is needed to draw firm conclusions with respect to the impact of both interventions on AMH.

Strengths

Our study is the first RCT that compares the effectiveness of the treatment of hydrosalpinges by Essure® devices to laparoscopic salpingectomy. This study is an excellent example that true progress usually requires randomized evaluation. As the Essure® technique is applied successfully for sterilization, thus implying perfect obstruction of the Fallopian tube, one would anticipate equal effectiveness from Essure® when compared with salpingectomy, as both interventions are supposed to interrupt the communication between hydrosalpinges and the uterine cavity. Introduction of Essure® in clinical practice without proper evaluation, as we have done in this trial, would have led to decreased success rates for couples undergoing IVF, a loss that would not have been compensated by the non-invasiveness of this method.

Limitations

Ideally, we would have selected a fixed endpoint in time, for example 6 months after the randomization. However, since some couples delayed IVF/ICSI for a longer time after having surgery, and since the investigated treatments could only show their effect after an IVF/ICSI cycle, the use of a fixed endpoint would have implicated that some couples would not have started their IVF/ICSI treatment at the time of analysis and the potential treatment effect could not be measured. Although we found a difference in ongoing pregnancy rates in favour of the treatment of hydrosalpinges by laparoscopic salpingectomy, our small sample size resulted in a wide CI, with the upper limit of 25% difference in the ongoing pregnancy rate accepted as non-inferior. A larger study population would have given a more accurate treatment effect with smaller CIs. However, we found a difference of 30% in the ITT analysis versus 36% in the PP analysis, so we believe that the issue of adequate power is less relevant.

The interventions and IVF/ICSI treatments in this study are time-consuming. First, women had to be scheduled for surgery, then after the treatment of the hydrosalpinges they had to wait another 12 weeks before IVF/ICSI treatment could be started. Therefore, it is not surprising that this study had a protocol violation rate of up to 24%. Furthermore, we only studied patients with hydrosalpinges large enough to be visible on ultrasound, because these are associated with the poorest pregnancy outcomes following IVF (Andersen *et al.*, 1994; de Wit *et al.*, 1998; Strandell *et al.*, 1999). This limits the generalizability of the results to all women with hydrosalpinges who are planned for IVF/ICSI. There is, however, no reason to assume that Essure® would be non-inferior to salpingectomy in women with smaller hydrosalpinges. Finally, we did not perform a second-look hysteroscopy following Essure® insertion to confirm proximal tubal occlusion, as HSG is recommended by the American College of Obstetricians and Gynaeoclogists (ACOG) as the confirmation test following Essure® placement (ACOG, 2010). Transvaginal ultrasonography was used to verify the deep intramural position of the Essure® devices (Veersema *et al.*, 2005).

Future implications

In view of our results, laparoscopic salpingectomy remains the recommended treatment for women with sonographically visible hydrosalpinges undergoing IVF/ICSI. However, 5 of the 43 women randomized for laparoscopic salpingectomy could not be treated sufficiently by laparoscopy due to extensive intra-abdominal adhesions and needed an Essure® insertion in a second attempt. Two of these women had an ongoing pregnancy after one IVF treatment following Essure® insertion. Therefore, Essure® treatment could still be considered in women with hydrosalpinges who are laparoscopically inaccessible, although it is questionable whether the ongoing pregnancy rates may improve compared with no intervention at all. The observed RR of ongoing pregnancy following Essure® compared with salpingectomy is comparable with the RR of ongoing pregnancy following no intervention compared with salpingectomy, as reported in the landmark study of Strandell (RR: 0.44; 95% CI: 0.20–0.96) (Strandell *et al.*, 1999).

Furthermore, we should realize that in case of double-sided tubal pathology, salpingectomy denies the woman future natural conception, thus making IVF her only possibility to conceive. Indeed, one woman in the salpingectomy group with a unilateral hydrosalpinx on the left side and a proximal occlusion of her contralateral Fallopian tube, had a natural conception prior to treatment. One could imagine that a more tubal preserving approach, such as transvaginal aspiration of hydrosalpingeal fluid, establishes a similar beneficial effect on the IVF outcome as salpingectomy, while natural conception remains possible. We, therefore, would welcome a randomized study with a similar design, in which we compare transvaginal aspiration of hydrosalpingeal fluid with salpingectomy.

Conclusion

In summary, we could not demonstrate non-inferiority of hysteroscopic proximal tubal occlusion with Essure® devices when compared with salpingectomy in women with ultrasound visible hydrosalpinges scheduled for IVF/ICSI. Salpingectomy therefore remains the procedure of choice for women with hydrosalpinges who are planned for IVF/ICSI.

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Authors' roles

K.D., M.C.I.L. and V.M. included all patients and performed all HSG procedures. V.M. performed almost all laparoscopic salpingectomies. M.H.E. placed almost all Essure® devices. K.D., M.C.I.L. and V.M. collected all data. K.D. and M.C.I.L. and J.W.R.T. analysed the data. K.D. is the principal author. M.H.E., R.S., J.W.R.T., P.G.A.H. and V.M. participated in the invention of the study design. M.C.I.L., M.H.E., R.S., B.W.J.M., P.G.A.H. and V.M. critically discussed the manuscript. V.M. is main co-author.

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Conflict of interest

P.G.A.H. has received non-financial support from Conceptus, Inc. during the conduct of this study. He has received grants from Ferring B.V., Merck Serono and Abbott outside the submitted work. M.H.E. has received personal fees from Smith and Nephew and IQ Medical Ventures outside the submitted work.

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