RBMO

REVIEW

Safety of oil-based contrast medium for hysterosalpingography: a systematic review

BIOGRAPHY

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KEY MESSAGE

The most frequently reported complication after an HSG with oil-based contrast is intravasation, occurring in 2.7% of HSG procedures. In total only four cases with serious consequences of oil embolisms in subfertile women were published. Therefore, safety concerns should not be the reason to deny the use of oil-based contrast for tubal testing in women with unexplained subfertility.

ABSTRACT

Recent meta-analyses have shown that a hysterosalpingography (HSG) with oil-based contrast increases pregnancy rates in subfertile women. However, the frequency of complications during or after an HSG with oil-based contrast in subfertile women and/or their offspring is still unclear. This systematic review and meta-analysis, without restrictions on language, publication date or study design, was performed to fill this knowledge gap. The results show that the most frequently reported complication was intravasation of contrast, which occurred in 2.7% with the use of oil-based contrast (31 cohort studies and randomized controlled trials [RCT], 95% CI 1.7–3.8, absolute event rate 664/19,339), compared with 2.0% with the use of water-based contrast (8 cohort studies and RCT, 95% CI 1.2–3.0, absolute event rate 18/1006). In the cohort studies and RCT there were 18 women with an oil embolism (18/19,339 HSG), all without serious lasting consequences. Four cases with serious consequences of an oil embolism were described (retinal oil embolism [n = 1] and cerebral complaints [n = 3]); these reports did not describe the use of adequate fluoroscopy guidance during HSG. In conclusion, the most frequently reported complication after an HSG with oil-based contrast is intravasation occurring in 2.7%. In total four cases with serious consequences of oil embolisms in subfertile women were published.

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KEYWORDS

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INTRODUCTION

Hysterosalpingography (HSG) to assess tubal patency is an essential part of the work-up for subfertile couples (*National Institute for Health and Care Excellence, 2017*). The first HSG was performed in 1910 by Rindfleisch (*Rindfleisch, 1910*). From 1914 iodized oils were used as an alternative to the water-based contrasts, which were irritative to the peritoneum (*Cary, 1914*; *Nielsen, 1946*; *Soules and Spadoni, 1982*). Different iodized oils were introduced, such as Lipiodol®, Iodochlorol, Ethiodol, Jodipin, Jodumbrin and Lipiodol® Ultra Fluid. The oil-based contrasts available today are Lipiodol® Ultra Fluid (Guerbet, Villepinte, France) and Ethiodized Poppyseed Oil (Heng Rui Pharmaceuticals, Jiangsu, China), the latter being currently only available in Asia.

Lipiodol was developed in 1901 as a solution containing iodine, and was used for a wide range of indications, including the reduction of struma and infection prevention. After the discovery of its radiological qualities, it was used for visualization of the uterine cavity and Fallopian tubes, but also in myelography, bronchography and later in lymphography. In 1960 a transesterified version of Lipiodol was developed, Lipiodol Ultra Fluid, which had a lower viscosity (*Bonnemain and Guerbet, 1995*; *Simescu et al., 2002*).

For nearly seven decades, the therapeutic effect of oil-based contrast during HSG in the fertility work-up has been debated. Recently two meta-analyses have shown a favourable effect of oil-based contrast on fertility outcomes, with an OR of 1.47 (95% CI 1.12–1.93) for ongoing pregnancy and 2.18 (95% CI 1.30–3.65) for live birth when comparing HSG with oil-based contrast to water-based contrast (*Fang et al., 2018*; *Wang et al., 2019*). This generated a worldwide renewed interest in the use of oil-based contrast for fertility enhancement. However, some clinicians are still hesitant about its use because of complications that have been reported in the past.

In 1929 the first report of intravasation of oil-based contrast during HSG was published (*Pujol y Brull et al., 1929*). Intravasation is the inflow of contrast in the venous or lymphatic system, and is visualized by radiography, ideally with the use of fluoroscopy screening. Even though water-based contrast can also intravasate, only oil-based contrast is known to enter the circulation as droplets because of its hydrophobic qualities. These oil droplets can reach organs such as the lungs or brain as oil emboli and cause inflammation and/or occlusion of the vasculature (*Uzun et al., 2004*). After this first case, more reports of intravasation followed, but most patients had only minor symptoms and recovered after observation. Intravasation was therefore regarded as innocuous (*Soules and Spadoni, 1982*). Currently, intravasation with the use of oil-based contrast is estimated to occur in around 5% of the HSG in the Netherlands (*Roest et al., 2020*).

In spite of this, a recent case report describes a patient falling into a comatose state as a result of an oil embolus after HSG (*Uzun et al., 2004*). Although this might be a rare complication, it does emphasize the importance of safety and knowledge of the complication rates after HSG with the use of oil-based contrast.

