Review Article

Review of lipiodol treatment for infertility – an innovative treatment for endometriosis-related infertility?

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A lipiodol hysterosalpingogram was the routine test for tubal patency as recently as the 1970s. Observational studies, then randomised controlled trials, provided evidence of a fertility enhancing effect of lipiodol. It has been found to improve fertility for women with normal tubal patency, particularly where the woman has a history of endometriosis. Previous successful treatment for infertility with lipiodol is a marker of further successful treatment for infertility in a repeat procedure. Whilst lipiodol is probably effective at flushing debris that could hinder fertility from fallopian tubes, it also exerts immunobiological effects in pelvic peritoneum and on the endometrium that could be responsible for fertility enhancement. Effects of lipiodol on the endometrium that might be important at the time of the implantation window are a reduced expression of osteopontin and an increased number of uterine natural killer cells postlipiodol. The effect of lipiodol uterine bathing for women with endometriosis, repeat *in vitro* fertilisation (IVF) implantation failure and other reproductive disorders merits further investigation. Lipiodol presents a new, simple, low invasive, inexpensive treatment option for endometriosis-related infertility and might have wider applications.

Key words: endometriosis, infertility, lipiodol, tubal flushing, uterine bathing.

History of Lipiodol in Improving Fertility

A hysterosalpingogram (HSG) with oil soluble contrast media (OSCM), of which lipiodol (an iodised poppy seed oil, used as a contrast medium in radiology for more than a century) is one example, was the standard test for tubal patency until approximately 40 years ago. Potential fertility benefit from diagnostic HSGs has been recognised for more than 60 years.[1] The use of OSCM was gradually replaced in diagnostic HSGs by water soluble contrast media (WSCM), primarily owing to superior imaging of fallopian tubes. Records kept in radiology units suggested that the improved fertility following HSGs was not as prominent with WSCM as with OSCM.[2] Observational studies, then randomised controlled trials (RCTs) seemed to confirm the fertility benefit of OSCM and the first systematic review of RCTs showed a clear fertility benefit of OSCM versus no intervention.[3] The efficacy appeared more pronounced amongst women with unexplained infertility,[3] and it was speculated that lipiodol might be improving fertility benefit by dislodging nonocclusive but pregnancy-hindering debris from otherwise undamaged fallopian tubes.[4,5]

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The Relative Merits of Lipiodol as a Treatment for Endometriosis-Related and Unexplained Infertility

Our original randomised trial of a lipiodol HSG versus no intervention to treat unexplained infertility in 158 women found overall benefit from lipiodol (pregnancy rate relative risk (RR) 2.3, 95% confidence interval (CI) 1.3–4.1, $P = 0.002$).[6] We were surprised to find a much greater short-term fertility benefit amongst the 62 women with endometriosis that was approximately fourfold (clinical pregnancy RR 4.4, 95% CI 1.6–12.2, $P = 0.001$; live birth RR 3.7, 95% CI 1.30–10.5, $P = 0.007$) than amongst 96 women without a history of endometriosis (clinical pregnancy RR 1.6, 95% CI 0.8–3.2, $P = 0.17$; live birth RR 1.6, 95% CI 0.7–3.6, $P = 0.13$).[6]

For women under 40 years old in the RCT, 48.0% of women with endometriosis (with median duration of infertility five years) and 33.3% of women with unexplained infertility (with mean duration of infertility four years and seven months) achieved pregnancy within six months of the lipiodol procedure,[6] results that have now been borne out by our observational studies that

followed the RCT.[7] The majority of the pregnancies that eventuated had occurred within four months of the lipiodol procedure, with the cycle following lipiodol having the most conceptions (Table 1). Whilst the apparent fertility benefit only lasted for six months for women with endometriosis, the benefit for women with unexplained infertility in the absence of endometriosis appeared to last at least two years, at which time women with unexplained infertility in the absence of endometriosis who had undergone lipiodol procedures had an approximate doubling of the chance of pregnancy (hazard ratio 2.0, 95% CI 1.1–3.5).[8]

Our previously unpublished analysis of 19 consecutive women who underwent a second lipiodol procedure from 2004 to 2008 (Table 2) from a larger cohort of women treated with lipiodol[7] showed a 50.0% live birth rate amongst the ten women whose outcome after the first procedure had been a live birth and one-third of the nine women who did not have a live birth following their first procedure had a live birth following their second lipiodol procedure. The best prognosis group was women with endometriosis who had previously had a live birth following lipiodol, in whom the live birth rate was 62.5% (five from eight).

