

Cost-effectiveness modelling of three different hysterosalpingography diagnostic strategies in addition to standard fertility management for couples with unexplained infertility in the United Kingdom

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Unstructured abstract 200 words

Previous studies have demonstrated hysterosalpingography (HSG) in general, and specifically with an oil-soluble contrast medium, directly increases pregnancy rates. Decision modelling was performed to compare fertility management using three HSG diagnostic strategies, Lipiodol® Ultra Fluid HSG (LUF-HSG), no HSG and water-soluble contrast medium (WSCM) HSG for women aged ≤ 39 years with unexplained infertility. Four reimbursement scenarios were modelled to reflect the various funding arrangements across the regions of the UK. Compared with WSCM-HSG, the live birth rates after 24 months increased by 3.4% with LUF-HSG and decreased by 2.7% with no HSG. From a patient perspective, fertility management with LUF-HSG is the most cost-effective strategy with cost-savings ranging from £299 - £857 per patient depending on the funding arrangement for IVF. From an NHS perspective, fertility management with LUF-HSG is cost-effective when 2 or more IVF cycles are NHS-funded. If none of the IVF cycles are NHS-funded, fertility management with LUF-HSG can be considered cost-effective if society is willing to pay £8,353 for an additional live birth. The findings from this analysis suggest that fertility management with WSCM-HSG is cost-effective compared to no HSG and LUF-HSG is the most cost-effective with increased live birth rates after 24 months.

Keywords: hysterosalpingography; cost-effectiveness; decision tree modelling; contrast media; unexplained infertility

Introduction

Tubal patency testing with hysterosalpingography (HSG) using a water-soluble contrast medium (WSCM) is standard practice in the UK. Initially introduced as a diagnostic test, it has long been suggested that HSG in general, and specifically with an oil-soluble contrast medium (OSCM), directly increases pregnancy rates (Watson et al., 1994). Recent evidence suggests that tubal flushing with an OSCM may increase the probability of pregnancy and

live birth compared to tubal flushing with a WSCM (Dreyer et al., 2017) or no intervention (Mohiyiddeen et al., 2015).

The findings of the H2Oil study (Dreyer et al., 2017) have the potential to change the perspective of fertility management. Given the high costs of assisted reproductive treatments such as intrauterine insemination (IUI) and invitro fertilisation (IVF), HSG offers potential cost savings to the patient and health system when implemented with fertility management. In particular, for couples with unexplained infertility, when results from standard female and male infertility tests are normal (Quaas & Dokras, 2008), and accounts for 27% of infertility cases (over 30,000 women) in the UK in 2015-16 (Human Fertilisation and Embryology Authority, 2016).

Access to NHS-funded IVF in England is determined by local clinical commissioning groups (CCGs) whose criteria often differ from the NICE recommendations (National Health Service, 2018). Women not eligible for NHS-funded treatment can access IVF treatment at private clinics at their own cost.

In this study, cost-effectiveness modelling was performed to compare three strategies involving a different fertility diagnostic approach (HSG with a WSCM, HSG with an OSCM (Lipiodol® Ultra Fluid) and no HSG) in addition to standard fertility management for women with unexplained infertility in a UK setting. Four different reimbursement scenarios were modelled to reflect the various funding arrangements across the regions of the UK.

Materials and methods

Decision modelling enables the comparison of the costs and outcomes of alternative treatment strategies in the absence of clinical trials (Drummond and Jefferson, 1996; Sonnenberg and Beck, 1993).

Three strategies involving a different fertility diagnostic approach in addition to standard fertility management were modelled in this analysis:

- (1) Water-soluble contrast medium (WSCM)-HSG
- (2) Lipiodol® Ultra Fluid (LUF)-HSG
- (3) No HSG

For each strategy in this analysis, a woman would begin 6 months of expectant management relying on natural conception after an HSG, or no HSG, followed by a maximum of 6 months (3 cycles) of IUI (van Eekelen et al., 2020) and a maximum of 12 months (3 cycles) of fresh IVF for those who have not conceived. For strategies 1 and 2, the HSG approach described represents the test for tubal patency as part of the standard fertility assessment. Couples with a diagnosis of unexplained infertility from either of these approaches were included in this analysis. For strategy 3, it was assumed that a proportion of the population who did not have a HSG procedure would have suspected (undiagnosed) unexplained infertility.

The main outcomes considered were live birth rate and health care costs for each strategy at 24 months.

Decision model

To compare the costs and outcomes of each strategy for couples experiencing unexplained infertility, a decision tree was constructed with a 24-month time horizon, chosen to reflect the average duration of fertility management. Figure 1 is a simplified version of the decision tree illustrating the possible pathways for the three strategies (three main branches).

Data sources: probabilities

Natural pregnancy and live birth probabilities for expectant management 6 months after no

HSG and HSG with an OSCM or WSCM were based on data from a randomised controlled trial comparing LUF-HSG with WSCM-HSG in women ≤ 39 years of age (Dreyer et al., 2017) and a network meta-analysis (Wang et al., 2019), respectively. The population from which the probabilities for the no HSG strategy were derived, applied the following exclusion criteria: female age ≥ 40 years, severe male infertility, previously known severe tubal infertility and suspected anovulation (Lindborg et al., 2009).

Pregnancy and live birth probabilities per IUI and fresh IVF cycles were derived from the HFEA anonymised register for 2015-16 (Human Fertilisation and Embryology Authority, 2016) and restricted to women aged ≤ 39 years with unexplained infertility. The probability of discontinuing IVF treatment was based on the number of couples who discontinued IVF treatment over a 6-year period in the UK (Rajkhowa et al., 2006).

