

Intralipid-Iodine for Hysterosalpingography in Infertile Women

Joseph Eldor^{1*}¹Theoretical Medicine Institute, Jerusalem, Israel**Abstract**

Tubal disease is the cause of female infertility in approximately 30% of women and 10-25% of these are due to proximal tubal obstruction. Selective salpingography represent an approach in the diagnosis and treatment of proximal tubal abnormalities. Intralipid (IL) is a synthetic product composed of 10% soybean oil, 1,2% egg yolk phospholipids, 2.25% glycerin, and water. When indicated, IL is infused 7-10 days prior to embryo transfer (ET), Rates of ongoing pregnancy and live births were higher among women who underwent hysterosalpingography with oil contrast than among women who underwent this procedure with water contrast. It is the first time that intralipid-iodine is suggested to be used for hysterosalpingography in infertile women.

Keywords: Intralipid-Iodine, Hysterosalpingography, Infertility.

Introduction

Tubal disease is the cause of female infertility in approximately 30% of women [1] and 10-25% of these are due to proximal tubal obstruction [2]. Selective salpingography represent an approach in the diagnosis and treatment of proximal tubal abnormalities. The common indications for selective salpingography are to differentiate spasm from true obstruction [3]. In addition to that it allows clarifying findings from an equivocal hysterosalpingogram. Isthmic as well as intramural blockages were included. The tubal obstruction may due to amorphous materials occluding the tubal lumen, inflammatory changes and adhesions [4]. The use of selective salpingography and fallopian tube recanalization has revolutionized the diagnosis and treatment of infertility [3]. Diagnostic procedure has been used since 1980 [3]. It consists on opacification of the fallopian tube directly through a catheter placed in the tubal ostium. The objective is to differentiate spasm from true obstruction and to clear it with a catheter and guide wire system.

Pregnancy Rates After Hysterosalpingography

Pregnancy rates among infertile women have been reported to increase after hysterosalpingography, but it is unclear whether the type of contrast medium used (oil-based or water-soluble contrast) influences this potential therapeutic effect.

Dreyer et al. performed a multicenter, randomized trial in 27 hospitals in the Netherlands in which infertile women who were undergoing hysterosalpingography were randomly assigned to undergo this procedure with the use of oil-based or water-based contrast [5]. Subsequently, couples received expectant management, or the women underwent intrauterine insemination. The primary outcome was ongoing pregnancy within 6 months after randomization. Outcomes were analyzed according to the intention-to-treat principle.

A total of 1119 women were randomly assigned to hysterosalpingography with oil contrast (557 women) or water contrast

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(562 women). A total of 220 of 554 women in the oil group (39.7%) and 161 of 554 women in the water group (29.1%) had an ongoing pregnancy (rate ratio, 1.37; 95% confidence interval [CI], 1.16 to 1.61; $P < 0.001$), and 214 of 552 women in the oil group (38.8%) and 155 of 552 women in the water group (28.1%) had live births (rate ratio, 1.38; 95% CI, 1.17 to 1.64; $P < 0.001$). Rates of adverse events were low and similar in the two groups.

Rates of ongoing pregnancy and live births were higher among women who underwent hysterosalpingography with oil contrast than among women who underwent this procedure with water contrast.

Hysterosalpingography, which should be done in the follicular phase of the cycle, evaluates the contour of the uterine cavity, cervical canal, and tubal lumina. Other than being diagnostic, it can prove to be therapeutic. The instrument used to introduce the radio-opaque medium should be chosen to give the least discomfort and to cause no leakage of dye from the cervix. Water-soluble medium is usually used rather than an oil-based medium.

Fluoroscopy with image intensification gives the best results. Insufficient dye injection will give an incomplete study. Too much dye injection, especially under pressure, might cause extravasation of the dye into the vascular system or conceal the fimbrial ends of the tubes [6].