As previously mentioned, Lipiodol contains iodine, and the iodine concentration in Lipiodol is higher than in water-based contrast (480 mg iodine/ml in Lipiodol versus 240–300 mg iodine/ml in water-based contrast). Iodine exposure can cause a transient decrease in the synthesis of thyroid hormone (*Wolff and Chaikoff, 1948*). Subclinical hypothyroidism is associated with pregnancy complications (*van den Boogaard et al., 2011*). Furthermore, the HSG procedure has a risk of infection.

The systematic reviews and meta-analyses to date have primarily focused on fertility outcomes and have excluded case reports. This systematic review and meta-analysis included all study types, to provide an overview of the frequency and clinical consequences of all possible complications during or after HSG with the use of oil-based contrast in subfertile women.

MATERIALS AND METHODS

The protocol of this review was prospectively registered on PROSPERO (https://www.crd.york.ac.uk/prospero/, registration ID: CRD42018102382, registration date: 24 July 2018). The methodology used was as described in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (*Moher et al., 2009*).

Information sources and search strategies

Electronic databases including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to June 2020. Textbooks as well as reference lists of identified publications were also manually screened. The key search items included 'hysterosalpingography', 'oil contrast', 'ethiodized oil', 'ethiodol', 'lipiodol', 'adverse effect', 'side effect', 'complication', 'thyroid', 'intravasation', 'embolization', 'granuloma', 'anaphylaxis', 'pelvic inflammatory disease', and 'adnexitis' (Supplementary Tables 1–3).

Eligibility criteria

All types of studies were included: randomized controlled trials (RCT), prospective and retrospective cohort studies, case series and case reports that report complications occurring during or after HSG with the use of oil-based contrast, with or without comparison to water-based contrast, in women trying to conceive or their offspring. No limitations on language or publication period were applied. Colleagues who were fluent in the foreign languages assisted in translating.

Outcomes

The outcomes included adverse events of HSG with the use of oil-based contrast (versus water-based contrast) in subfertile women and their offspring, such as: intravasation of the contrast medium, embolization of the contrast medium, pelvic inflammatory disease, lipogranuloma formation, retention of contrast, maternal or fetal thyroid dysfunction, and anaphylactic reactions. The clinical consequences included additional treatments, hospital stay, morbidity and mortality.

Study selection, data collection and quality assessment

Study eligibility was evaluated by two reviewers (IR and KR) independently; disagreements between the two reviewers were solved by consensus or by consultation with another reviewer (CK) when necessary. A predesigned form was used to extract the data and assess the quality of the included studies.

The following information was collected: name of the first author, publication year, study design, study population, participants' characteristics, types of contrast, details of interventions and co-interventions, sample sizes and outcomes. Full-text articles of English cohort and randomized studies were screened by a second reviewer (KR).

Risk of bias was assessed for all studies, excluding the case reports/series, in accordance with the quality assessment checklist for prevalence studies (*Hoy et al., 2012*) (Supplementary Table 4). This checklist contains nine questions, each scored with 0 or 1 points. A total of 0–3 points is classified as an overall low risk of study bias, 4–6 points as moderate risk and 7–9 points as high risk. The risk of bias was assessed by two reviewers independently for the English studies.

Statistical analysis

The prevalence of complications occurring with the use of oil-based contrast was calculated, and where possible comparisons were made to the use of water-based contrast. Meta-analyses were performed using Review Manager Version 5.3. Statistical heterogeneity was estimated by performing a chi-squared test and calculating I^2. Pooled weighted prevalences and the 95% CI were calculated using the MetaXL tool (Version 5.3, 2016; EpiGear International Pty Ltd, Queensland, Australia). A non-pre-specified sensitivity analysis was performed, selecting the cohorts and RCT to calculate the prevalence of complications. Case reports and case series were included to report all (and rare) complications.

