

# Safety and efficacy of tubal flushing with ethiodized oil

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## IMPACT PARAGRAPH

### Research

This thesis has investigated the safety of ethiodized oil (oil-based contrast) during tubal patency testing in subfertile women. Furthermore, it focused on elucidating the underlying mechanism of the fertility-enhancing effect of ethiodized oil and the feasibility of its use during other methods of tubal flushing than hysterosalpingography (HSG).

The studies included in this thesis have shown that the use of ethiodized oil during HSG, with fluoroscopic guidance, in euthyroid subfertile women, is safe for the women and their offspring. During transvaginal hydrolaparoscopy (THL) additional tubal flushing with a maximum of 10 mL ethiodized oil is also safe and acceptable to patients, without the use of fluoroscopic guidance. However, we do advise to only perform tubal flushing with ethiodized oil in procedures without fluoroscopic guidance, such as during THL, after establishing at least unilateral tubal patency to water-based media. This advice is based on the assumption that in the case of bilaterally blocked tubes intravasation is more likely to occur due to a higher pressure build-up proximal to a tubal obstruction. We have proposed five different hypotheses for the fertility-enhancing effect of tubal flushing, especially with ethiodized oil. The hypotheses are divided between the biochemical effects of the contrast media and the interfacial effects. As a start of investigating the different hypotheses on the interfacial effects of ethiodized oil, we have shown a possible method of analysing the in-vivo pressure build-up within the reproductive tract during HSG, and have shown in-vivo observation of the interaction between ethiodized oil and human tissue during a THL.

### Relevance

Subfertility, the lack of conception after 12 months of timed unprotected intercourse, is a global health issue, which affects almost one out of six couples. It is estimated that worldwide 48.5 million couples suffer from unwilling childlessness after having tried to conceive for 5 years (Zegers-Hochschild *et al.*, 2009; Mascarenhas *et al.*, 2012; Thoma *et al.*, 2013). The burden of subfertility on women and men should not be underestimated, 57% of women and 32% of men undergoing fertility treatment and/or investigations have significant depressive symptoms (Pasch *et al.*, 2016)

Already from 1948 onwards, the therapeutic value of ethiodized oils on fertility has been investigated (Rutherford, 1948). Decennia later, its fertility-enhancing effect could finally be confirmed by two well-powered RCTs, which showed a 10% and 9% higher ongoing pregnancy rate with the use of ethiodized oil, compared to different types of

water-based contrast (Dreyer *et al.*, 2017; Zhang *et al.*, 2022). This conclusion is also supported by two recent meta-analyses (Fang *et al.*, 2018; Wang *et al.*, 2019) and a Cochrane systematic review (Wang *et al.*, 2020). However, the root cause of the fertility-enhancing effect of ethiodized oil remained unclear after decades of speculation, and some questions regarding its safety were still unanswered.

After the clear conclusion of the recent meta-analyses on the effect of ethiodized oil on fertility rates, it was high time to have updated knowledge on its safety, the feasibility of its use during other tubal flushing methods, and finally elucidating the underlying root cause of the fertility-enhancing effect. This thesis aimed to tackle the aforementioned topics, that have been speculated about for decennia.

### **Target group**

This thesis and its results are especially relevant to clinicians investigating and treating couples with subfertility, guidelines developers, fellow researchers, the healthcare industry, and of course the couples suffering from subfertility themselves.

It is important for clinicians in the field of subfertility to be aware of the increased clinical pregnancy rates after the use of ethiodized oil, the safety of its use, and its possible implementation during other tubal patency testing methods than HSG. To assist implementation of this new evidence into daily clinical care it is essential that guideline developers are aware of this. We are optimistic that, after finishing the multiple ongoing clinical trials on the topic of ethiodized oil and tubal patency testing, clinical guidelines will be updated to provide clinicians guidance in determining the optimal timing and method of tubal patency testing for each woman with subfertility. Furthermore, hopefully, the knowledge of the proposed hypotheses on the root cause of the fertility-enhancing effect of tubal flushing, inspires fellow (including non-medical) researchers and the healthcare industry to continue performing research on the remaining questions regarding ethiodized oil and fertility. With additional knowledge on the root cause of the fertility-enhancing effect of ethiodized oil, researchers and the healthcare industry may develop a new tubal flushing medium, with the same efficacy, but possibly without its (high) iodine content. Finally, the new insights from this thesis provide vital information for subfertile couples on the possible treatment options.

### **Activities**

In performing the research of this thesis we have worked with an international team, consisting of both medical doctors and engineers. This interdisciplinary collaboration has widened the scope of the performed research. The results of the different studies in this thesis have been published in international scientific research journals. The

full articles of the published studies have all been made freely accessible to anyone interested through open access sources. Furthermore, most of the studies and their results have been presented and discussed at international scientific meetings. To involve patients we presented part of this research at a symposium of the Dutch patient association “Freya” for people experiencing fertility problems.

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