Probabilities for selected complications (see Data sources: costs) were included in the analysis.

Table 1 provides details on all the model input probabilities.

It was assumed that women who had a pregnancy that did not result in a live birth would continue to receive the next scheduled treatment until a live birth or the end of the specified 24-month time horizon.

Data sources: costs

The cost-effectiveness analysis was performed from a societal and health care system perspective. Direct health care (e.g. interventions, fertility treatments, pregnancy and delivery) and direct non-health care costs (e.g. productivity loss) were considered. The direct health care costs for the NHS and the patient (out-of-pocket) were estimated and reported. Selected complications (multiple birth, severe OHSS and ectopic pregnancy) that incurred high costs and were considered to differ significantly across the types of fertility treatment

were included. All costs were standardised to 2019 prices using consumer price index data. No discounting was applied due to the short time horizon. Table 2 provides details on all the model input costs.

For the intervention, an estimated cost of an HSG procedure plus the current cost of LUF (£198 per unit) and WSCM (£5 per unit) for the NHS was modelled (Guerbet, UK). No intervention cost was assigned to the no HSG strategy.

Given that the NHS funding for IVF cycles is postcode-dependent, four different reimbursement scenarios were modelled:

- (1) RS-1: No NHS-funded IVF treatment (patient pays in full, i.e. all out-of-pocket)
- (2) RS-2: NHS funds 1 IVF cycle
- (3) RS-3: NHS funds 2 IVF cycles
- (4) RS-4: NHS funds 3 IVF cycles

Cost-effectiveness analysis

The incremental cost-effectiveness ratio (ICER) per additional live birth was calculated by dividing the difference in total costs by the difference in outcome for each strategy. A cost-effectiveness plane was generated to graphically represent the joint differences in costs and outcomes for the four strategies. Costs were separated by cost sub-groups (intervention, infertility treatments, pregnancy and delivery) to determine how each contributed to the differences in costs, and by costs to the NHS or patient (out-of-pocket) to determine the potential cost savings for both.

Sensitivity analyses

One-way deterministic sensitivity analyses were performed to examine the impact of estimated probabilities and costs on the findings. The lower and upper 95% limits were tested

for all the input probabilities. The lower and upper range limits for estimated health care cost inputs were tested.

Results

Across all reimbursement scenarios, the live birth rate after 24 months for the WSCM-HSG strategy was 75.2%. Comparatively, there was a 3.4% increase and a 2.7% decrease in the live birth rates after 24 months for the LUF-HSG and no HSG strategies, respectively (Tables 3 and 4).

The differences in the costs associated with the interventions and pregnancy and delivery did not change across the reimbursement scenarios (Tables 3 and 4). The funding arrangements for infertility treatments had the greatest impact on the cost-effectiveness of each treatment strategy.

LUF-HSG compared with WSCM-HSG

For the patient, the LUF-HSG strategy was the dominant strategy with potential out-of-pocket cost-savings across all reimbursement scenarios (Table 3 and Figure 2). The potential out-of-pocket cost-savings were greatest (£857 per patient) when the patient pays in full (RS-1). As the number of IVF cycles funded by the NHS increased with RS-2 to RS-4, the potential out-of-pocket cost-savings decreased (Table 3).

For the NHS, the additional costs per patient for the LUF-HSG strategy in RS-1 and RS-2 had corresponding ICERs of £8,353 and £731 per additional live birth, respectively (Table 3 and Figure 3). The LUF-HSG strategy was the dominant strategy when 2 or more IVF cycles were funded by the NHS (RS-3 and RS-4) (Table 3).

No HSG compared with WSCM-HSG

For the patient, the No HSG strategy was dominated by the WSCM HSG strategy with

additional potential out-of-pocket costs per patient across all reimbursement scenarios (Table 4 and Figure 2). The additional out-of-pocket costs per patient were greatest (£686 per patient) when the patient pays in full (RS-1). As the number of IVF cycles funded by the NHS increased with RS-2 to RS-4, the additional out-of-pocket costs decreased (Table 4).

For the NHS, the potential cost-savings with the No HSG strategy when none of the IVF cycles were funded by the NHS (RS-1) had a corresponding ICER of £5,265 for foregoing an additional live birth (Table 4 and Figure 3). The No HSG strategy was dominated by the WSCM-HSG strategy when 1 or more IVF cycles were funded by the NHS (RS-2 to RS-4) (Table 4).

Sensitivity analyses

Uncertainty around the pregnancy and live birth rates for LUF-HSG and WSCM-HSG had the greatest impact on the effectiveness (live birth rates) of LUF-HSG compared with WSCM-HSG, with absolute differences of up to 1.6%. Similar findings for no HSG compared with WSCM-HSG, with absolute differences of up to 1.3%. Uncertainty around the remaining input parameters had little or no effect on the live birth rates after 24 months.

For LUF-HSG compared with WSCM-HSG, uncertainty around the cost of LUF-HSG and for an IVF cycle had the greatest effect on the cost savings to the NHS. Uncertainty around the pregnancy rates for LUF-HSG and WSCM-HSG and the per-cycle cost of IVF and IUI had the greatest effect on the cost savings to the patient (out-of-pocket costs).

For no HSG compared with WSCM-HSG, uncertainty around the per-cycle cost of 1 IVF cycle and the pregnancy rates for WSCM-HSG had the greatest effect on the cost savings to the NHS. Uncertainty around the pregnancy and live birth rates for WSCM-HSG and the per-cycle costs of IVF and IUI had the greatest effect on the cost savings to the patient (out-of-pocket costs).