RESULTS

Characteristics of included studies

The search identified 492 records. A total of 8 RCT, 41 cohort studies (4 prospective cohorts, 24 retrospective cohorts, 13 cohort studies which were not further specified) and 59 case reports/case series were included within the review. In these studies, a total of 23,536 HSG procedures were performed with the use of oil-based contrast (23,298 HSG in cohort studies/RCT). Sixteen of the included studies reported on HSG with water-based contrast as well, with a total of 1,975 HSG with water-based contrast (1,973 HSG in cohort studies/RCT) (for flow chart see Supplementary Figure 1). The included studies were published between 1928 and 2020 (see Supplementary Table 5 for the characteristics of the included studies) (*Alper et al., 1986*; *Aznar et al., 1969*; *Bang, 1950*; *Barqawi et al., 2007*; *Bateman et al., 1980*; *Bergin, 1951*; *Bersi, 1977*; *Binder et al., 1976*; *Bohm and Seewald, 1972*; *Böttger and Fleck, 1955*; *Brent et al., 2006*; *Brown et al., 1949*; *Buytaert and Meulyzer, 1977*; *Charawanamuttu et al., 1973*; *Claus and Dochez, 1966*; *Coventry, 1934*; *Dan et al., 1990*; *Dreyer et al., 2017*; *Drukman and Rozin, 1951*; *Effkemann, 1935*; *Eisen and Goldstein, 1945*; *Elliott et al., 1965*; *Faris and McMurrey, 1947*; *Feiner, 1942*; *Flew, 1944*; *Fochem and Ulm, 1954*; *Frischkorn, 1958*; *Geary et al., 1969*; *Gotoh et al., 2010*; *Grant et al., 1957*; *Grosskinsky et al., 1994*; *Grossmann, 1946*; *Gunsberger, 1958*; *Heinen and Schussler, 1966*; *Hemmeler, 1938*; *Hirst, 1928*; *Hohlbein, 1965*; *Ishizuki et al., 1992*; *Johnson et al., 2004*; *Kaneshige et al., 2015*; *Karshmer and Stein, 1951*; *Kika, 1954*; *Kilroe and Hellman, 1933*; *Kuzavova, 1964*; *La Sala et al., 1982*; *Lau, 1969*; *Levinson, 1963*; *Li et al., 2018*; *Lin and Tsou, 1935*; *Lindequist et al., 1991*, *1994*; *Liu et al., 2010*; *Ma et al., 2016*; *Mackey et al., 1971*; *Madsen, 1942*; *Malter and Fox, 1972*; *Meaker, 1934*; *Mekaru et al., 2008*; *Miyazaki et al., 2020*; *Morii et al., 2013*; *Netter and Weill-Fage, 1950*; *Nordio, 1938*; *Norris, 1956*; *Novak, 1930*; *Nugent et al., 2002*; *Nunley et al., 1987*; *Omoto et al., 2013*; *Palmer, 1960*; *Pear and Boyden, 1967*; *Piatt, 1947*; *Porcher, 1935*; *Pujol y Brull et al., 1929*; *Rasmussen et al., 1987*; *Riche and Fayot, 1931*; *Ries, 1929*; *Robins and Shapira, 1951*; *Rubin, 1928*; *Rutherford, 1948*; *Sappey et al., 1952*; *Sasaki et al., 2017*; *Satoh et al., 2015*; *Schaffer, 1954*; *Schultze, 1932*; *Schutte et al., 2006*; *Schwabe et al., 1983*; *Shapiro et al., 1957*; *Slater et al., 1959*; *So et al., 2017*; *Solal, 1932*; *Steiner et al., 2003*; *Stoll and Zeitz, 1956*; *Takeyama et al., 2014*; *Tan et al., 2019*; *Ueda et al., 2016*; *Uzun et al., 2004*; *van Welie et al., 2020*; *Vara, 1950*; *Volk, 1936*; *Weise et al., 1973*; *Weitzner, 1935*; *Werner, 1952*; *Williams, 1944*; *Witwer et al., 1930*; *Woltz et al., 1958*; *Wong et al., 1932*; *Yamazaki et al., 2019*; *Zachariae, 1955*; *Zacharin, 1933*).

Quality of evidence of the studies

Of the 49 cohort studies and RCT, 16 studies were classified as low risk, 31 studies as moderate risk and two studies as high risk of study bias. In 18 studies, there was no clear definition of the reported complications. Mainly, there was no predefined definition of intravasation or oil embolism. There is no reliable or valid classification method for intravasation, therefore 44 of the 48 studies were classified as high risk of bias for the reliability and validity of the study instrument that measured the parameter of interest (see Supplementary Table 6 for the classification of all studies).

Intravasation and oil embolisms

Eight studies (three RCT and five cohort studies) compared the frequency of intravasation between HSG with the use of oil-based and water-based contrast (FIGURE 1) (*Alper et al., 1986*; *Barqawi et al., 2007*; *Frischkorn, 1958*; *Lindequist et al., 1991*, *1994*; *Liu et al., 2010*; *Tan et al., 2019*; *Zachariae, 1955*). Rates of intravasation were 2.8% (38/1353) after HSG with oil-based contrast and 1.8% (18/1006) after HSG with water-based contrast (OR 5.05; 95% CI 2.27–11.22; $P < 0.0001$) based on the RCT and 1.23 (95% CI 0.50–3.07; $P = 0.65$) based on the cohort studies), showing that intravasation occurs more frequently with the use of oil-based contrast.

Twenty-three additional cohort studies reported on the prevalence of intravasation with the use of oil-based contrast alone. The overall pooled weighted frequency of intravasation in the 31 RCT and cohort studies with the use of oil-based contrast was 2.7% (95% CI 1.7–3.8, absolute event rate 664/19,339), compared with 2.0% (95% CI 1.2–3.0, absolute event rate 18/1,006) in the eight studies with the use of water-based contrast. When including only studies published from 2000 onwards, the pooled frequency of intravasation with the use of oil-based contrast was 2.8% (95% CI 1.2–5.1, absolute event rate 12/471), compared with 1.8% (95% CI 0.0–5.9, absolute event rate 8/403) with the use of water-based contrast.

