The FLUSH Trial—Flushing with Lipiodol for Unexplained (and endometriosis-related) Subfertility by Hysterosalpingography: a randomized trial

N.P. Johnson1,2,3,5, C.M. Farquhar1,2, W.E. Hadden4, J. Suckling1, Y. Yu1 and L. Sadler1

1University of Auckland Department of Obstetrics and Gynaecology, National Women’s Hospital, Auckland, 2Fertility Plus, National Women’s Hospital, Auckland, 3University Specialists, Mercy Specialist Centre, Epsom, Auckland and 4Auckland Radiology Group, 641 Manukau Road, Royal Oak, Auckland, New Zealand

5To whom correspondence should be addressed at: University of Auckland Department of Obstetrics and Gynaecology, National Women’s Hospital, Auckland, New Zealand. E-mail: n.johnson@auckland.ac.nz

BACKGROUND: To assess the effectiveness of flushing with the oil-soluble contrast medium lipiodol in women with unexplained infertility. METHODS: An open randomized controlled trial design in a single centre secondary and tertiary level infertility service setting. A total of 158 women with unexplained infertility were stratified into two populations: 96 women without confirmed endometriosis and 62 women with endometriosis who had normal Fallopian tubes and ovaries. Randomization was computer-generated, with allocation concealment by opaque sequentially numbered envelopes. Lipiodol flushing was tested versus no intervention. The main outcome measures were clinical pregnancy (assessed at 6 months following randomization) and live birth. RESULTS: Lipiodol flushing resulted in a significant increase in pregnancy [48.0 versus 10.8%, relative risk (RR) 4.44, 95% confidence interval (CI) 1.61–12.21] and live birth (40.0 versus 10.8%, RR 3.70, 95% CI 1.30–10.50) rates versus no intervention for women with endometriosis, although there was no significant difference in pregnancy (33.3 versus 20.8%, RR 1.60, 95% CI 0.81–3.16) or live birth (27.1 versus 14.6%, RR 1.86, 95% CI 0.81–4.25) rates for women with unexplained infertility without confirmed endometriosis. CONCLUSIONS: Lipiodol flushing is an effective treatment for couples with unexplained infertility (based on meta-analysis data), but is particularly effective for women with endometriosis who have normal Fallopian tubes and ovaries.

Key words: endometriosis/lipiodol/oil soluble contrast media/randomized trial/unexplained infertility

Introduction

A possible therapeutic effect of diagnostic tubal patency testing has been debated in the literature for over half a century. A possible increase in the pregnancy rate following a hysterosalpingogram (HSG) with oil-based media was reported by Weir and Weir (1951). Subsequently, many reports of non-randomized studies (Gillespie, 1965; Barwin, 1971; Mackey et al., 1971; Acton et al., 1988; DeCherney et al., 1980; Yaegashi et al., 1987) supported the hypothesis of the fertility-enhancing effect of oil-soluble contrast media (OSCM). Most gynaecologists are aware of patients who have conceived immediately after a diagnostic tubal patency test following lengthy infertility. Historically a variety of agents have been used to ‘flush’ the Fallopian tubes. Some of these agents have been used primarily for diagnostic purposes in assessing tubal patency, such as Methylene Blue water-soluble dye in conjunction with laparoscopy and the water-soluble contrast media (WSCM) and OSCM used for HSG. Other agents have traditionally been used primarily for therapeutic purposes, such as oil injection and carbon dioxide tubal insufflation (Massouras, 1970), although tubal flushing treatment does not form part of current routine practice.

Diagnostic HSG were originally performed with OSCM. Their use was gradually replaced by WSCM for a number of reasons: lower cost; better imaging of the tubal mucosal folds and ampullary rugae than OSCM (Soules and Spadoni, 1982); lower viscosity and more prompt demonstration of tubal patency (reducing the need for a delayed film); less likelihood of persistence of contrast medium within the pelvic cavity and of complications such as intravasation resulting in allergic reactions or anaphylaxis or long-term lipogranuloma formation. There were several reports of deaths after the use of oily media in radiology (before the use of fluoroscopy screening) but none was reported after 1967 (Lindequist et al., 1991). It is reassuring that the advent of fluoroscopy screening appears to have abolished severe adverse reactions following the use of oil-based media in radiology (Lindequist et al., 1991) and the safety of HSG with OSCM in this context has been confirmed (Nunley et al., 1987). Lipogranuloma formation has not been reported in
The objective of this trial was to ascertain the effectiveness of lipiodol flushing for enhancing fertility in women with unexplained infertility.