There have been precious few advances in treatments for endometriosis, whether for fertility or treatment of other symptoms of endometriosis.[9] It is concerning that so few clinical trials assessing interventions in women with endometriosis have been registered, yet fewer published and still fewer have shown any promise in terms of treatment success.[9] The promise of fertility benefit from other innovative treatments, including pentoxifylline, rosiglitazone, mifepristone, traditional Chinese medicine and vitamins, has not been fulfilled in clinical trials and there remains insufficient evidence to support use of these agents.[10] It is true that our trial was not initially designed to detect this marked benefit amongst women with endometriosis (who were a subgroup of the total trial population);[6] therefore, it is important to see a duplication of these results, although the benefit from lipiodol was highly significant in this subgroup of our overall trial population.[6] Nonetheless, the best estimate of lipiodol treatment effect in women with endometriosis on live birth (Peto odds ratio (OR) 5.17), albeit with wide confidence

Table 1 Time relationship of randomisation to conception in FLUSH Trial (data previously unpublished)[6]

Cycle number following randomisation	Unexplained		Endometriosis		Total population	
	Lipiodol	Control	Lipiodol	Control	Lipiodol	Control
0	2	3	3	1	5	4
1	5	1	2	0	7	1
2	3	1	1	1	4	2
3	3	2	3	2	6	4
4	2	3	1	0	3	3
5	1	0	2	0	3	0

Table 2 Reproductive outcomes amongst women undergoing a second lipiodol procedure to treat infertility

	1st Lipiodol outcome: live birth				1st Lipiodol outcome: miscarriage/ectopic				1st Lipiodol outcome: no pregnancy			
	Unexplained $n = 2$	Endometriosis $n = 8$	Other cause $n = 0$	Total $n = 10$	Unexplained $n = 1$	Endometriosis $n = 2$	Other cause $n = 2$	Total $n = 5$	Unexplained $n = 1$	Endometriosis $n = 2$	Other cause $n = 1$	Total $n = 4$
Pregnancy (%)	2 (100.0)	5 (62.5)	-	7 (70.0)	1 (100.0)	2 (100.0)	1 (50.0)	4 (80.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (25.0)
Live birth (%)	1 (50.0)	4 (50.0)	-	5 (50.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (25.0)
Miscarriage (%)	1 (50.0)	0 (0.0)	-	1 (10.0)	0 (0.0)	2 (100.0)	1 (50.0)§	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ectopic (%)	0 (0.0)	1 (12.5)†	-	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No Pregnancy (%)	0 (0.0)	3 (37.5)‡	-	3 (30.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (20.0)	1 (100.0)	2 (100.0)	0 (0.0)	3 (75.0)¶

†This woman conceived again eight months after lipiodol and had a live birth.
‡One of these women conceived seven months after lipiodol and had a live birth.
§This woman was later found to have a translocation.
¶Two of these women were >40 years of age.

intervals (95% CI 1.55–17.23)[11] even compares favourably with established treatments recognised to improve fertility, such as laparoscopic removal of endometriosis (live birth and ongoing pregnancy at 20 weeks Peto OR 1.64, 95% CI 1.05–2.57).[12] However, it must be emphasised that lipiodol has never been compared directly with laparoscopic surgery for endometriosis in a randomised trial setting.

