

Lipiodol - A Revolutionary Treatment for Endometriosis Related Infertility

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ABSTRACT

A lipiodol hysterosalpingogram has been the routine test for tubal patency until around 40 years ago. The fertility-enhancing effect of Lipiodol was seen in observational studies and confirmed in randomised controlled trials, with particularly successful outcomes in women with a history of endometriosis. The mechanism of action of Lipiodol is unclear, but may relate to either flushing of debris from fallopian tubes, an endometrial bathing effect or an immunological effect on the peritoneum. Lipiodol hysterosalpingography has been demonstrated as being superior to water soluble contrast media in improving fertility and should be considered as a first-line treatment option for all women with endometriosis at low risk of tubal disease. Lipiodol offers a simple, minimally-invasive, cost effective treatment option for infertility related to endometriosis.

LIPIODOL IN INFERTILITY

Hysterosalpingography has for many years been used as a standard investigation of tubal patency. Historically, oil soluble contrast media (OSCM) have been used for the procedure, until approximately 40 years ago. Lipiodol, comprising ethyl esters of iodised fatty acids of poppy seed oil, is one example of OSCM and has been used for more than a century in radiological procedures. Water soluble contrast media (WSCM) subsequently became a more commonly used contrast due to its superior ability to image the fallopian tubes. The positive impact on fecund ability following a hysterosalpingogram (HSG) was recognised not to be as great with WSCM as OSCM when observations were made using records kept in radiology units [1]. Interventional trials using OSCM followed, confirming this observation, and the first systematic review of randomised controlled trials (RCTs) showed a clear fertility benefit of OSCM over no intervention [2]. The effect, which was particularly pronounced for women with unexplained infertility [2] was considered likely to be as a result of the mechanical flushing of pregnancy-hindering debris through the fallopian tubes [3].

Of particular interest in our FLUSH trial (RCT comparing Lipiodol with no intervention for women with unexplained and endometriosis-related infertility [4]), was the short-term benefit conferred to women with mild endometriosis and otherwise unexplained fertility delay (clinical pregnancy relative risk (RR) 4.4, 95% confidence interval (CI) 1.6 to 12.2, $p=0.001$), which was markedly better than the women without a history of endometriosis (clinical pregnancy RR

1.6, 95% CI 0.8 to 3.2, $p=0.17$). Longer term benefits are observed in women without endometriosis, persisting up to 2 years after the procedure [5].

In 2017, Dreyer et al. [6] published a large multicentre Dutch RCT of 1119 women with infertility that were randomised to either OSCM or WSCM HSG, results of which showed a marked increase in rates of on-going pregnancy and live birth in those women undergoing HSG using OSCM. 39.7% of women in the OSCM group and 29.1% in the WSCM group had an on-going pregnancy 6 months after the procedure (RR 1.37, 95% CI 1.16-1.61), NNT=10. This is hugely important information for women undergoing investigation for the cause of infertility and raises the question whether a Lipiodol HSG should become the standard first line tubal patency test for women at low risk of tubal disease. There were no incidences of intravasation of contrast reported.

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PROPOSED MECHANISM OF ACTION

The mechanism of action of fertility improvement remains unclear, with postulated effects being mechanical (a flushing of pregnancy-hindering debris from the fallopian tubes), a uterine bathing effect [7] or an effect on peritoneal macrophage activity [8-11]. Studies looking at an endometrial effect have shown preliminary evidence of an endometrial impact that could improve endometrial receptivity through gene transcript regulation and effects on endometrial leukocyte populations [12-14] following the use of Lipiodol. In women with endometriosis, evidence suggests impaired endometrial receptivity as a cause of subfertility [15-17]. Lipiodol appears to be associated with a consistent down-regulation of osteopontin (a known ligand of endometrial integrins that has been recognised to be over-expressed in the endometrium of women with endometriosis [14]) and with an up-regulation of endometrial uterine natural killer (uNK) cell numbers [12]. Observation of an increased chance of pregnancy following Lipiodol use, despite it not flushing through the fallopian tubes, also supports the theory of an endometrial bathing mechanism of effect [18]. Further evidence of this endometrial immunomodulation effect is necessary.

Reilly et al. [18] tested the endometrial bathing theory in their randomised trial of Lipiodol versus no intervention in women undergoing IVF, with a history of recurrent implantation failure or endometriosis. The trial suffered from difficulties in recruitment due to the desire of women to obtain the treatment outside of the trial setting, hence was underpowered to detect an important effect. However, there was no apparent difference in the chance of success of fresh embryo transfer in the group receiving Lipiodol prior to IVF and therefore it is not currently recommended as an adjunct to IVF outside of a future trial setting [19]. Whether there might be benefit in women due to undergo an embryo transfer of a frozen-thawed embryo (as far as the endometrium is concerned, much more akin to natural conception than to fresh embryo transfer in IVF, in which the endometrium is under considerable hormonal influence) remains uncertain.

POTENTIAL SIDE EFFECTS AND POST-PROCEDURE MONITORING

Follow-up studies of women undergoing HSG using Lipiodol have shown that approximately one quarter of women will develop sub-clinical hypothyroidism within 6 months of treatment, likely due to the high iodine load of the contrast. Consequences of thyroid dysfunction on chance of conception as well as outcomes of pregnancies conceived following HSG are important to consider, hence it is recommended that thyroid function tests are performed for 5 months after Lipiodol HSG, enabling prompt correction of sub-clinical hypothyroidism, which we recognise as a transient abnormality.

More serious, but rare, risks of Lipiodol HSG include lipogranuloma formation in an already-damaged fallopian tube and complications associated with intravasation. Despite observing intravasation in approximately 1 in 50 women undergoing Lipiodol procedures, we have not seen any confirmed cases of clinical oil embolism in around 1,000 procedures undertaken in the last decade. Women in whom tubal damage is more likely, for example with a past history of pelvic infection, are usually recommended to first proceed with laparoscopic surgery or with WSCM HSG to test tubal patency, accepting that benefits of WSCM on fertility are not evident with this approach. Lipiodol HSG can be subsequently used as a therapeutic option for some women. Persistence of Lipiodol appears to be a fairly common phenomenon among women who have previously undergone a Lipiodol procedure – although there are no complications recognised in association with persistent Lipiodol, a trace of radio-opaque material may be seen in a substantial minority of women at an interval of months or even years post-Lipiodol HSG, and women should be made aware of this phenomenon in advance of undergoing the procedure. Other risks of HSG are common to both types of contrast, namely risk of infection, minimal radiation exposure through fluoroscopy screening and discomfort of the procedure (which is usually well-tolerated). However, the risks associated with Lipiodol HSG, as long as it is undertaken carefully under fluoroscopy screening, appear to be extremely low.

FUTURE DEVELOPMENT

Endometriosis suffers from a lack of progress in terms of research, both in relation to symptomatic management of the condition and the subfertility commonly associated with it. Few treatment options have been shown to be effective in improving endometriosis-related subfertility, yet Lipiodol has offered great hope as both a valuable, but also cost-effective and minimally-invasive therapy [20]. Gynecologists, fertility specialists and radiologists should consider the merits of Lipiodol HSG as the routine first line test for tubal patency in women at low risk for tubal disease. Whether Lipiodol, through its immune-modulatory effects, evidence for which is now beginning to emerge, could prove to be a disease modifier in women with endometriosis, remains to be seen, but may be worthy of further investigation.

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