Materials and methods
A single-centre open parallel randomized trial of lipiodol was undertaken in couples with unexplained infertility. Approval for the trial was granted by the Auckland Ethics Committee prior to commencement and annually thereafter; the ethical standards of the Helsinki Declaration of 1975, as revised in 1983, were met.

Protocol
The inclusion criteria for women in the study population were as follows: unexplained infertility (or endometriosis where the Fallopian tubes and ovaries were unaffected by endometriotic disease, in the context of otherwise unexplained infertility) of duration ≥12 months; full investigation for the cause of infertility completed; age 18–39 years inclusive; early follicular FSH level of ≤10 IU/l; mid-luteal progesterone level of ≥25 nmol/l in a spontaneous cycle; bilateral tubal patency confirmed either by dye studies at laparoscopy or by HSG. The partner’s semen analysis had to be normal by World Health Organization (1992) criteria. Exclusion criteria for women were: abnormal Fallopian tubes or a history of tubal ectopic pregnancy; laparoscopic evidence of endometriosis which had affected either the Fallopian tubes or ovaries; iodine allergy. Eligible couples who had given consent were stratified into two populations prior to randomization: group A comprised women with unexplained infertility; group B comprised women with endometriosis in the context of normal Fallopian tubes and ovaries and otherwise unexplained infertility. Women in the endometriosis population had previously had a laparoscopy at which endometriosis was visualized.

Women were randomized to receive lipiodol flushing performed by a HSG technique with fluoroscopic X-ray screening, or to no intervention. Both groups received the same fertility information sheet, which reinforced the principle of the pre-ovulatory fertile phase of the cycle, the timing of sexual intercourse to the fertile phase and the optimal sexual frequency (at least every 48 h) in the fertile phase. The lipiodol contrast medium was Lipiodol Ultra Fluide (Guerbet, France), an iodized poppy seed oil, obtained by substitution of ethyl esters for the glyceryl esters of lipiodol. One millilitre of Lipiodol Ultra Fluide contains 0.48 g iodine. Lipiodol flushing was carried out by one of two authors (W.H., N.J., n = 45; N.J., n = 27) in the follicular phase of the cycle between the end of menses and day 12 of the cycle. With the woman in the left lateral or supine position, using a ‘no-touch’ technique after antisepptic solution application, the cervix was cannulated by a Leech–Wilkinson cannula (Dows Distributors, New Zealand) under speculum visualization. In the supine position and with intermittent fluoroscopic X-ray guidance, pre-warmed (37°C) lipiodol was slowly instilled into the uterine cavity. Typically 10 ml of lipiodol was instilled with the instillation being stopped once unequivocal bilateral spill of contrast from the Fallopian tubes into the peritoneal cavity had been observed. If no peritoneal spill was observed after use of 10 ml, further lipiodol was instilled. If intravasation of lipiodol was observed on X-ray (contrast apparent in the venous system), the instillation was immediately stopped.

The primary outcomes were clinical pregnancy (a positive urine or serum pregnancy test in association with an intrauterine gestation sac on ultrasound scan or histological evidence of trophoblastic tissue in the context of a miscarriage or ectopic pregnancy) at 6 months following randomization and live birth (once data for pregnancy outcomes became available). Secondary outcomes were miscarriage, ectopic pregnancy, multiple pregnancy, any other complications including a diagnosis of lipogranuloma, and a comparison of pre- and post-randomization sexual frequency and focus to the fertile stage of the cycle. These latter sexual behaviour variables were based on an estimate of sexual frequency before randomization and at the completion of follow-up. (For couples achieving a pregnancy during the 6 month follow-up phase, these estimates of sexual behaviour were based on that occurring prior to pregnancy.) A subjective increase in sexual frequency and a greater focus of sexual activity to the fertile phase of the cycle were both defined as that estimated by the woman at the 6 month follow-up; an objective increase in sexual frequency was defined by a comparison of the woman’s estimate of sexual frequency at the 6 month follow-up compared to her estimate prior to randomization. For those undergoing lipiodol HSG, data were collected for the HSG appearances, procedural pain, intravasation and other lipiodol HSG-related complications.