Tornado diagrams illustrating the impact of the uncertainty around the true values of the estimated model input parameters are provided in the supplementary online material.

Discussion

The findings from this analysis suggest that LUF-HSG is a cost-effective strategy for women with unexplained infertility with increased live birth rates after 24 months and overall cost-savings to patients and the NHS.

From a patient perspective, LUF-HSG is the most cost-effective strategy with increased live birth rates after 24 months and cost-savings across all reimbursement scenarios. Compared with WSCM-HSG (standard practice), the no HSG strategy was not cost-effective with decreased live birth rates after 24 months and additional costs across all reimbursement scenarios.

From an NHS perspective, the additional costs for LUF-HSG and pregnancy and delivery were offset when at least 2 IVF cycles were NHS-funded. Where the NHS funded none or 1 IVF cycle, the LUF-HSG strategy could be considered cost-effective if society is willing to pay up to £8,353 and £731 for an additional live birth, respectively. To provide perspective, NICE uses a cost-effectiveness threshold, the maximum cost per health outcome that a health system is willing to pay, of £20,000-£30,000 per quality-adjusted life year (QALY, the value of a statistical life based on quality and length of life) for medical interventions (National Institute for Health and Care Excellence, 2013). The most recent evidence-based estimate of the NICE cost-effectiveness threshold (based on 2008 NHS expenditure) was £12,936 per QALY (Claxton et al., 2015).

The no HSG strategy was not cost-effective when 1, 2 or 3 IVF cycles were funded by the NHS, as there were additional overall costs to the NHS and a decrease in live birth rates.

Limitations

There is uncertainty regarding the data sources used to populate the decision model and estimate the costs and effects of the three strategies. However, the sensitivity analyses suggests the parameter estimates are robust and provide a comparative analysis of the costs and benefits of a LUF-HSG strategy for women with unexplained infertility. This study was based on UK data and costs (where available). Globally, the cost difference between the two contrast media vary widely, thus limiting the generalisability of our findings. This modelling was also based on women ≤ 39 years of age with unexplained infertility and should not be generalised to other groups of infertile women.

A societal perspective was included using an estimate of productivity losses due to absence from work for IVF treatment but other indirect costs associated with pregnancy and delivery, such as care of other children or transportation, were not included. It could be expected that the cost differences between the strategies would increase over a two-year period.

The third strategy of no HSG was included to reflect the practice that some fertility specialists consider immediate IVF treatment for certain patients. HyCoSy (hysterosalpingo-contrast-sonography) and HyFoSy (hysterosalpingo-foam-sonography) are other potential strategies that have become increasingly popular (Graziano et al., 2013; Lo Monte et al., 2015) but were not included as it was considered to be equivalent to the no HSG strategy (Lindborg et al., 2009). Though it should be noted that HyCoSy and HyFoSy have additional costs of approximately £500 and £450 for a private patient, respectively (Nurture Fertility, 2020).

Comparison with other studies

The live birth rates after two years for each of the three strategies reported in this analysis are

consistent with the fertility-enhancing effect of tubal flushing with an OSCM reported from a recent network meta-analysis (Wang et al., 2019).

A recent long-term cost-effectiveness analysis of the H2Oil trial (Van Welie et al., in press) also reported increased live birth rates with HSG using an OSCM (75%) compared with HSG using a WSCM (67%) for equivalent costs over a 5-year follow-up period. Compared to the model in this analysis using UK data (where available), the Dutch follow-up trial reported higher live birth rates after IUI and increased rates of IUI cycles that also differed between treatment groups. For women who required infertility treatments following an HSG in the Dutch trial, the oil group reported a mean 4.0 IUI cycles and the water group a mean 4.5 IUI cycles over a 5-year period. In our analysis, the oil group had a mean 2.3 IUI cycles and the water group a mean 2.0 IUI cycles over an 18-month period after 6 months of expectant management. The rates of IVF cycles were the same for the Dutch trial and this analysis (mean 1.6 IVF cycles). For this analysis, the focus was on the impact of having an HSG and whether it was used with an oil- or water-based contrast medium, so the live birth rates after IUI and IVF were kept constant across all three strategies. This would explain the higher live birth rates after 24 months for the WSCM HSG and LUF-HSG strategies and the smaller difference in live birth rates reported in our analysis.

Implications

Public funding for fertility treatments is a contentious issue for any Government. In the UK, the CCGs organise the delivery of health services to the community and determine the eligibility for NHS-funded IVF. This analysis illustrates the potential for LUF-HSG to increase the live birth rate with cost-savings to both the NHS and patient. The LUF-HSG strategy may also enable some women to avoid the physical and psychosocial impacts of IVF treatment.

The findings from this analysis suggest that LUF-HSG is a cost-effective strategy with increased live birth rates after 24 months. From a patient perspective, LUF-HSG is the most cost-effective strategy. From an NHS perspective, LUF-HSG could be considered a cost-effective strategy if society is willing to pay, at most, £8,353 for an additional live birth. Otherwise, the additional costs for LUF-HSG and pregnancy and delivery would be offset when at least 2 IVF cycles were NHS-funded.