Hysterosalpingography (HSG) Increases the Conception Rate

To determine whether hysterosalpingography (HSG) increases the conception rate and to compare the therapeutic effectiveness of oil and water-soluble contrast media, the histories of 744 women who attended the Yale Infertility Clinic in 1965-69 were reviewed. Exclusion of women who had been infertile less than 1 year before coming to the clinic, in whom a HSG was done outside the clinic, and in whom there was no follow-up resulted in a study population of 460. The pregnancy rate for the study group (49%) was identical to that for the larger population. The study group was divided into women who became pregnant during their clinic attendance or within 1 year of terminating clinic care and women who did not become pregnant in this period. These 2 categories were then subdivided according to whether a HSG was done. To determine the relative effectiveness of different media, the conception rate following HSG in the Yale Clinic, where the iodized oil Ethiodol was used, was compared with that among 63 women who had HSG done by a private practitioner with the water-soluble dye Salpix. 221 women were in the Ethiodol HSG group, 121 (55%) of whom conceived. Of the 239 Yale Clinic patients who did not have HSG, 103 (43%) became pregnant. Exclusion of couples with organic factors that could account for infertility resulted in a pregnancy rate of 58% for the HSG group and 47% for the non-HSG group. 25 (40%) of the 63 women in the Salpix group conceived, but exclusion of couples with organic factors lowered the pregnancy rate to 38% in this group. The average length of infertility was 0.5 years longer in the non-HSG group than in the Ethiodol HSG group, but shorter in the Salpix HSG group compared to the Ethiodol group. These results suggest that Ethiodol HSG may enhance

fertility. Although the oil media has been criticized on the basis that it may cause granuloma formation or embolization, documented complications in the Yale series were rare. In contrast to earlier studies, unilateral nonpatency on x-ray was not found to affect eventual conception (58% pregnancy rate among women in the Ethiodol HSG group with normal tubes compared with 50% in those with filling of only 1 tube) [7].

Hysterosalpingography (HSG) Using Oil as Compared with Aqueous Contrast Medium

Previous studies have suggested increased fertility rates following hysterosalpingography (HSG) using oil as compared with aqueous contrast medium. To compare the possible fertility-enhancing effects of two agents used for HSG, this prospective randomized study evaluated the subsequent fertility rates in 121 patients who underwent HSG, in which either oil or aqueous contrast medium was used. After random assignment to either agent, patients were observed for four menstrual cycles after HSG without resorting to any therapy other than clomiphene citrate where indicated. The pregnancy rates for the four cycles after HSG were compared with chi-square analysis in the total study and in the diagnostic subgroups. The subgroup with infertility of unknown cause had a significantly higher pregnancy rate after HSG with oil than after HSG with aqueous contrast medium. No significant difference was seen for any other subgroup or for the overall cohort [8].

In a prospective randomized study, the number of pregnancies after hysterosalpingography (HSG) was estimated in 398 patients who had been infertile for longer than 1 year. Iohexol was used in 101 patients, ioxaglate in 102 patients, diatrizoate meglumine in 97 patients, and ethiodized poppy-seed oil in 98 patients. Ten months after HSG, the patient, referring physician, and/or hospital department was consulted for information about pregnancies. Questionnaires were obtained from the patients who became pregnant during the waiting period of 3 months. No differences in demographic parameters, infertility status, or diagnosis made with HSG were detected among the four contrast media groups. Significantly more patients became pregnant after HSG in the ethiodized poppy-seed oil group than in the three water-soluble contrast media groups (P less than .01). When only intrauterine pregnancies resulting in full-term births were considered, significant differences in pregnancy rates between the oil-soluble and the water-soluble contrast media groups became more obvious. In the group that received ethiodized poppy-seed oil, almost one-third of the infertile women had normal pregnancies and childbirths after HSG [9].

Meta-analysis of four randomized clinical trials (RCTs) and six nonrandomized controlled studies evaluated pregnancy rates after the use of oil- or water-soluble contrast media during HSG.

Four identified RCTs studied 800 patients and six nonrandomized studies comprised an additional 1,806 patients, all experiencing primary or secondary infertility.

Pregnancy rates were significantly higher in the oil-soluble contrast media group compared with the water-

soluble contrast media group in the RCTs. Inclusion of the six nonrandomized studies did not alter this conclusion. This apparent benefit was greatest for patients with unexplained infertility.

Oil-soluble contrast media have a therapeutic effect compared with water-soluble media and this effect is greatest for patients who have been diagnosed as having unexplained infertility. New techniques for the evaluation of tubal patency support the hypothesis that tubal "plugs" may be involved in proximal tubal blockage [10].