A power calculation had been undertaken within the overall population to determine an appropriate sample size to demonstrate what was deemed to be a clinically important treatment effect of lipiodol.
flushing (Johnson et al., 2004). For couples with unexplained infertility (which could include women without confirmed endometriosis and women with confirmed endometriosis in the context of otherwise unexplained infertility), in order to have 80% power at the 95% confidence level to detect an increase in the pregnancy rate at 6 months post-randomization from 7% with no treatment to 25% with lipiodol flushing, 150 participants would be required for analysis. It was determined to allow a maximum of 3 years to attain this number, but recruitment was stopped once 158 couples had been recruited.

Data were collected from study participants by a telephone consultation with a research nurse; data concerning the lipiodol flushing procedure were collected in the presence of the study participant by the clinician performing the procedure. Numbers are presented as counts (percentages) for dichotomous data; continuous data are presented as either median (interquartile range) or mean (SD). Pregnancy outcomes for the unexplained infertility population (group A) and endometriosis population (group B) are presented separately. The results are also pooled in a ‘total population’, according to the a priori specification upon which the power calculation was based. Statistical analyses were performed using a $\chi^2$-test or Fisher’s exact test for dichotomous data and either Student’s $t$-test or Mann–Whitney test for continuous data using SPSS software. The primary analysis was conducted a priori on an intention-to-treat (ITT) basis, but an exploratory per-protocol analysis was also carried out.

**Assignment**
Women were recruited from publicly funded and private secondary level gynaecology clinics and a tertiary level fertility clinic in Auckland, New Zealand. Some women from other similar clinics throughout New Zealand contacted the trial co-ordinators to express interest and were evaluated for eligibility. Having given informed consent to participate, women were randomized in the menstrual phase of the cycle in which they had committed to attend for a lipiodol HSG if their randomization allocated them to receive the treatment procedure.

Randomization was performed using two computer-generated random number sequences (unknown to the research nurse, the executor of the assignment), known as group A (women with unexplained infertility without confirmed endometriosis) and group B (women with endometriosis in the context of otherwise unexplained infertility) at the beginning of the cycle on which it had been determined that a lipiodol flushing procedure would be performed. Allocation concealment was securely maintained by storage in sealed, sequentially numbered opaque envelopes until the interventions were assigned. The randomization sequences were unblocked with up to 110 available in group A (96 actually randomized) and 90 available in group B (62 randomized). Allocation was strictly maintained sequentially, all envelopes in the sequence being used, with the allocated groups analysed on an ITT basis.

**Blinding**
It was not possible to blind participants to treatment allocation since the treatment involved a HSG procedure and the control involved no intervention. There was also no blinding of the executor of the assignment, the clinician performing the lipiodol flushing procedure, nor of the assessor at follow-up.

**Results**
**Participant flow**
A total of 285 women were evaluated for eligibility, with 221 offered entry to the trial over 35 months between February 2000 and December 2002 inclusive (Figure 1). Of women offered the trial, 53 declined, the majority citing the possibility of randomization to ‘no treatment’ followed by a 6 month ‘stand down’ during which they were asked not to undergo any other fertility treatments, in the context of their urgent desire for pregnancy, as the reason for declining the trial. In all, 168 couples gave informed consent; of these, 10 elected not to proceed with randomization. A total of 158 women were randomized; 96 in the population with unexplained infertility without confirmed endometriosis, 62 in the population with endometriosis. Recruitment was closed after 2 years and 11 months, the number of women required by the power calculation having been surpassed.

Unblocked randomization led to dissimilar numbers in the endometriosis population undergoing lipiodol flushing and no intervention. At the end of the trial, the randomization master schedule was checked and it was confirmed that no breach of the randomization sequence had occurred.

Three women were lost to follow-up. There were two known deviations from the protocol post-randomization, both in women randomized to lipiodol flushing. One woman from group A underwent a further laparoscopy and chromotubation procedure (which confirmed bilateral tubal patency) after a lipiodol HSG had shown neither fill nor spill of contrast from the Fallopian tubes, then conceived with IVF treatment within the 6 month follow-up phase. One woman from group B conceived prior to the flushing procedure, the presumed ‘menstrual period’ at the time of randomization being an implantation bleed, pregnancy then being confirmed prior to the planned flushing procedure. These two women both had live births.

The baseline characteristics of the women at entry to the trial are presented in Table I. The groups randomized to lipiodol flushing compared to no treatment were similar regarding all factors known to be influential on fertility.

