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**Summary**

## SUMMARY

### Advances in diagnosis and treatment of tubal subfertility

Subfertility, defined as failure to conceive within 12 months of unprotected intercourse, is a major health problem that affects up to 1 in 10 couples trying to get pregnant. One of the most common types of subfertility is tubal subfertility, with an incidence of 15-30%. This thesis evaluated different aspects of diagnosis and treatment of tubal subfertility and is divided into three parts. The first part of this thesis focused on the therapeutic effect of the diagnostic tubal patency test hysterosalpingography (HSG). The second part of this thesis evaluated two different aspects (pain experience and accuracy) of the recently introduced sonographic tubal patency test hysterosalpingo-foam sonography (HyFoSy). The third part assessed the effectiveness of a new and minimal invasive treatment option for subfertile women with hydrosalpinges and the impact of this new treatment on pregnancy outcomes following IVF/ICSI.

[Chapter 1](#) gives an outline of the research presented in this thesis.

### PART I: Therapeutic effect of diagnostic tubal patency testing

The therapeutic effect of the diagnostic tubal patency test hysterosalpingography was evaluated in [Chapter 2](#). This chapter described a secondary data-analysis of a prospective cohort of 4547 couples with unexplained subfertility included in 38 clinics in the Netherlands between January 2002 and December 2004. The analysis showed that diagnostic tubal patency testing by HSG increased ongoing pregnancies in couples with unexplained subfertility. The estimated probability of natural conception was almost one and a half-fold higher following HSG compared to no HSG (Hazard Ratio 1.4; 95% CI 1.3 to 1.5).

Whether or not the therapeutic effect of HSG was influenced by the type of contrast medium used was evaluated in the study described in [Chapter 3](#). This study described the results of a multi-centre, randomised controlled trial investigating whether the use of oil-based contrast medium during HSG could increase ongoing pregnancies as compared to the use of water-based contrast medium (H2Oil study). Between February 2012 and October 2014, a total of 1119 subfertile women were included in 27 clinics in the Netherlands. Following randomisation 557 women underwent an HSG with oil-based contrast medium and 562 women underwent an

HSG with a water-based contrast medium. The results showed that in subfertile women undergoing an HSG for tubal patency testing, use of an oil-based contrast medium increased the six months ongoing pregnancy rate as compared to the use of water-based contrast medium (39.7% (220/554) versus 29.1% (161/554)) (RR 1.37; 95% CI 1.16 to 1.61). The study in [Chapter 3](#) advised that flushing the tubes with oil-based contrast medium should be offered routinely to subfertile women as part of the fertility workup.

### PART II: Sonographic tubal patency testing

Hysterosalpingography is a minimally invasive test that can be performed on an outpatient basis and is therefore the test of first choice during the fertility workup in many clinics in the Netherlands. However, most women experience moderate to severe pain during this procedure. In 2011 hysterosalpingo-foam sonography (HyFoSy) was introduced as less invasive alternative first line tubal patency test. Furthermore, HyFoSy was suggested to be a less painful procedure than HSG. In [Chapter 4](#) we evaluated if HyFoSy is indeed a less painful outpatient tubal patency test compared to HSG. In this two-centre randomized controlled trial (VAS study), a total of 40 women were included who had an indication for tubal patency testing as part of the fertility work-up. Women were randomized for tubal patency testing by HyFoSy or by HSG. Experienced pain during tubal patency testing was measured by a Visual Analogue Scale (VAS) in centimetres. The VAS study showed that HyFoSy was a less painful and less time-consuming procedure for tubal patency testing compared with HSG. The median VAS score for pain perception during the HyFoSy procedure was 1.7 cm (interquartile range: 2.1) compared to 3.7 cm (interquartile range: 4.2) during HSG ( $p < 0.01$ ). The median procedure time of HyFoSy was 5.0 minutes (interquartile range: 3.0) compared to 12.5 minutes (interquartile range: 16.0) for HSG ( $p < 0.01$ ).

The study described in [Chapter 5](#) evaluated if HyFoSy was as accurate as HSG to confirm proximal tubal occlusion after placement of an Essure<sup>®</sup> device as treatment for a hydrosalpinx before IVF. This prospective diagnostic accuracy study included 26 women, with in total 38 hydrosalpinges, which were all treated by hysteroscopic

proximal occlusion by Essure® intratubal devices. Proximal tubal occlusion was assessed by HyFoSy and verified in all patients with an HSG. 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. Therefore it was concluded that HyFoSy was as able as HSG to confirm proximal tubal occlusion after placement of an Essure® device.

### PART III: Treatment of hydrosalpinges by Essure® devices

Women with the most severe form of tubal pathology, hydrosalpinges, are often designated to IVF to become pregnant. However, the presence of hydrosalpinges during IVF treatment has been found to markedly reduce pregnancy outcomes following IVF with almost 50%. Laparoscopic salpingectomy prior to the start of IVF is found to increase ongoing pregnancy rates by almost 50% compared to no intervention and is therefore currently considered as the standard treatment in these women. In [Chapter 6](#) the effectivity and feasibility of a less invasive alternative treatment, hysteroscopic proximal tubal occlusion by Essure® devices, was evaluated. The prospective, single-arm, clinical study described in this chapter included 20 women with ultrasound visible uni- or bilateral hydrosalpinges, who were planned for IVF but had a contraindication for a laparoscopy. The study showed that hysteroscopic placement of Essure® devices was highly effective with a proximal tubal occlusion rate of 96%. Furthermore, the ongoing pregnancy rate following one IVF treatment cycle was 35%, representing adequate reproductive outcomes.

In [Chapter 7](#) a randomised controlled non-inferiority trial was described evaluating the effectivity of Essure® devices in women with hydrosalpinges. In this DESH trial (Dutch Essure® versus Salpingectomy for Hydrosalpinges) a total of 85 women with ultrasound visible hydrosalpinges were included between October 2009 and December 2014 in the Netherlands. Women were randomised to hysteroscopic proximal occlusion by intratubal Essure® device placement or to laparoscopic salpingectomy. The ongoing pregnancy rate following one IVF/ICSI treatment cycle per patient was 11/42 (26.2%) after Essure® treatment versus 24/43 (55.8%) after laparoscopic salpingectomy (relative risk (RR) 0.47 95% CI 0.27 – 0.83). As these results could not demonstrate non-inferiority of hysteroscopic proximal tubal occlusion with Essure® devices, salpingectomy remains the procedure of choice for women with hydrosalpinges who are planned for IVF/ICSI.

In [Chapter 8](#) the obstetrical outcomes of all pregnancies after Essure® intratubal device placement in the Netherlands before December 2010 were evaluated. In theory, the presence of the micro-inserts during pregnancy could cause tissue effects with subsequent myometrial contractions, chorioamnionitis or rupture of membranes with premature delivery as result. The case series in this chapter described a total of 50 pregnancies in 43 women. Seventeen of these pregnancies were terminated. Two pregnancies ended in an immature delivery, 3 in a premature delivery. There were 23 life births, all healthy without congenital anomalies. The results of this case series showed that it was unlikely that the presence of Essure® micro-inserts interfered with the developing amniotic sac and fetus.

[Chapter 9](#) contains a general discussion of this thesis and describes implications for future research.