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References

- Claxton, K., Martin, S., Soares, M., Rice, N., Spackman, E., Hinde, S., Devlin, N., Smith, P. C., & Sculpher, M. (2015). Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technology Assessment, 19*(14). <https://doi.org/10.3310/hta19140>
- Dreyer, K., van Rijswijk, J., Mijatovic, V., Goddijn, M., Verhoeve, H. R., van Rooij, I. A. J., Hoek, A., Bourdrez, P., Nap, A. W., Rijnsaardt-Lukassen, H. G. M., Timmerman, C. C. M., Kaplan, M., Hooker, A. B., Gijzen, A. P., van Golde, R., van Heteren, C. F., Sluijmer, A. V., de Bruin, J. P., Smeenk, J. M. J., de Boer, J. A. M., Scheenjes, E., Duijn, A. E. J., Mozes, A., Pelinck, M. J., Traas, M. A. F., van Hooff, M. H. A., van Unnik, G. A., de Koning, C. H., van Geloven, N., Twisk, J. W. R., Hompes, P. G. A., & Mol, B. W. J. (2017). Oil-Based or Water-Based Contrast for Hysterosalpingography in Infertile Women. *N Engl J Med, 376*(21), 2043-2052. <https://doi.org/10.1056/NEJMoa1612337>
- Graziano, A., Lo Monte, G., Soave, I., Caserta, D., Moscarini, M., & Marci, R. (2013). Sonohysterosalpingography: a suitable choice in infertility workup. *J Med Ultrason (2001), 40*(3), 225-229. <https://doi.org/10.1007/s10396-012-0417-0>

- Human Fertilisation and Embryology Authority. (2016). *HFEA anonymised register data 2015-16*. hfea.gov.uk/about-us/our-data
- Lindborg, L., Thorburn, J., Bergh, C., & Strandell, A. (2009). Influence of HyCoSy on spontaneous pregnancy: a randomized controlled trial. *Human reproduction*, 24(5), 1075-1079.
- Lo Monte, G., Capobianco, G., Piva, I., Caserta, D., Dessole, S., & Marci, R. (2015). Hysterosalpingo contrast sonography (HyCoSy): let's make the point! *Arch Gynecol Obstet*, 291(1), 19-30. <https://doi.org/10.1007/s00404-014-3465-4>
- Mohiyiddeen, L., Hardiman, A., Fitzgerald, C., Hughes, E., Mol, B. W., Johnson, N., & Watson, A. (2015). Tubal flushing for subfertility. *Cochrane Database Syst Rev*(5), Cd003718. <https://doi.org/10.1002/14651858.CD003718.pub4>
- National Health Service. (2018, June 2018). *IVF Overview* <https://www.nhs.uk/conditions/ivf/>
- National Institute for Health and Care Excellence. (2013). *Guide to the methods of technology appraisal 2013*. NICE. <https://www.nice.org.uk/process/pmg9/chapter/the-reference-case>
- Nurture Fertility. (2020, April 2019). *Full pricelist for treatment*. Retrieved March 2020 from <https://www.nurturefertility.co.uk/prices/full-pricelist/>
- Quaas, A., & Dokras, A. (2008). Diagnosis and treatment of unexplained infertility. *Rev Obstet Gynecol*, 1(2), 69-76.
- Rajkhowa, M., McConnell, A., & Thomas, G. E. (2006). Reasons for discontinuation of IVF treatment: a questionnaire study. *Hum Reprod*, 21(2), 358-363. <https://doi.org/10.1093/humrep/dei355>
- van Eekelen, R., Rosielle, K., van Welie, N., Dreyer, K., van Wely, M., Mol, B. W., Eijkemans, M. J., Mijatovic, V., & van Geloven, N. (2020). Does the effectiveness of IUI in couples with unexplained subfertility depend on their prognosis of natural conception? A replication of the H2Oil study. *Hum Reprod Open*, 2020(4), hoaa047. <https://doi.org/10.1093/hropen/hoaa047>
- Van Welie, N., Pham, C. T., Van Rijswijk, J., Dreyer, K., Verhoeve, H. R., Hoek, A., De Bruin, J. P., Nap, A. W., Van Hooff, M. H. A., Goddijn, M., Hooker, A. B., Gijzen, A. P., Traas, M. A. F., Smeenk, J. M. J., Sluijmer, A. V., Lambers, M. J., Van Unnik, G. A., De Koning, C. H., Mozes, A., Timmerman, C. C. M., Lambalk, C. B., Karnon, J. D., Mijatovic, V., & Mol, B. W. (in press). The long-term costs and effects of tubal

flushing: a follow-up study of a randomized trial comparing oil- versus water-based contrast for hysterosalpingography. *Reproductive BioMedicine Online*.

Wang, R., van Welie, N., van Rijswijk, J., Johnson, N. P., Norman, R. J., Dreyer, K., Mijatovic, V., & Mol, B. W. (2019). Effectiveness on fertility outcome of tubal flushing with different contrast media: systematic review and network meta-analysis. *Ultrasound Obstet Gynecol*, 54(2), 172-181. <https://doi.org/10.1002/uog.20238>

Watson, A., Vandekerckhove, P., Lilford, R., Vail, A., Brosens, I., & Hughes, E. (1994). A meta-analysis of the therapeutic role of oil soluble contrast media at hysterosalpingography: a surprising result? *Fertil Steril*, 61(3), 470-477. [https://doi.org/10.1016/s0015-0282\(16\)56578-9](https://doi.org/10.1016/s0015-0282(16)56578-9)

Table 1. Model input probabilities (per cycle*).