Possible Endometrial Effect of Lipiodol

The difference in treatment effect for women with endometriosis compared to those with unexplained infertility in the absence of endometriosis[6,8] suggested a possible immunobiological mechanism of action of lipiodol rather than a tubal flushing mechanism. Certainly, there were recognised intraperitoneal effects amongst rodents exposed to lipiodol, including a change in production of cytokines by peritoneal macrophages and an inhibition of sperm phagocytosis by peritoneal mast cells or macrophages.[13] However, the occurrence of eight pregnancies following lipiodol procedures amongst the seventeen women in whom the lipiodol had failed to flush either of the fallopian tubes[7] – a pregnancy rate of 47.1% in this small group of women that compares quite favourably with the pregnancy rate following lipiodol amongst all women (40.2%)[7] – raised the possibility of an endometrial bathing mechanism of effect.

It has been debated whether the adverse impact of endometriosis on fertility results purely from established poorer egg quality[14] or whether the endometrium of women with endometriosis is less receptive. The eutopic endometrium of women with endometriosis has been recognised to have different expression of biomarkers associated with the implantation window compared with women who do not have endometriosis.[15] In particular, women with endometriosis have been shown to overexpress endometrial osteopontin,[16,17] a molecule whose binding with αvβ3 integrins is important to promote endometrial implantation receptivity and whose expression to just the right level in endometrium appears to be exacting in its impact on implantation receptivity.[18]

Our RCT in 60 Swiss white mice showed significant changes in uterine dendritic cells in the endometrium of mice that had been exposed to lipiodol (an increase in CD1+ dendritic cells and a decrease in CD205+ dendritic cells).[19] A small pilot study in which four women were able to act as their own controls showed that women who had undergone uterine bathing with lipiodol had osteopontin downregulated in their endometrium.[20] They also had significantly increased numbers of uterine natural killer (uNK) cells postlipiodol.[21] Although uNK cells seem likely to be important in implantation receptivity, their precise role remains unclear.[22]

Further Investigation of the Role of Lipiodol

We have analysed results from our previously unpublished cohort of 19 consecutive women who underwent a lipiodol procedure prior to medically assisted reproduction (*in vitro* fertilisation (IVF) or intracytoplasmic sperm injection (ICSI)) between 2004 and 2008 (Table 3) from the newly published larger cohort of women undergoing lipiodol procedures.[7] The group who had the best outcome from IVF/ICSI preceded by lipiodol approximately 4–5 weeks prior to oocyte retrieval were the ten women with endometriosis (pregnancy rate 90.0%, live birth rate 40.0%). We are currently undertaking a pilot RCT examining the effect of a lipiodol procedure prior to IVF for women with endometriosis and women who have experienced repeat implantation failure. Interim results from only 38 women showed the pregnancy rate at six months was 47.1% (eight from 17) in the group receiving lipiodol prior to IVF/ICSI and 19.0% (four from 21) in the group treated with IVF/ICSI alone; this difference was not significant ($P = 0.065$)[23], and the trial is ongoing (ClinicalTrials.gov identifier NCT00894946).

Table 3 Reproductive outcomes amongst women undergoing a lipiodol procedure prior to *in vitro* fertilisation (IVF)

	Unexplained infertility $n = 4$	Endometriosis-related $n = 10$	Other $n = 5$	Total population $n = 19$
Pregnancy (%)	0 (0.0)	7 (70.0)†	0 (0.0)	7 (36.8)
Live birth (%)	0 (0.0)	4 (40.0)	0 (0.0)	4 (21.1)
Miscarriage (%)	0 (0.0)	2 (20.0)	0 (0.0)	2 (10.5)
Biochemical pregnancy (%)	0 (0.0)	1 (10.0)	0 (0.0)	1 (5.3)
Ectopic (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No pregnancy (%)	4 (100.0)	3 (30.0)	5 (100.0)	12 (63.2)

†There were nine pregnancies in seven women with endometriosis-related infertility; one woman had a miscarriage and conceived again resulting in a live birth, and another woman had two biochemical pregnancies. The results expressed in the table represent the best outcomes achieved by each woman. [Correction added on 6 Nov 2013, after first online publication: The Total Population values for Pregnancy, Miscarriage and Biochemical pregnancy were amended.]

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