The details of the 72 lipiodol flushing procedures are presented in Table II. Two women had to re-attend for a procedure following an initial unsuccessful cervical cannulation and abandoned procedure on the randomization cycle. These women both had a successful procedure during the subsequent cycle. One woman did not attend for the lipiodol flushing procedure until the third cycle after randomization. Outcomes were assessed at 6 calendar months post-randomization, irrespective of any delays in the lipiodol flushing procedures, for women in the treatment and control groups. There were two cases in whom intravasation was confirmed at the time of lipiodol HSG, although these intravasations were asymptomatic and without sequelae. There were no other complications and, specifically, no diagnosed cases of lipogranuloma over the formal 6 month follow-up phase and no cases have come to light since the end of follow-up.

**Follow-up and analysis**
Six month follow-up data are presented in Table III (ITT analysis) and Table IV (per-protocol analysis). The ITT analysis (Table III) demonstrated a statistically significant increase in the pregnancy rate [relative risk (RR) 4.44, 95% confidence interval (CI) 1.61–12.21] and live birth rate
(RR 3.70, 95% CI 1.30–10.50) in favour of lipiodol flushing in women with endometriosis. This effect was also present in the pooled total population (pregnancy rate RR 2.33, 95% CI 1.33–4.08; live birth rate RR 2.43, 95% CI 1.27–4.65). The difference in pregnancy rate (RR 1.60, 95% CI 0.81–3.16) and live birth rate (RR 1.86, 95% CI 0.81–4.25) in women with unexplained infertility without confirmed endometriosis was not statistically significant. Analysis of the data on a per-protocol basis (Table IV) gave results of similar magnitude and statistical significance.

There was no significant difference in the number of couples reporting increased sexual frequency or an increased focus of sexual activity to the fertile phase of the cycle after trial entry for those randomized to lipiodol flushing versus those randomized to no intervention (Table V).

**Discussion**

Our trial is the first prospective RCT to report on the effectiveness of lipiodol flushing as a fertility treatment in women with endometriosis. We have demonstrated that lipiodol flushing results in an increased pregnancy rate and increased live birth rate in couples where the woman has endometriosis with unaffected Fallopian tubes and ovaries in the context of otherwise unexplained infertility. This effect was not demonstrated in couples with unexplained infertility without confirmed endometriosis (although we had insufficient numbers within this sample to detect a RR < 2.5, given 80% power and 95% confidence). Furthermore, no adverse events occurred in women who had lipiodol flushing. There were insufficient miscarriages, ectopic pregnancies and multiple pregnancies to draw meaningful conclusions of any effect of lipiodol flushing. There were no multiple pregnancies following lipiodol flushing, which distinguishes it from most other fertility treatments.

When our data are considered in light of data from previous RCT (Johnson et al., 2004), the effectiveness of lipiodol flushing is confirmed not only in the endometriosis population, but also in the population with unexplained infertility.
infertility in a meta-analysis when appropriate pooling of RCT is carried out. In women with unexplained infertility, meta-analysis of women with unexplained infertility without confirmed endometriosis from our trial and those with unexplained infertility from the trial of Nugent et al. (2002) gives a RR for pregnancy of 2.05 (95% CI 1.07–3.93) for lipiodol flushing versus no intervention (compared to RR 1.60, 95% CI 0.81–3.16 from this trial alone). The estimate of the number needed to treat (NNT) to achieve one additional pregnancy in women with endometriosis, based on our trial data, is 3 (95% CI 2–6; control pregnancy rate 10.8%); NNT for one additional pregnancy in women with unexplained infertility, based on meta-analysis data, is ~6 (95% CI 3–39; control pregnancy rate 15.4%).

The main strengths of this study were the randomized design with secure allocation concealment and the analysis on both ITT and per protocol basis. The main weaknesses were that the randomization was not blocked and the absence of blinding. It was our a priori intention to present pooled data for the total population (group A and group B) as the primary analysis and the power calculation for sample size was based on the pooling of these populations. However,
the data suggest that the populations were dissimilar in baseline fertility (the no-intervention pregnancy rates were 10.8% for women with endometriosis and 20.8% for women with unexplained infertility without confirmed endometriosis), which is consistent with the reduced natural fecundity (by a factor of approximately one-half) previously reported in women with minimal or mild endometriosis (Jansen, 1986; Toma et al., 1992), and dissimilar in the response to lipiodol treatment. Moreover, owing to unblocked randomization, there was an over-representation of women with endometriosis in the no-intervention group (43.5%) compared to the lipiodol flushing group (34.2%) in the total population that has the potential to bias the pooled results in favour of lipiodol flushing. Although results for the pooled total population are presented, they must be interpreted cautiously.