Model inputs	Base estimate	Range†	Source
PREGNANCY			
EM for 6 months			
No HSG	0.210	0.206 – 0.214	Wang et al. (2019)
WSCM HSG	0.290	0.254 – 0.329	Dreyer et al. (2017)‡
LUF-HSG	0.390	0.357 – 0.438	Dreyer et al. (2017)‡
IUI	0.170	0.158 – 0.182	HFEA register data for 2015-16 Human Fertilisation and Embryology Authority (2016)
IVF	0.300	0.295 – 0.305	HFEA register data for 2015-16 Human Fertilisation and Embryology Authority (2016)
LIVE BIRTH			
EM for 6 months			
No HSG	0.200	0.196 – 0.204	Wang et al. (2019)
WSCM HSG	0.280	0.244 – 0.319	Dreyer et al. (2017)‡
LUF-HSG	0.380	0.347 – 0.429	Dreyer et al. (2017)‡
IUI	0.140	0.129 – 0.151	HFEA register data for 2015-16 Human Fertilisation and Embryology Authority (2016)
IVF	0.250	0.245 – 0.255	HFEA register data for 2015-16 Human Fertilisation and Embryology Authority (2016)
OTHER			
Discontinue IVF	0.340	0.304 – 0.372	Rajkhowa et al. (2006)
Multiple birth			
EM	0.013	0.012 – 0.015	Office for National Statistics (2019) (2018 data)
IUI	0.100	0.076 – 0.126	HFEA register data for 2015-16 Human Fertilisation and Embryology Authority (2016)
IVF	0.100	0.095 – 0.106	Human Fertilisation and Embryology Authority (2019) (2017 data)
Severe OHSS	0.005	0.004 – 0.006	Delvigne and Rozenberg (2002)
Ectopic pregnancy			
EM	0.011	0.0112 – 0.0114	Cantwell et al. (2011)

IUI	0.020	0.019 – 0.022	Dreyer et al. (2017)
IVF	0.045	0.038 – 0.053	Marcus and Brinsden (1995)

* unless stated otherwise; † for sensitivity analyses; ‡ aggregate estimates for ongoing

pregnancy and live birth for WSCM HSG and LUF-HSG were reported and include conception from expectant management, intrauterine insemination and in vitro fertilisation but over 70% were conceived from expectant management and only couples with low prognosis of conceiving naturally receiving further intervention.

EM, expectant management; HSG, hysterosalpingography; IUI, intrauterine insemination; IVF, in vitro fertilisation; LUF, Lipiodol® Ultra Fluid; OHSS, ovarian hyperstimulation syndrome; WSCM, water-soluble contrast medium.

Table 2. Model input costs.

Model inputs	Unit cost	Range*	Source
Intervention			
No HSG	£0		
HSG procedure†	£65	£54 - £86	NHS Improvement (2019)
WSCM HSG	£5		Guerbet, UK
LUF-HSG	£198	£250	Guerbet, UK
Treatment: IUI (per cycle)			
NHS cost	£0		
Patient out-of-pocket cost	£1,150	£900 – £1,300	Nurture Fertility (2020)
Treatment: IVF (per cycle)			
NHS cost	£3,483	£1,343 - £5,788	Fertility Fairness (2017)
Patient out-of-pocket cost	£5,000	£3,000 - £8,000	Nurture Fertility (2020)
Pregnancy & delivery			
Single			
Antenatal	£1,754	£1,096 - £2,919	NHS Improvement (2019)
Delivery + postnatal	£2,245	£1,833 - £3,384	NHS Improvement (2019)
Multiple			
Antenatal	£2,919	£1,824 - £4,858	NHS Improvement (2019)
Delivery + postnatal	£4,577	£3,721 - £6,869	NHS Improvement (2019)
Complications			
Severe OHSS	£1,500	£1,184 - £1,776	Wechowski et al. (2009)
Ectopic pregnancy‡	£1,484		Thomas and Cameron (2013)
Direct non-health care§ (per IVF cycle)	£618	£519 - £717	Bouwman et al. (2008)

Costs are indexed to 2019 using a consumer price index. * For sensitivity analyses; † based on HRG codes RD30Z, RD31Z and RD32Z relating to Contrast Fluoroscopy Procedures, as there are no specific codes for an HSG procedure; ‡ only a cost estimate was reported in the source publication so lower and upper estimates were not tested for sensitivity for this input parameter; § based on productivity losses due to absence from work.

HSG, hysterosalpingography; IUI, intrauterine insemination; IVF, in vitro fertilisation; LUF, Lipiodol® Ultra Fluid; OHSS, ovarian hyperstimulation syndrome; WSCM, water-soluble contrast medium.

Table 3. Differences in costs and outcome for LUF-HSG relative to WSCM HSG and the corresponding ICERs after 24 months split by costs to the NHS and patient.