Ninety-three patients with unilateral or bilateral proximal tubal occlusion confirmed by hysterosalpingography or laparoscopy underwent FTR with use of water-soluble contrast material alone (n=50) or also had an oil-based agent injected into each tube after recanalization (n=43). Pregnancy rates and outcomes of the two groups were studied retrospectively.

With respect to differences between groups, only the body mass index proved to be a significant predictor (oil, 28.4; water, 24.7; $P=0.008$). Mean age, duration of infertility, type of infertility, and initial diagnosis were comparable. There was a weak trend toward a higher pregnancy rate in the oil-based contrast material group, but it was not significant ($P=0.64$). The average time to pregnancy was 4.4 months with use of oil-based contrast material, compared to 7.7 months with use of only water-soluble contrast material ($P=0.03$).

The use of an oil-based agent had little effect on the rate of conception, but time to conception was reduced by more than 3 months [11].

Safety and Diagnostic or Therapeutic Efficacy of Water-soluble Versus Oil-based Contrast Media

Hysterosalpingography is used commonly in the evaluation of infertility and in the diagnosis of anomalies of the uterus and fallopian tubes. There is continued debate over the safety and diagnostic or therapeutic efficacy of water-soluble versus oil-based contrast media.

A 29-year-old woman with secondary infertility underwent hysterosalpingography with both water-soluble and oil-based contrast. The fallopian tubes appeared normal. Six months later, a plain abdominal radiograph obtained at the occasion of a minor motor vehicle accident revealed evidence of retained loculated pelvic contrast material. Subsequent laparoscopy identified adhesions and cul-de-sac implants strongly suspicious for endometriosis. Biopsy and pathologic study documented lipogranuloma.

Oil-based contrast media instilled into the pelvis at hysterosalpingography can persist for prolonged periods and create granulomatous lesions mimicking endometriosis. In view of the controversy whether oil-based contrast materials are superior to water-soluble media, the routine use of oil-based contrast media should be considered carefully [12].

Hysterosalpingography (HSG) has assumed a diagnostic and possibly therapeutic role in the evaluation of the

infertile couple. The procedure is done using either an oil-based (OBCM) or a water-based (WBCM) contrast medium. Data from several retrospective studies suggest that higher pregnancy rates may be achieved when OBCM is used. Interpretation of these results, however, may be confounded by various methodologic flaws in study design and comparisons of heterogeneous populations. Letterie and Rose sought to compare the therapeutic benefit of OBCM and WBCM in a prospective randomized study of infertile patients, controlling for pelvic anatomy by laparoscopic assessment [13]. They used ethiodized oil (Ethiodol) or iothalamate meglumine (Conray 60) for tubal lavage at the time of laparoscopy only in patients with normal pelvic anatomy. Of the 225 patients who had diagnostic laparoscopy in the evaluation of infertility, 40(18%) had normal pelvic anatomy and an otherwise unremarkable evaluation. Adequate follow-up was available on 29 patients randomized to receive either OBCM (n=15) or WBCM (n=14). A significant difference in pregnancy rates was noted between OBCM (40%) and WBCM (14%) by chi-square analysis. No short- or long-term adverse reactions were noted. Results of this study suggest that in patients with normal pelvic anatomy as assessed laparoscopically, OBCM may offer a therapeutic benefit not evident with WBCM [13].

Moore et al. evaluated the effect of different iodinated contrast agents on the fallopian tube and adnexal tissue in 15 rabbits [14]. Ethiodized oil, an oil-soluble agent, was used in five rabbits. The following water-soluble agents were used: iothalamate meglumine 30% (n=3), iothalamate meglumine 60% (n=3), and ioxilan (n=4). The agents were injected through catheters placed in the fallopian tubes. Fallopian tubes and peritoneal cavities were histologically evaluated. The contralateral tube served as a control. Ioxilan and iothalamate meglumine 30% produced no pathologic response in the tube or peritoneal cavity. Iothalamate meglumine 60% was associated with mild inflammatory infiltrate, mucosal edema, giant cell reaction, and periovarian adhesions that were bilateral but more pronounced on the injected side. Use of ethiodized oil resulted in papillary fibrous adhesions on the ovarian surface, and fat granulomas were seen in the periovarian tissues. The safety of oil-based contrast agents for use in hysterosalpingography is therefore questioned. No significant differences were found among the water-soluble contrast agents [14].