It is recognized that lack of understanding of the fertile phase of the cycle and the optimal timing and frequency of intercourse to maximize fertility is widespread even in couples attending for tertiary assisted conception treatment (Blake et al., 1997). Our policy of providing a fertility information sheet to all trial participants was designed to maximize the number of pregnancies in the treatment and control groups. With our non-blinded design, it was possible that women undergoing lipiodol flushing could have increased their sexual frequency compared to the control group. However, our data do not support a difference in sexual behaviour (in terms of an increase in sexual frequency or an improved focus of sexual activity to the fertile phase of the cycle) amongst women assigned to lipiodol flushing treatment compared to those assigned to no intervention. Thus the increased pregnancy rate following lipiodol flushing is not explained by changes in sexual behaviour following treatment.

An exploratory per-protocol secondary analysis was deemed appropriate owing to the possibility of bias in favour of lipiodol flushing from the primary ITT analysis, given that two pregnancies in women randomized to receive lipiodol flushing could not be attributed to this intervention (one woman conceived prior to lipiodol flushing and another conceived in IVF treatment following lipiodol flushing). The conclusions from the trial were the same, whether based on an ITT or per-protocol analysis.

This RCT is one of two RCT assessing tubal flushing known to have been completed since the most recent update of the systematic review of RCT in 2002 (Johnson et al., 2004). The other trial suggested that the beneficial effect of adding OSCM to a WSCM, which shortened the time to pregnancy, attenuated over time and had disappeared by 18 months (Steiner et al., 2003). Whilst most RCT showed a significant benefit of OSCM over WSCM in terms of the subsequent pregnancy rate (Johnson et al., 2004), one of the largest and methodologically most robust trials comparing OSCM versus WSCM (Spring et al., 2001) failed to demonstrate any relative benefit and this question remains unresolved.

There is now little doubt of the efficacy of lipiodol flushing versus no intervention and the effect is unlikely to be due to changes in sexual behaviour following the procedure. The mechanism of the fertility-enhancing effect of OSCM is unknown. One theory was that OSCM may be highly effective at ‘flushing out’ debris from otherwise undamaged tubes (Watson et al., 1994). Such debris may not necessarily block the Fallopian tube, but may hinder conception or embryo transport along the Fallopian tube. An alternative, immunological hypothesis was that OSCM may enhance fertility for women with unexplained infertility or mild endometriosis by affecting peritoneal macrophages (Johnson et al., 1992)—OSCM have been shown to alter interleukin and prostaglandin production by peritoneal macrophages (Sawatari et al., 1993) and to modulate macrophage activity in phagocytosis of sperm (Mikulska et al., 1994). However, the pregnancy-enhancing effect may simply lie at the level of the endometrium. For most couples having unsuccessful IVF treatment, the outcome hinges on failed implantation: it stands to reason that a treatment which substantially increases the likelihood of conception is likely to have some effect on endometrial receptivity. This theory is supported by two spontaneous pregnancies in our series where lipiodol was not seen to spill from either Fallopian tube (although bilateral tubal patency had previously been confirmed). There is increasing evidence that the infertility related to mild endometriosis may be related to implantation failure owing to impaired endometrial receptivity (Kao et al., 2003). The greater treatment effect in women with endometriosis compared to those with unexplained infertility in our study might result from a mechanism where lipiodol corrects an endometrial implantation dysfunction. The effect of lipiodol on the endometrium merits further investigation.

The current options for management of unexplained infertility include expectancy, use of empirical clomiphene citrate which may approximately double the per-cycle chance of conception (Hughes et al., 2004), intrauterine insemination (IUI) or IVF. Data are sparse on the relative advantages of these treatment options (Pandian et al., 2004). Women with endometriosis have the further option of laparoscopic surgical treatment of endometriosis (Jacobson et al., 2004). Lipiodol flushing now presents an alternative treatment option which

### Table II. Characteristics of lipiodol flushing procedures

<table>
<thead>
<tr>
<th></th>
<th>Unexplained (n = 48)</th>
<th>Endometriosis (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median VAS for pain (QR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) procedural time in minutes—speculum inserted to instillation complete</td>
<td>16.0 (6.5)</td>
<td>11.2 (4.6)</td>
</tr>
<tr>
<td>Median (IQR) volume (ml) lipiodol used</td>
<td>10.0 (10.0–20.0)</td>
<td>10.0 (8.0–12.5)</td>
</tr>
<tr>
<td>Mean (SD) fluoroscopy screening time (min)</td>
<td>2.7 (1.8)</td>
<td>2.5 (1.8)</td>
</tr>
<tr>
<td>Mean (SD) no. X-ray films taken</td>
<td>4.2 (1.5)</td>
<td>3.7 (1.3)</td>
</tr>
<tr>
<td>No. (%) with uterus filling defect</td>
<td>7 (14.6)</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>No. (%) with Fallopian tube spill</td>
<td>37 (77.1)</td>
<td>18 (75.0)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>7 (14.6)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>4 (8.3)</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Neither</td>
<td>2 (4.1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