Parameter	WSCM HSG	LUF-HSG	Difference	
	Estimate	Estimate	NHS	Patient*
OUTCOME				
Live birth at 24 months	75.2%	78.7%	3.4%	
COSTS				
RS-1				
Intervention	£70	£263	£193	£0
Infertility treatments	£6,147	£5,290	£0	- £857
Pregnancy + delivery	£3,373	£3,465	£92	£0
Total live birth costs	£9,590	£9,018	£285	- £857
ICER	Reference		£8,353	Dominant
RS-2				
Intervention	£70	£263	£193	£0
Infertility treatments	£5,456	£4,695	- £260	- £501
Pregnancy + delivery	£3,373	£3,465	£92	£0
Total live birth costs	£8,899	£8,423	£25	- £501
ICER	Reference		£731	Dominant
RS-3				
Intervention	£70	£263	£193	£0
Infertility treatments	£5,172	£4,451	- £369	- £352
Pregnancy + delivery	£3,373	£3,465	£92	£0
Total live birth costs	£8,614	£8,179	- £83	- £352
ICER	Reference		Dominant	Dominant
RS-4				
Intervention	£70	£263	£193	£0
Infertility treatments	£5,069	£4,363	- £408	- £299
Pregnancy + delivery	£3,373	£3,465	£92	£0
Total live birth costs	£8,512	£8,091	- £122	- £299
ICER	Reference		Dominant	Dominant

*Out-of-pocket costs. HSG, hysterosalpingography; ICER, incremental cost-effectiveness ratio; LUF, Lipiodol® Ultra Fluid; RS-1, Reimbursement scenario 1 (no NHS-funded IVF treatment); RS-2, Reimbursement scenario 2 (1 NHS-funded IVF cycle); RS-3,

Reimbursement scenario 3 (2 NHS-funded IVF cycles); RS-4, Reimbursement scenario 4 (3 NHS-funded IVF cycles); WSCM, water-soluble contrast medium.

Table 4. Differences in costs and outcome for No HSG relative to WSCM HSG and the corresponding ICERs after 24 months split by costs to the NHS and patient.

Parameter	WSCM HSG	No HSG	Difference	
	Estimate	Estimate	NHS	Patient*
OUTCOME				
Live birth at 24 months	75.2%	72.5%	- 2.7%	
COSTS				
RS-1				
Intervention	£70	£0	- £70	£0
Infertility treatments	£6,147	£6,833	£0	£686
Pregnancy + delivery	£3,373	£3,299	- £74	£0
Total live birth costs	£9,590	£10,132	- £144	£686
ICER	Reference		£5,265	Dominated
RS-2				
Intervention	£70	£0	- £70	£0
Infertility treatments	£5,456	£6,065	£208	£401
Pregnancy + delivery	£3,373	£3,299	- £74	£0
Total live birth costs	£8,899	£9,364	£64	£401
ICER	Reference		Dominated	Dominated
RS-3				
Intervention	£70	£0	- £70	£0
Infertility treatments	£5,172	£5,748	£295	£282
Pregnancy + delivery	£3,373	£3,299	- £74	£0
Total live birth costs	£8,614	£9,047	£151	£282
ICER	Reference		Dominated	Dominated
RS-4				
Intervention	£70	£0	- £70	£0
Infertility treatments	£5,069	£5,634	£326	£239
Pregnancy + delivery	£3,373	£3,299	- £74	£0
Total live birth costs	£8,512	£8,933	£182	£239
ICER	Reference		Dominated	Dominated

*Out-of-pocket costs. HSG, hysterosalpingography; ICER, incremental cost-

effectiveness ratio; RS-1, Reimbursement scenario 1 (no NHS-funded IVF treatment);

RS-2, Reimbursement scenario 2 (1 NHS-funded IVF cycle); RS-3, Reimbursement

scenario 3 (2 NHS-funded IVF cycles); RS-4, Reimbursement scenario 4 (3 NHS-funded IVF cycles); WSCM, water-soluble contrast medium.

