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Diagnostic accuracy of hysterosalpingo-foam-sonography to confirm tubal occlusion after Essure[®] placement as treatment for hydrosalpinges



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Abstract Consensus globally is that hydrosalpinges need to be treated before IVF owing to their negative influence on outcomes. The current standard treatment is laparoscopic salpingectomy. A potential less invasive treatment is proximal occlusion of a hydrosalpinx by hysteroscopic placement of an Essure[®] device. Tubal occlusion after Essure[®] placement needs to be verified by hysterosalpingography (HSG). However, this is a painful examination, that exposes patients to radiation. Hysterosalpingo-foam sonography (HyFoSy) is a less invasive alternative test to confirm proximal tubal occlusion. This prospective diagnostic accuracy study evaluated if HyFoSy is as accurate as HSG to confirm proximal tubal occlusion after placement of an Essure[®] device as treatment for a hydrosalpinx before IVF. Thirty-eight treated hydrosalpinges in 26 women were evaluated. Proximal occlusion was verified by HyFoSy (index test) and HSG (standard reference). The accuracy of HyFoSy was 97.4% (95% CI 92.3% to 100.0%). Sensitivity and specificity were 97.1% (95% CI 84.6% to 99.5%) and 100.0% (95% CI 40.2% to 100.0%), respectively. After an Essure[®] device is placed as treatment for a hydrosalpinx before IVF, HyFoSy is as able as HSG to confirm proximal tubal occlusion. If HyFoSy demonstrates tubal patency, a subsequent HSG needs to be carried out to validate this finding. 

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Introduction

In all women presenting with subfertility caused by tubal pathology, hydrosalpinges are found in 10–30% (Andersen et al., 1994; Blazar et al., 1997; Murray et al., 1998; Strandell et al., 1994). The presence of a hydrosalpinx can severely reduce the chance of pregnancy from IVF by almost 50% (Johnson et al., 2010; Zeyneloglu et al., 1998). Therefore, hydrosalpinges need to be treated before IVF. The current standard treatment is a laparoscopic salpingectomy (Johnson et al., 2010). A potential less invasive alternative is proximal occlusion of a hydrosalpinx by hysteroscopic placement of an Essure® intratubal device (Conceptus Inc., San Carlos, CA), originally developed for female sterilization (Arora et al., 2014; Galen et al., 2011; Hitkari et al., 2007; Inocencio et al., 2013; Matorras et al., 2013; Mijatovic et al., 2010, 2012; Omurtag et al., 2009; Ozgur et al., 2014; Rosenfield et al., 2005; Sonigo et al., 2013; Thebault et al., 2012). Occlusion of the proximal part of the hydrosalpinx might also prevent leakage of hydrosalpingeal fluid towards the uterine cavity and could thereby reduce the negative influence on pregnancy rates. This new alternative treatment is currently being evaluated in a randomized controlled trial (Dutch Essure® versus Salpingectomy for Hydrosalpinx trial, NTR2073). The tubal occlusion after Essure® (Conceptus Inc.) placement results from a benign fibrotic reaction with tissue ingrowth (Valle et al., 2001). This reaction takes on average 3 months to achieve complete occlusion (Valle et al., 2001). To determine whether the device prevents leakage of hydrosalpingeal fluid, a confirmation test needs to be carried out 12 weeks after placement. The American College of Obstetricians and Gynaecologists (ACOG) recommends a hysterosalpingogram (HSG) to confirm proximal occlusion after Essure® (Conceptus Inc.) device placement (ACOG Committee Opinion, 2010). A HSG, however, is a painful examination and exposes women to radiation (Dreyer et al., 2014). A possible less invasive alternative test is a hysterosalpingo-foam sonography (HyFoSy). This new ultrasonographic tubal patency test was introduced in 2011 and is suggested to be an accurate test to demonstrate tubal patency (Emanuel and Exalto, 2011; Emanuel et al., 2012; van Schoubroeck et al., 2013). The aim of the present study was to evaluate if HyFoSy is an accurate test to confirm proximal tubal occlusion after Essure® device (Conceptus Inc.) placement as treatment for hydrosalpinges before IVF.