In the whole group of HSGs with the use of oil-based contrast performed in RCT and cohort studies, there were 18 women with oil embolisms (18/19,339, 0.1% of HSG; 18/664, 2.7% of cases with intravasation). In six of these cases pulmonary embolisms were described, while the other 12 cases only described the contrast moving rapidly out of the pelvis. The latter were all asymptomatic and serious lasting consequences were not reported (see FIGURE 2).

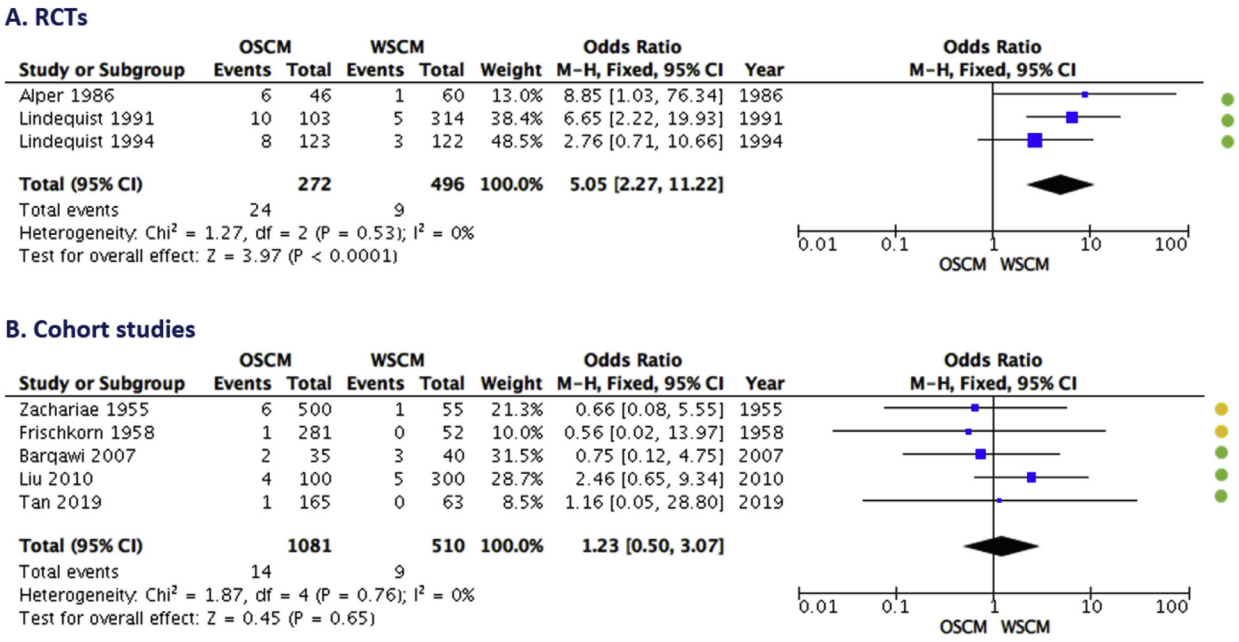

FIGURE 1 Prevalence of intravasation of oil-based contrast versus water-based contrast in HSG for subfertility. Forest plot of meta-analysis reporting on intravasation with the use of oil-based contrast compared with water-based contrast. (A) RCT. (B) Cohort studies. OR and 95% CI. OR < 1 favour oil-based contrast (fewer adverse events); OR > 1 favour water-based contrast (fewer adverse events). The risk of bias of individual studies is represented by coloured dots: green (low risk of bias) and yellow (moderate risk of bias). HSG = hysterosalpingography; OSCM = oil-based contrast media; RCT = randomized controlled trial; WSCM = water-based contrast media.

Additionally, there were 197 cases of intravasation after an HSG with the use of oil-based contrast in the case reports/series. In 22 of these women this led to the formation of an oil embolism (22/197, 11.2%). Four of these women were asymptomatic, 18 were symptomatic. Symptoms included a transient cough and/or dyspnoea and neurological symptoms. Four cases were described of women with serious consequences of an oil embolism (TABLE 1) (*Charawanamuttu et al., 1973*; *Dan et al., 1990*; *Flew, 1944*; *Uzun et al., 2004*).

When including only the studies (including the case reports) that used fluoroscopy screening, there were 250 women with intravasation after an HSG with the use of oil-based contrast. In this group there were 16 women with oil embolisms (16/250, 6.4%), of which two had symptoms of coughing and one temporary impaired vision as a result of a retinal oil embolism (3/16, 18.8%). The authors reported that the fluoroscopy images were of poor quality, and over 20 ml of contrast was used during this last procedure (*Charawanamuttu et al., 1973*).