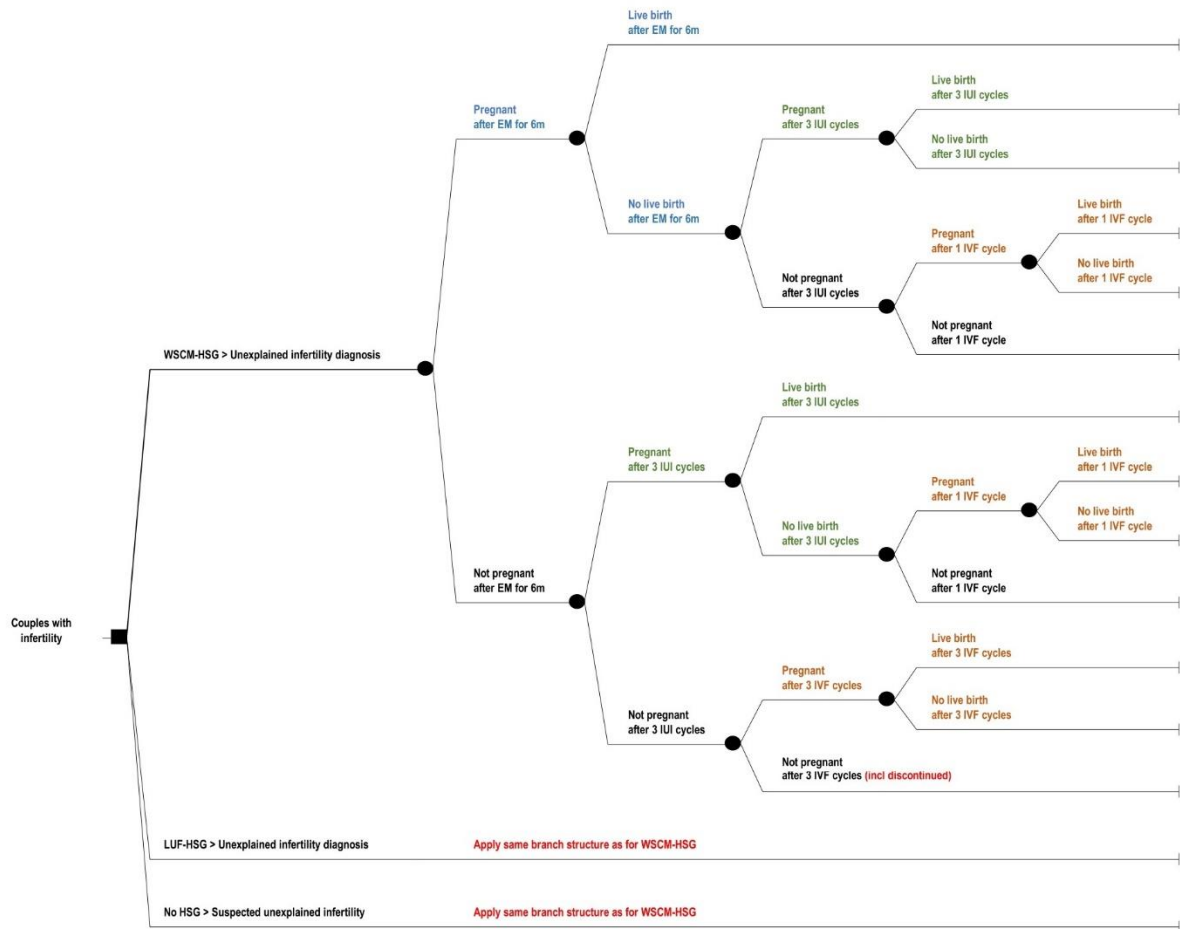


Figure 1. Simplified decision tree model over a 24-month time horizon

Square denotes decision node and circle denotes chance node.

EM, expectant management (natural conception); HSG, hysterosalpingography; IUI, intrauterine insemination; IVF, in vitro fertilisation; LUF, Lipiodol® Ultra Fluid; WSCM, water-soluble contrast medium.

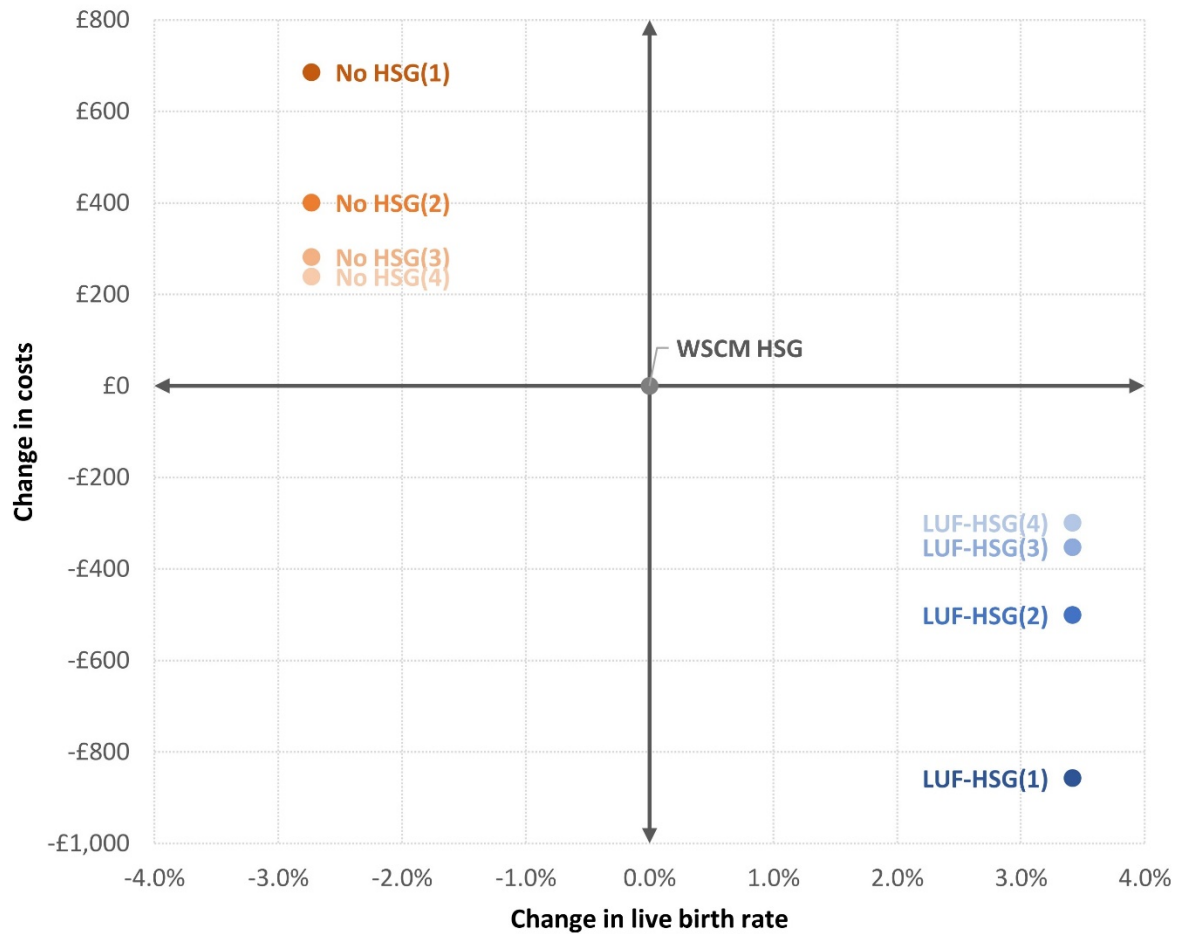


Figure 2. Cost-effectiveness plane representing the **patient out-of-pocket costs** and effects (live birth rate) of LUF-HSG and no HSG relative to WSCM HSG after 24 months

For the cost-effectiveness plane, estimates in the north western quadrant indicate the intervention is less effective and more costly; estimates in the south western quadrant indicate the intervention is less effective and less costly; estimates in the south eastern quadrant indicate the intervention is more effective and less costly; estimates in the north eastern quadrant indicate the intervention is more effective and more costly. Circles represent the incremental cost-effectiveness ratio (ICER) estimate.