Material and methods

A prospective diagnostic accuracy study was conducted to evaluate HyFoSy as confirmation test for proximal tubal occlusion after Essure® placement (Conceptus Inc.) as treatment for hydrosalpinges (Linnet et al., 2012). The secondary outcome measures included procedure time, volume of contrast medium and pain experienced during HyFoSy (index test) and HSG (reference standard), measured by Visual Analogue Scale (VAS) scores (1.0–10.0 cm). Patients treated for a hydrosalpinx by an Essure® device (Conceptus Inc.) as part of the DESH trial were recruited. The DESH trial (Dutch Essure® versus Salpingectomy for Hydrosalpinges, NTR 2073) is an ongoing multicentre randomized controlled trial evaluating if the treatment of a hydrosalpinx by an Essure® device

(Conceptus Inc.) before starting IVF is even as effective as a laparoscopic salpingectomy. This diagnostic accuracy study is a sub-study of the larger DESH trial, which took place between March 2011 and May 2014. Women who were excluded from the DESH trial because of a contraindication for laparoscopy, but still had an off-label Essure® (Conceptus Inc.) placement for their hydrosalpinges within this period, were also invited to participate. For more details of the DESH trial, we refer to the Netherlands Trial Register (NTR 2073). All women underwent a HyFoSy followed by a HSG. This study was conducted according to the STARD (Standard for the reporting of diagnostic accuracy studies) and approved by the Institutional Review Board of the VU University Medical Center on 21 August 2009 (reference number: 2008/337). All participating women gave informed consent.

Clinical methods

Details about the procedure used for the hysteroscopic placement of the Essure® devices (Conceptus Inc.) have been published previously (Mijatovic et al., 2010, 2012). A HyFoSy (index test) as well as a HSG (reference standard) 12 weeks after placement was conducted to confirm the occlusion of the treated hydrosalpinges. During both tests, patients were placed in a supine position. A Trelat vaginal speculum (Gynesol, Pakistan) was inserted to visualize the cervix. During HyFoSy, a cervical balloon-less catheter was placed, through which approximately 5 ml foam was infused into the uterine cavity. This foam was created by mixing 10 ml of ExEm® gel (IQ Medical Ventures B.V. Delft, the Netherlands) with 10 ml of purified water. The created foam was sufficiently stable to demonstrate echogenicity for at least 5 min, and was sufficiently fluid to pass through patent tubes (Emanuel and Exalto, 2011). During infusion of the foam, proximal occlusion of the treated hydrosalpinx was checked by a vaginal ultrasonography. For HSG, a cervix adapter by Semm® (WISAP Medical Technology GmbH, Brunenthal/Hofolding, Deutschland) was placed and through this special catheter approximately 5 ml of contrast medium (Telebrix Hystero®, Guerbet Nederland B.V.) was infused into the uterine cavity. Three to four X-rays (AXIOM Iconons R200; Siemens) were made to check if the hydrosalpinges were occluded by the Essure® devices (Conceptus Inc.). All women were premedicated with naproxen 500 mg (Accord Healthcare, The Netherlands) the evening before and 2 h before the confirmation tests. All HyFoSy and HSG procedures were conducted by two doctors with sufficient experience with both tests. To preclude test review bias, all HyFoSy (index test) procedures were carried out before HSG (reference standard). During HSG, the readers were not blinded for the results of HyFoSy.

Statistical analyses

Statistical analyses were conducted to assess the agreement in test results between HyFoSy (index test) and HSG (reference standard). The primary outcome, the accuracy of HyFoSy, was measured by the sum of the true positives and true negatives divided by the sum of the true positives, true negatives, false positives and false negatives. (Linnet et al., 2012) The sensitivity (true occluded rate), specificity (true

patency rate), positive predictive value (probability that a hydrosalpinx is occluded when assessed as occluded by HyFoSy) and negative predictive value (probability the hydrosalpinx is not occluded when assessed as patent by HyFoSy) were calculated with their corresponding 95% confidence intervals. Differences in continuous data were tested for significance using a Wilcoxon signed rank test. These data are presented with a median and interquartile range. A *P*-value of <0.05 indicated statistically significant differences, and all values were calculated using a two-tailed significance level. The IBM Statistical Package for Social Sciences (SPSS) version 20.0 (IBM Corp., USA) was used for statistical analyses.

Results

Between March 2011 and May 2014, 26 women who were treated for their hydrosalpinges by an Essure® device (Conceptus Inc.) before starting their IVF treatment, were enrolled in this study in the VU University Medical Center, Amsterdam (Figure 1). Demographic and clinical characteristics are presented in Table 1.

Table 1 Demographic and clinical characteristics.

	n = 26
Age (years)	33.5 (IQR 29.1–37.8)
Para	
Nulliparous	23/26 (88.5%)
Multiparous	3/26 (11.5%)
Treatment	
Unilateral Essure® placement	14/26 (53.8%)
Bilateral Essure® placement	12/26 (46.2%)

IQR = interquartile range.