When excluding the studies with known fluoroscopy guidance, there were 611 women with intravasation after an HSG with the use of oil-based contrast. In this group there were 24 women with oil embolisms (24/611, 3.9%), of which 19 (19/24, 79.2%) had, mostly transient, pulmonary symptoms. Of the 24 women with oil embolisms there were three women with serious lasting consequences of cerebral complaints after an oil embolism (TABLE 1) (*Dan et al., 1990*; *Flew, 1944*; *Uzun et al., 2004*).

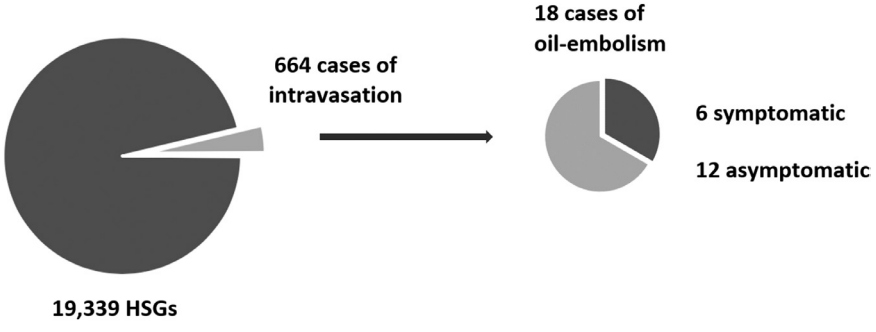

FIGURE 2 Intravasation and oil embolisms in HSG with oil-based contrast for subfertility in cohort studies and RCT. HSG = hysterosalpingography; RCT = randomized controlled trial.

Infection

Two RCT and 18 cohort studies reported on the frequency of infection after HSG with the use of oil-based contrast. The overall pooled weighted frequency of infection was 0.90% (95% CI 0.47–1.50, 70/11,287 women). Two RCT and two cohort studies compared HSG with the use of oil-based contrast to HSG using water-based contrast. The frequency of infection with the use of water-based contrast was 1.9% (95% CI 0.27–4.60, 17/564 women). Including only the studies published in or after 1960, the overall pooled frequency of infection was 0.55% (95% CI 0.23–1.00) after HSG with the use of oil-based contrast and 0.35% (95% CI 0.00–7.30) with the use of water-based contrast. The use of antibiotic prophylaxis was not systematically reported.

Mortality

Five cases of mortality were reported after HSG with the use of oil-based contrast in subfertile women. Four of these cases were infection-related,

TABLE 1 CHARACTERISTICS OF SERIOUS CONSEQUENCES OF OIL EMBOLISM AFTER HSG

Study	Contrast	Risk factors	Organ system involved	Consequences
Flew, 1944	Lipiodol (not specified)	HSG on day 24 of menstrual cycle; use of fluoroscopy not reported	Pulmonary and cerebrum	Hemiplegia, survived
Charawanamuttu et al., 1973	Lipiodol Ultra Fluid	>20 ml of contrast, poor definition of fluoroscopy images	Pulmonary and retina	3 months of impaired vision
Dan et al., 1990	Lipiodol Ultra Fluid	Use of fluoroscopy not reported	Pulmonary, central nervous system	Comatose for 11 days, afterwards normal mental/motor function
Uzun et al., 2004	Lipiodol (not specified)	Use of fluoroscopy not reported	Pulmonary, central nervous system	Comatose for 10 days, afterwards mental/motor function progressively improved

HSG = hysterosalpingography.

and they were published in the period between 1942 and 1950 (*Bang, 1950*; *Feiner, 1942*; *Rutherford, 1948*).

The fifth case described a woman that passed away minutes after a recurrent HSG with 9 ml of lipoiodine under light cyclopropane anaesthesia, possibly due to an allergic reaction to the oil-based contrast or the anaesthesia used (*Faris and McMurrey, 1947*).

Additionally, two cases were reported in 1928 and 1930 where tubal blockage was found on the HSG. These women underwent surgery 1 and 5 days later, and died shortly after, presumably from infectious complications of the surgery (*Hirst, 1928*; *Novak, 1930*).

Lipogranuloma and oil remnants

Eleven studies reported on 41 women with lipogranuloma formation after an HSG with the use of different types of oil-based contrast. These included three cohort studies, one case series and seven case reports. The contrasts used were: Lipiodol not further specified (33 cases), oil-based/iodized contrast not further specified (five cases), Jodipin (two cases), Ethiodol (one case). In nine cases histology examination was mentioned, in 32 cases this was not mentioned.