HSG, hysterosalpingography; LUF, Lipiodol® Ultra Fluid; (1), Reimbursement scenario 1 (no NHS-funded IVF treatment); (2), Reimbursement scenario 2 (1 NHS-funded IVF cycle); (3), Reimbursement scenario 3 (2 NHS-funded IVF cycles); (4), Reimbursement scenario 4 (3 NHS-funded IVF cycles); WSCM, water soluble contrast medium.

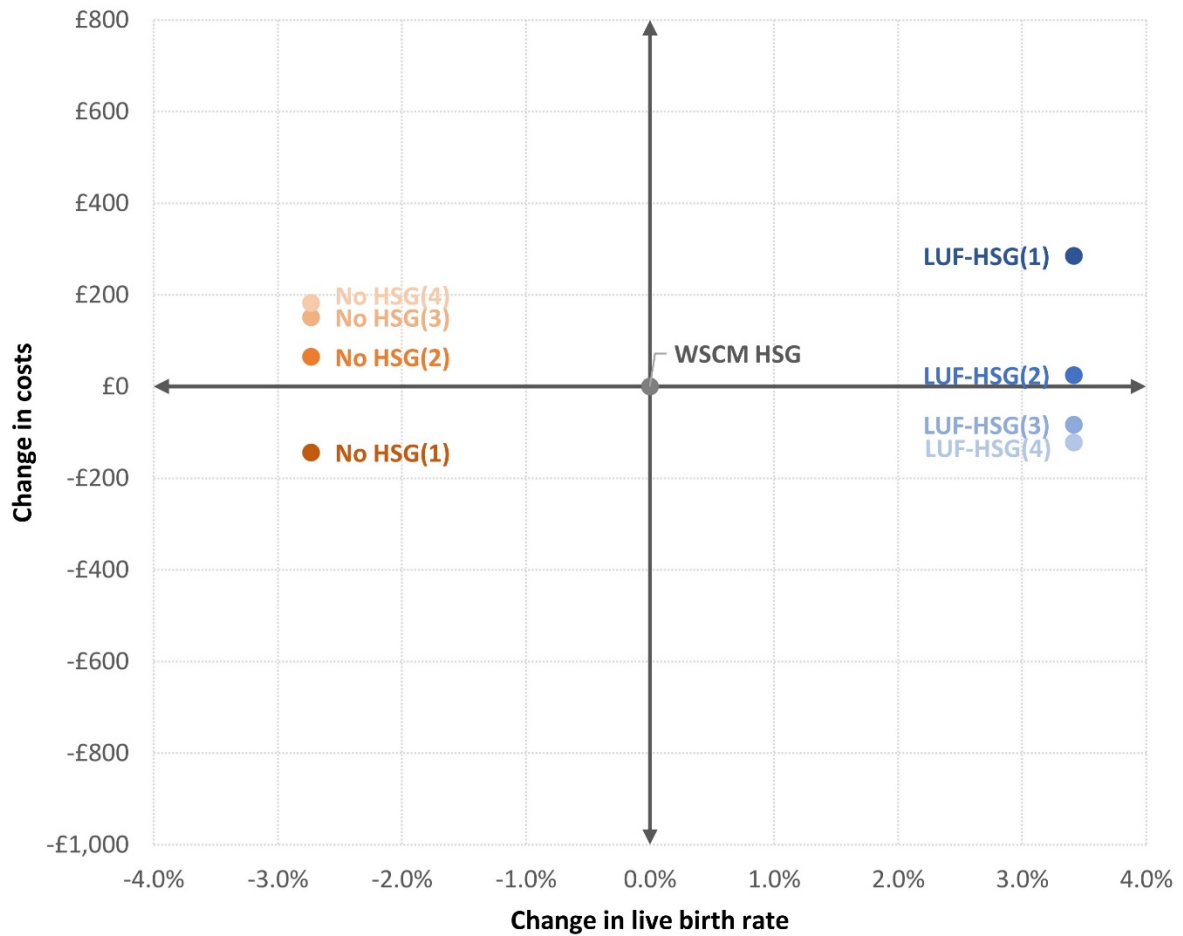


Figure 3. Cost-effectiveness plane representing the **NHS costs** and effects (live birth rate) of LUF-HSG and no HSG relative to WSCM HSG after 24 months

For the cost-effectiveness plane, estimates in the north western quadrant indicate the intervention is less effective and more costly; estimates in the south western quadrant indicate the intervention is less effective and less costly; estimates in the south eastern quadrant indicate the intervention is more effective and less costly; estimates in the north eastern quadrant indicate the intervention is more effective and more costly. Circles represent the incremental cost-effectiveness ratio (ICER) estimate.

HSG, hysterosalpingography; LUF, Lipiodol® Ultra Fluid; (1), Reimbursement scenario 1 (no NHS-funded IVF treatment); (2), Reimbursement scenario 2 (1 NHS-funded IVF cycle); (3), Reimbursement scenario 3 (2 NHS-funded IVF cycles); (4), Reimbursement scenario 4 (3 NHS-funded IVF cycles); WSCM, water soluble contrast medium.