QR = interquartile range; VAS = visual analogue scale.
### Table III. Intention-to-treat analysis of follow-up data at 6 months

<table>
<thead>
<tr>
<th></th>
<th>Unexplained infertility</th>
<th>Endometriosis-related infertility</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lipiodol $(n = 48)$</td>
<td>No flush $(n = 48)$</td>
<td>Lipiodol $(n = 25)$</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>16</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Live birth</td>
<td>13</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Miscarriage &lt; 20 weeks</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Termination</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Relative risk: $1.60 (0.81–3.16)$, $1.86 (0.81–4.25)$, $1.60 (0.81–4.25)$, $1.86 (0.81–4.25)$, $1.60 (0.81–4.25)$.

Pregnancy was assessed at 6 months post-randomization; pregnancy outcomes were subsequently ascertained for women achieving pregnancy by that time. The termination of pregnancy was carried out at gestation 20 weeks owing to a fetal trisomy 21.

### Table IV. Per-protocol analysis of follow-up data at 6 months

<table>
<thead>
<tr>
<th></th>
<th>Unexplained infertility</th>
<th>Endometriosis-related infertility</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lipiodol $(n = 46)$</td>
<td>No flush $(n = 47)$</td>
<td>Lipiodol $(n = 23)$</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>15</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Live birth</td>
<td>12</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Miscarriage &lt; 20 weeks</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Termination</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Relative risk: $1.53 (0.77–3.05)$, $1.75 (0.76–4.05)$, $1.53 (0.77–3.05)$, $1.75 (0.76–4.05)$, $1.53 (0.77–3.05)$.

For per-protocol analysis: (i) protocol breaches excluded from analysis of pregnancy outcomes; (ii) losses to follow-up excluded from analysis.

Clinical pregnancy was assessed at 6 months post-randomization; pregnancy outcomes were subsequently ascertained for women achieving pregnancy by that time. The termination of pregnancy was carried out at gestation 20 weeks owing to a fetal trisomy 21.
Table V. Relationship of sexual activity and treatment assignment

|                          | Lipiodol (n = 73) | No flush (n = 85) | P  
|--------------------------|-------------------|------------------|-----
| Sexual activity Subjective increase | 6                 | 4                | 0.5  
| Objective increase       | 7                 | 6                | 0.6  
| Subjectively more focused to fertile phase | 14                | 20               | 0.5  

*Fisher’s exact test’ otherwise P-values based upon χ²-test

may be more appealing to many couples. The advantages of lipiodol flushing are that the technique is less invasive than IVF or laparoscopic surgery, is relatively low cost (in New Zealand, comparable to the cost of a single IUI cycle), pregnancy is achieved by sexual intercourse thus it is regarded as more ‘natural’ and there is no increased risk of multiple pregnancy, a problem which has been associated with many other fertility treatment options.

In conclusion, lipiodol flushing is effective in enhancing fertility for women with unexplained infertility and women with mild endometriosis in the context of otherwise unexplained infertility. The greatest benefit is apparent in women with endometriosis. It should be considered as a possible first-line fertility treatment for such women, especially in circumstances where resources for other assisted reproductive technologies are limited.

Acknowledgements
Marianne Weston-Webb assisted with most of the lipiodol HSG. Marjorie Sprecher assisted with data collection. Sabrina Young and Sue Hall provided valuable secretarial assistance. Margaret Merri- lees assisted with defining outcome measures. Andrew Watson pro- vided collaborative support in sharing experience and expertise in lipiodol flushing whilst the trial was being established. The major financial support for the trial came from the Auckland Medical Research Foundation, which contributed towards the salary of a research nurse. The University of Auckland Research Committee and the Auckland Research Centre for Reproductive Medicine contributed seed funding. The lipiodol was provided without charge by Guerbet and supplied free of charge initially by Aventis (New Zealand), later by Biotech (New Zealand). None of the funding sources played any role in study design, data collection, analysis and interpretation, manuscript preparation, nor the decision to submit for publication. These functions were entirely the work of the authors.

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