Of the 26 included women, 14 had an unilateral hydrosalpinx, and 12 had bilateral hydrosalpinges. A total of 38 Essure® devices (Conceptus Inc.) were placed.

All women underwent a HyFoSy followed by a HSG after a median of 12.2 weeks (interquartile range 11.3–13.5 weeks) after Essure® placement (Conceptus Inc.). Of the 38 treated hydrosalpinges, 34 were successfully occluded as confirmed by HSG. Of the 34 occluded hydrosalpinges, HyFoSy was able to correctly identify 33 (Figure 2), resulting in a sensitivity of 97.1% (95% CI 84.6% to 99.5%) and a positive predictive value of 100.0% (95% CI 89.3% to 100.0%). Furthermore, HyFoSy correctly identified all four patent hydrosalpinges (specificity of 100.0% (95% CI 40.2% to 100.0%) and negative predictive value of 80.0% (95% CI 28.8% to 96.7%)). The overall accuracy of HyFoSy was 97.4% (95% CI 92.34% to 100.0%).

The secondary outcome, experienced pain, was significantly lower during HyFoSy than during HSG (*P* < 0.01). The mean time to sufficiently investigate tubal status was significantly shorter for HyFoSy than for HSG (Table 2). No difference in volume of contrast media was found. No complications occurred (bleeding or infection) during this study.

Discussion

To the best of our knowledge, this is the first study evaluating the accuracy of HyFoSy to confirm proximal tubal occlusion after an Essure® device (Conceptus Inc.) was placed as treatment for a hydrosalpinx before IVF. Our results show that HyFoSy is an accurate test with a sensitivity of 97.1% (95% CI 84.6% to 99.5%) and a specificity of 100.0% (95% CI 40.2% to 100.0%), and could therefore substitute HSG in most women.

Whether or not a hydrosalpinx is successfully occluded by an Essure® intratubal device (Conceptus Inc.) needs to be confirmed before commencement of IVF. Currently, a HSG is carried out to check proximal occlusion. However, it is a painful examination, and exposes women to radiation (Dreyer

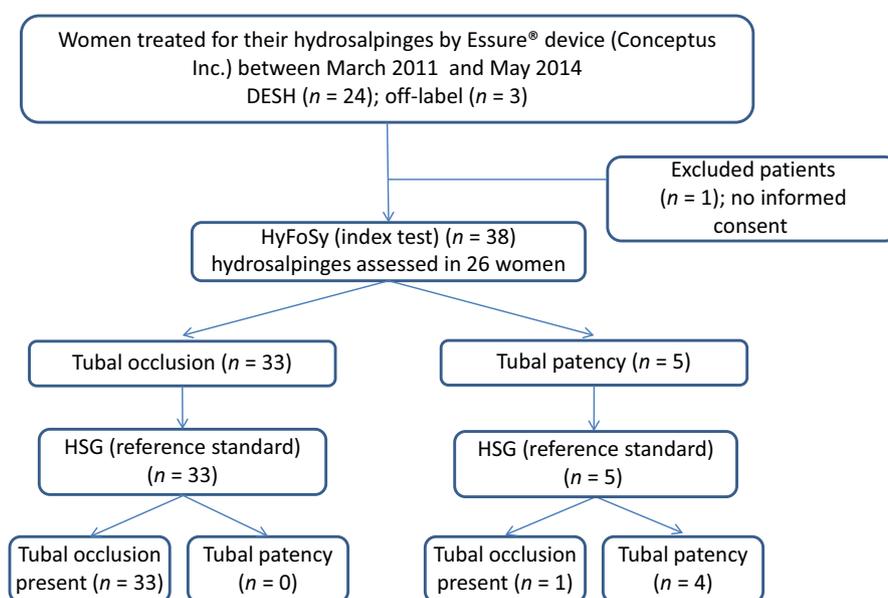


Figure 1 STARD (Standard for the reporting of diagnostic accuracy studies) flow diagram. DESH = Dutch Essure® versus Salpingectomy for Hydrosalpinges, NTR 2073; HSG = hysterosalpingography; HyFoSy = hysterosalpingo-foam sonography.