Additionally, there were 85 reports of oil remnants after an HSG with the use of oil-based contrast. These were reported in nine studies; three cohort studies and six case reports. Forty-four cases were discovered within 2 weeks after the procedure, while 41 were discovered up to 27 years after the HSG procedure. Fifty-six cases were diagnosed after laparoscopy; 29 cases were diagnosed after radiology imaging. Histological examination was only reported in one case.

Thyroid dysfunction

TABLE 2 shows four cohort studies and four case reports/series on maternal

TABLE 2 MATERNAL THYROID FUNCTION AFTER HSG

Study design		Procedure	Thyroid function pre-HSG	Outcome
Case reports				
Li et al., 2018	China	Oil-based contrast	Unknown	Fourteen women with increased urinary iodine content: 50% (7/14) (subclinical) hypothyroidism. All neonates tested negative during congenital thyroid screening.
Sasaki et al., 2017	Japan	Oil-based contrast	Unknown	Case of hypothyroidism, no treatment. Fetal goitre.
Ma et al., 2016	China	Oil-based contrast 100 ml	Euthyroid	Hyperthyroidism, no treatment, resolved spontaneously after 1.5 months.
Ishizuki et al., 1992	Japan	Lipiodol	Graves' disease	Thyroiditis, goitre, treated with steroids for 2 months.
Cohorts/RCT				
So et al., 2017	Japan	Lipiodol Max 5 ml	Euthyroid	Oil-based contrast: 22.6% subclinical hypothyroidism after 1–30 days, 24.4% after 31–180 days. Water-based contrast: 9.5% subclinical hypothyroidism after 1–30 days, 3.6% after 31–180 days.
Kaneshige et al., 2015	Japan	Lipiodol 6.1 ml (4.0–9.0)	Euthyroid: 27% goitre palpable	0% hypothyroidism (0/22). 13.6% (3/22) transient subclinical hypothyroidism.
Mekaru et al., 2008	Japan	Lipiodol 5–10 ml	76% euthyroid 12% subclinical hypothyroidism 12% subclinical hyperthyroidism	Euthyroid: 4/180 (2.2%) hypothyroidism, 28/180 (15.6%) subclinical hypothyroidism, 2/180 (1.1%) subclinical hyperthyroidism. Subclinical hypothyroidism: 10/28 (35.7%) hypothyroidism, three required thyroid hormone replacement. 1/28 (3.6%) subclinical hyperthyroidism. Subclinical hyperthyroidism: 4/12 (33.3%) normalization, 2/12 (16.7%) unchanged.
Slater et al., 1959	USA	Lipiodol	Clinically euthyroid	Oil-based contrast: 80% depression of iodine uptake, increase in protein-bound iodine for 4 months. Water-based contrast: no depression of iodine uptake. Increase in protein-bound iodine for 24–48 h.

HSG = hysterosalpingography.

thyroid function after HSG with the use of oil-based contrast.

Three cases of fetal goitre following an HSG with oil-based contrast were reported. In two of the cases the HSG had been performed in the month of conception (10 ml of Lipiodol and an unknown volume of unspecified oil-based contrast was used); in the third case three HSGs had been performed in the year before conception. In one case intra-amniotic levothyroxine was administered as treatment. After birth, hypothyroidism was diagnosed in one of the newborns, which resolved by day 7. The other neonates were euthyroid. One of the mothers had hypothyroidism during pregnancy; two were euthyroid. In one of the mothers, oil remnants were present in the abdominal cavity on a post-partum X-ray (*Omoto et al., 2013*; *Sasaki et al., 2017*; *Yamazaki et al., 2019*).

One retrospective cohort study from Japan (*Satoh et al., 2015*) evaluated the neonatal thyroid function after HSG with the use of Lipiodol. Abnormal congenital thyroid screening was seen in 2.4% (5/212); three cases of subclinical hypothyroidism and two cases of overt hypothyroidism. The median volume of contrast in the group with thyroid dysfunction was significantly higher than the group with normal thyroid function (20 ml [range 10–20 ml] versus 8 ml [range 3–25 ml], $P = 0.033$). However, the volume was only reported for three out of five neonates with abnormal thyroid function test results. Another retrospective cohort study investigated the thyroid function of 140 neonates born after a preconceptional HSG with oil-based contrast, Lipiodol Ultra Fluid ($n = 76$) or water-based contrast, Telebrix Hystero® ($n = 64$). None of the neonates tested positive during the congenital hypothyroidism screening. Furthermore, the volume of contrast used did not influence the thyroid function (median of 9.0 ml of oil-based contrast) (*van Welie et al., 2020*).

Other complications

One case of a tubal rupture, without ill effects, was described. The diagnostic method was not reported (*Witwer et al., 1930*). Additionally, one case report described abdominal pain, like Fitz-Hugh–Curtis syndrome, possibly due to the chemical stimulation of the iodized oil (not further specified) used during an HSG (*Morii et al., 2013*).