Hysterosalpingography can be accomplished with either oil or water-soluble contrast medium. This randomized prospective study compared pregnancy rates in women who had hysterosalpingography with either water- or oil-soluble contrast material and were followed for six months. Fifteen of 60 (25%) patients who received water-soluble dye conceived compared with 14 of 46 (30%) patients in the oil-soluble group, a statistically insignificant difference. Furthermore, no difference in pregnancy rates within each subgroup of fertility diagnosis was detected. Intravasation was more common in patients administered oil-based contrast materials (six of 46 versus one of 60 patients, $P=0.02$), although no serious consequences occurred. No difference in the amount of pain as assessed by pain scoring was experienced by patients in each group. The

authors conclude that pregnancy rates are similar after hysterosalpingography with oil- and water-soluble contrast material, during at least the first six months after the procedure [15].

Immunological Relationship Between Mother and Conceptus

Aspects of the immunological relationship between mother and conceptus still remain a mystery, although the recent advances in molecular biology have enlightened some of the parameters that participate in feto-maternal cross-talk during implantation [16]. The atypical expression of major histocompatibility complex (MHC), the specific roles of some hormones and cytokines, as well as the temporal and spatial distributions of uterine natural killer (uNK) cells, represent substantive parameters of feto-maternal immunotolerance during implantation [17]. Although human maternal and fetal immunology is difficult to investigate, aberrant immune responses and an imbalanced cytokine network may be related to infertility, implantation failures after IVF, and recurrent pregnancy losses [18]. Patients with recurrent implantation failure (RIF) should be tested for inherited and acquired thrombophilias. Each patient should be individually assessed and counseled regarding management with low-molecular-weight heparin (LMWH). Empirical treatment with LMWH, aspirin, or corticosteroids is not effective for women with RIF who have negative thrombophilic tests [19]. If thrombophilic tests are normal, patients should be tested for immunological causes. The findings of a recent study suggest that increases in the percentage of CD56(dim) cells and NK cytotoxicity in peripheral blood may be important contributing factors for both RSA and IVF failure [20]. Human leukocyte antigen (HLA)-DQA1*0505 sharing or the maternal killer immunoglobulin-like receptor (KIR) repertoire is associated with recurrent spontaneous abortion (RSA) or repeated implantation failure (RIF) [21] and if abnormal, the patient might then benefit from intravenous immunoglobulin (IVIg) therapy [19]. IVIg has been successful in the treatment of recurrent miscarriage and recurrent implantation failure among women with elevated anti-phospholipid antibodies (APA) and/or NK cell activity [22]. When the pregnancy outcomes of women with a history of reproductive failure and elevated NK cell cytotoxicity treated with intralipid were compared with women treated with IVIg, no differences were seen [22]. Side-by-side comparison showed that synthetic pre-implantation factor (sPIF) is equally effective to inhibit NK cell toxicity at a lower dose than intravenous gamma immunoglobulin or intralipid treatment currently used [23]. sPIF is not yet available commercially, but intralipid infusions are available globally. Intralipid (IL) is a synthetic product composed of 10% soybean oil, 1,2% egg yolk phospholipids, 2.25% glycerin, and water. When indicated, IL is infused 7-10 days prior to embryo transfer (ET), and one more time again after a positive pregnancy in women whose NKA is due to an autoimmune cause (antiphospholipid antibodies and/or antithyroid antibodies) [24]. In cases of alloimmune implantation dysfunction (DQa and/HLA matching between the embryo recipient and the male partner), the same applies, but in this situation, the infusion is repeated at 2-4

week intervals until the 24th week of pregnancy [24]. IL costs about 10 times less than IVIg, is not a blood product, and is without significant side effects [24].

Intralipid

Intravenous lipid emulsions have been used experimentally since at least the 19th century. An early product marketed in 1957 under the name Lipomul was briefly used in the United States but was subsequently withdrawn due to side effects. Intralipid was invented by the Swedish physician and nutrition researcher Arvid Wretling, and was approved for clinical use in Sweden in 1962 [25]. In the United States, the Food and Drug Administration initially declined to approve the product due to prior experience with another fat emulsion. It was approved in the United States in 1972.

Conclusion

It is the first time that intralipid-iodine is suggested to be used for hysterosalpingography in infertile women.

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