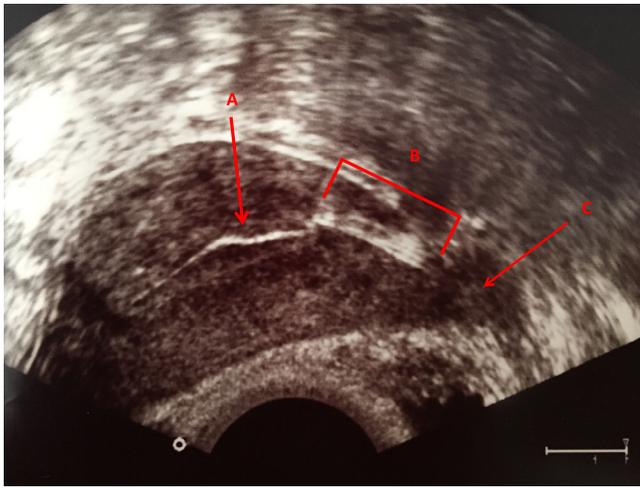


Figure 2 HyFoSy shows proximal tubal occlusion after Essure® placement (Conceptus Inc). Transversal section of the uterine cavity. (A) Uterine cavity filled with echogenic foam; (B) Essure® device (Conceptus Inc.); (C) no echogenic foam visible distal from the Essure® device (Conceptus Inc).

et al., 2014). Therefore, HyFoSy was evaluated to establish whether it is an accurate alternative to HSG to confirm proximal tubal occlusion in women treated for a hydrosalpinx by an Essure® device (Conceptus Inc.). The findings of the present study support the results of a previous study by van Schoubroeck et al. (2013). In their study, 20 subfertile women who were scheduled for tubal patency testing by laparoscopic chromopertubation underwent a HyFoSy before surgery. They found a 100% concordance in test results between HyFoSy and laparoscopic chromopertubation. In the present study, concordance of 97.4% was achieved in test results between HyFoSy and HSG. All tubes found to be occluded by HyFoSy were indeed occluded as confirmed by HSG (positive predictive value of 100.0%). Only one false negative assessment was observed (tubal patency during HyFoSy, but proximal occlusion during HSG). Therefore, it is advised that a patent tube

or uncertain proximal occlusion during HyFoSy needs to be validated by a HSG.

Hysterosalpingo-foam sonography does not require radiation exposure in contrast to HSG, and can therefore be carried out during regular office hours at the gynaecologic outpatient department. Another advantage of HyFoSy over HSG is that, by using ultrasonography, a full assessment of the uterus, ovaries and pelvis can be made at the same time. Such an assessment of the uterine cavity and the ovarian reserve needs to be done at the beginning of an IVF treatment. By confirming proximal occlusion in these women by HyFoSy, this assessment can be done during the same examination. Furthermore, HyFoSy showed to be a less painful and less time consuming test than HSG. This is in line with the results of our previous study, in which pain experience was compared during HyFoSy and HSG in 40 subfertile women (Dreyer et al., 2014).

Strengths and limitations

Some limitations of this study need to be addressed. First, the number of women studied and analysed was small, resulting in wide confidence intervals and thus limits the generalizability of the results. Second, the researchers who conducted the HSGs (standard reference) were not blinded for the results of HyFoSy (index test). This may have introduced diagnostic review bias. Strength of this study is that the researchers were blinded for the results of the reference standard (HSG) during the index test (HyFoSy). This was done to preclude test review bias.

In conclusion, HyFoSy is as able as HSG to confirm proximal tubal occlusion after placement of an Essure® device (Conceptus Inc.) as treatment for a hydrosalpinx before IVF. If HyFoSy demonstrates tubal patency, a subsequent HSG needs to be performed to validate this finding.

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Table 2 Primary and secondary outcomes.

Primary outcome	HyFoSy (n = 38 tubes)	HSG (n = 38 tubes)	P-value
Proximal occlusion after Essure® placement (Conceptus Inc.)			
Sensitivity	97.1% (95% CI 84.6% to 99.5%)	NA	
Specificity	100.0% (95% CI 40.2% to 100.0%)	NA	
Positive predictive value	100.0% (95% CI 89.3% to 100.0%)	NA	
Negative predictive value	80.0% (95% CI 28.8% to 96.7%)	NA	
Accuracy	97.4% (95% CI 92.3% to 100.0%)	NA	
Secondary outcome	HyFoSy (n = 26 women)	HSG (n = 26 women)	
VAS pain scores (cm)	2.0 (IQR 0.2 to 2.9)	5.1 (IQR 3.0 to 7.0)	<0.01
Procedure time (min)	5.5 (IQR 4.0 to 7.0)	9.5 (IQR 8.0 to 11.8)	<0.01
Volume of used contrast medium (ml)	3.5 (IQR 2.3 to 7.9)	4.0 (IQR 3.0 to 4.9)	NS

CI = confidence interval; HSG = hysterosalpingography; HyFoSy = hysterosalpingo-foam sonography; IQR = interquartile range; NA = not applicable; NS = not statistically significant.

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