HSG performed for non-subfertility indications

The primary intention of this study was to take into account HSGs performed for subfertility. However, in a non-systematic way, the study also identified one case of a massive oil embolism leading to death, published in 1931. A 60-year-old received an HSG with 8 ml Jodipin for postmenopausal blood loss which was suspected for malignancy. A massive oil embolism occurred in the cerebrum, pituitary gland, liver, spleen, kidney and heart, and the patient died within 5 h after the procedure. The use of fluoroscopy screening was not reported. It is likely that no adequate fluoroscopy was performed at the time (*Gajzago, 1931*).

Furthermore, a case report of a woman falling into a comatose state after an HSG was reported. This woman had had two unsuccessful curettage attempts for termination of pregnancy, after which she received an HSG with Lipiodol Ultra Fluid. The endometrium was injured after the several curettages, and so the contrast could flow directly into the bloodstream, leading to a massive intravasation with oil embolisms. After 81 days she was discharged with slight mental deficit (*Ogihara et al., 1991*).

This study also identified case reports of pulmonary oil embolisms after HSG performed in patients with: tubal ligation ($n = 2$) (*Roblee, 1945*), suspected endometrium carcinoma ($n = 1$) (*Breitländer and Hinrichs, 1941*), abdominal pain ($n = 1$) (*Ingersoll and Robbins, 1947*), uterus myomatosus ($n = 2$) (*Hodge and Price, 1969*; *Keller, 1943*) and missed abortion ($n = 1$) (*Hinaut et al., 1966*).

DISCUSSION

In this review of articles published from 1928 onwards, including a total of 23,536 HSG with the use of oil-based contrast, the most frequently reported complication of HSG performed for subfertility was intravasation of contrast. This occurred in 2.7% of the HSG with the use of oil-based contrast (31 studies, 95% CI 1.7–3.8), compared with 2.0% with the use of water-based contrast (8 studies, 95% CI 1.2–3.0) derived from cohort studies and RCT. Oil embolisms occurred in 0.1% of the HSG performed in cohort studies and RCT. In all studies, including the case reports, the percentage of symptomatic oil embolisms was strikingly lower in the group with fluoroscopy guidance during HSG compared with no fluoroscopy guidance (19% versus 79%). With the use of fluoroscopy guidance during HSG, no serious consequences of oil embolisms occurred.

The frequency of infection with the use of oil-based contrast was 0.90% (20 studies, 95% CI 0.47–1.50), compared with 1.9% (four studies, 95% CI 0.27–4.60) with the use of water-based contrast.

One case of non-infection-related mortality after an HSG, most likely due to an anaphylactic reaction, was reported in 1947.

There were 85 reports of oil remnants after an HSG. Half of the cases were diagnosed within 2 weeks of the procedure. Furthermore, there were 41 reports of lipogranuloma formation.

Women with subclinical hypothyroidism seem more likely to develop hypothyroidism after an HSG with oil-based contrast (35.7% versus 0–2.2% in euthyroid women), however this is based on only 28 and 202 women, respectively (*Kaneshige et al., 2015*; *Mekaru et al., 2008*; *So et al., 2017*). Results on the effect on thyroid function of the offspring are contradictory; a Japanese study showed abnormal congenital thyroid screening in 2.4% whereas a Dutch study did not show any abnormalities (*Satoh et al., 2015*; *van Welie et al., 2020*).

This is the first systematic review on the safety of HSG with oil-based contrast that includes all study types. Another strength of this systematic review is that no restriction on language or publication date was applied.

However, the systematic review has limitations. First, the quality of the included studies was moderate to low. This is attributable to the design and the publication year of the included studies. In most of the studies the primary outcome was pregnancy-related. Complications were often reported as secondary outcomes.

Second, the development of fluoroscopy guidance during HSG has helped clinicians to diagnose intravasation and oil embolisms, leading to timely

termination of the HSG procedure. This development is suggested as the reason for the increase in reported cases of intravasation and oil embolisms, however as mentioned previously, the percentage of symptomatic oil embolisms has therefore drastically decreased.

Oil embolisms, also known as fat embolisms, have not only been reported in the gynaecological literature. Bone marrow fat embolisms occur in 11–19% of trauma or orthopaedic surgery patients (*Mellor and Soni, 2001*). Fat embolisms may cause a fat embolism syndrome, with clinical symptoms varying from right heart failure and cardiovascular collapse to hypoxemia, pyrexia, petechial rash and neurological symptoms (*Mellor and Soni, 2001*). When reaching the lungs, the fatty substance mixes with the locally secreted lipase. Free fatty acids are released, causing inflammation to the pulmonary microvasculature and leading to a shock lung-like or acute respiratory distress syndrome-like syndrome (*Duran et al., 2018*). Suggested treatment is mainly supportive. Corticosteroids are proposed for their possible beneficial effect on the pulmonary capillary membrane, preventing pulmonary oedema (*Mellor and Soni, 2001*). The pathogenesis of oil embolisms after the use of oil-based contrast could be similar to that described after a bone marrow fat embolism, however, in the latter case it concerns autologous tissue, while in the case of the use of oil-based contrast it concerns foreign material. In the four cases with severe complications of oil embolisms that are summarized in this review, one case was treated with corticosteroids (*Charawanamuttu et al., 1973*), but in the other cases only supportive measures were reported.

In this systematic review of HSGs with oil-based contrast for subfertility, four cases of infection-related mortality were identified. It should be noted that these cases were all in the 1940s, when penicillin had been recently introduced and the treatment for infection was completely different from current practice (*Bud, 2007*). There are also reports in the literature of infection-related mortality following HSG with the use of water-based contrast (*Lachmann, 1944*). With the increased use and improvements of (prophylactic and therapeutic) antibiotics, the course of these infections has become less severe. The frequency of acute pelvic inflammatory disease after HSG is nowadays 0.5% with antibiotic prophylaxis and 1.4% without prophylaxis (*Li et al., 2018*).

There were more than twice the number of reports on oil remnants (n = 85) than lipogranuloma formation (n = 41) after HSG with the use of oil-based contrast. Lipogranuloma is a pathological diagnosis and may be missed if oil remnants are not sent for pathological examination. Lipogranuloma may result in adhesion formation (*Grosskinsky et al., 1994*).

After iodine exposure, there is an excess of iodine transportation into the thyroid gland. Through negative feedback, this causes a transient decrease in the synthesis of thyroid hormone, potentially leading to the development of subclinical hypothyroidism. The level of thyroid hormone production will normally be restored within 24–48 h. However, patients with underlying thyroid abnormalities may be unable to escape from this so-called acute Wolff–Chaikoff effect and therefore acquire an iodine-induced (transient) overt hypothyroidism (*Wolff and Chaikoff, 1948*). This is in line with the results of the cohort study by *Mekaru et al. (2008)*, which showed that 35.7% of women with a subclinical hypothyroidism develop overt hypothyroidism after an HSG with oil-based contrast, compared with 0–2.2% of euthyroid women (*Kaneshige et al., 2015*; *Mekaru et al., 2008*). Iodine-induced (transient) hyperthyroidism can also occur in susceptible patients due to activation of quiescent nodules (*Wolff and Chaikoff, 1948*). This was shown in a case report of a woman with Graves' disease, who developed hyperthyroidism after an HSG (*Ishizuki et al., 1992*).

Five out of eight studies included in this review, on maternal thyroid dysfunction after HSG, were performed in Japan. The effect of iodinated contrast on the thyroidal gland may vary between Japanese and Caucasian women, possibly because of a different background risk (i.e. iodine-rich diet). The consumption of iodine-rich foods by mothers in Japan has been shown to lead to neonatal hypothyroidism (*Nishiyama et al., 2004*). This may be reflected in the overall risk for congenital hypothyroidism, which is 0.7% in Japan compared with 0.04% in the Netherlands (*Tokyo Health Service Association, 2010*; *Verkerk et al., 2014*). Data on Asian women suggest that neonatal thyroid dysfunction after HSG is related to the amount of oil-based contrast used during the procedure, although volume of contrast was not reported for all procedures (*Satoh et al., 2015*).

It is unclear whether Caucasian women with an underlying thyroid disease are also at risk of developing hypothyroidism after an HSG with oil-based contrast. Until further studies have been performed, it is suggested that women with overt thyroid disease should not receive an HSG with oil-based contrast. In current practice, routine thyroid screening for women with subfertility varies. According to the NICE guidelines thyroid screening is not recommended as routine measurement in asymptomatic women presenting with subfertility (*NICE, 2017*). However, the ACOG committee opinion on fertility work-up does recommend routine thyroid testing for all subfertile women (*ACOG, 2019*). Moreover, the 2017 American Thyroid Association guidelines for the diagnosis and management of thyroid disease during pregnancy and the post-partum period advises maintaining serum TSH concentrations below 2.5 mIU/l pre-conceptually in the subfertility setting (*Alexander et al., 2017*).

In this systematic review of complications of HSG from 1928 onwards, the most frequently reported complication with oil-based contrast is intravasation, occurring in 2.7%. Only four cases of serious consequences of oil embolisms in subfertile women have been published since 1928. Therefore, safety concerns should not be the reason to deny the use of oil-based contrast for tubal testing in women with unexplained subfertility.

Further studies on the effect of oil-based contrast on maternal and neonatal thyroid function in Caucasian women are suggested. Furthermore, future research should investigate the mechanism of the pregnancy-enhancing effect of oil-based contrast. By gaining knowledge on the mechanism of action, it would be possible to determine which women would benefit most from an HSG with the use of oil-based contrast.

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