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Evaluation of diagnostic and therapeutic strategies in reproductive medicine: studies on hysterosalpingography and assisted conception

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Chapter

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Routine use of hysterosalpingography prior to laparoscopy in the fertility workup: a multicenter randomised controlled trial

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Abstract

Background: A multicenter randomised controlled trial with or without hysterosalpingography (HSG) was conducted to assess the usefulness of HSG as a routine investigation in the fertility workup prior to laparoscopy and dye.

Methods: From 1 April 1997 to 1 April 2002, subfertile women were allocated by a computer-based 1 : 1 ratio randomisation procedure, either for an HSG followed by laparoscopy and dye (the intervention group) or for laparoscopy and dye only (the control group) as a part of their fertility workup. Cumulative pregnancy rate (CPR) within 18 months after randomisation was the primary outcome of interest.

Results: 344 women were randomised to the intervention group ($n = 169$) and the control group ($n = 175$). There was no significant difference in CPR at 18 months in the intervention group (49.1%) [95% confidence interval (CI) 41.6 to 56.6] and the control group (50.3%) (95% CI 42.8 to 57.8), a difference of -1.2% (95% CI -11.8% to 9.5%).

Conclusion: The routine use of HSG at an early stage in the fertility workup prior to laparoscopy and dye does not influence CPR, compared with the routine use of laparoscopy and dye without HSG.

Introduction

After history taking, physical examination, semen analysis and investigation of ovulation, assessment of tubal patency is the next step in the standard examination of the subfertile couple. Owing to the noninvasive nature and low cost, hysterosalpingography (HSG) is widely used as a first-line approach to assess the patency of the Fallopian tubes in routine fertility workup^{1,2}, although laparoscopy and dye is considered the gold standard^{3,4}.

A reason for performing HSG instead of or prior to laparoscopy and dye cannot be found in the test characteristics of HSG. Comparing the accuracy of HSG with that of laparoscopy and dye in the diagnosis of tubal pathology, a meta-analysis demonstrated point estimates of 65% of sensitivity and 83% of specificity⁴. Furthermore, considerable variability in the interpretation as well as clinical consequences of HSG abnormalities has been shown among practitioners^{5,6}. Advantages of HSG relative to laparoscopy are the short outpatient procedure and the enhancement of pregnancy with oil-soluble contrast medium⁷, although water-soluble media are mostly used⁸. The therapeutic effect of tubal flushing with water-soluble media is, however, still unknown⁹.

The relative merits of HSG and laparoscopy in screening for tubal factors have been discussed for more than 30 years, but so far no randomised controlled trial has been reported¹. To assess the value of HSG prior to laparoscopy and dye in a routine clinical setting, we performed a pragmatic multicenter randomised controlled trial comparing fertility workups with or without HSG. In a pragmatic trial, effectiveness of an intervention is assessed under usual circumstances, in contrast to efficacy trials in which the intervention is examined under ideal conditions¹⁰. Is the patient better off with or without the extra intervention (in this case, HSG)? We compared the two strategies, with pregnancy as a clinical endpoint, in terms of cumulative pregnancy rate (CPR).

Subjects and methods

Patients and randomisation procedure

The study was performed in three teaching hospitals in The Netherlands. All newly referred and admitted subfertile women who visited the Department of Reproductive Medicine of Leiden University Medical Center (April 1997 to April 2002), the Department of Obstetrics and Gynaecology of the Medical Center Haaglanden, The Hague (April 1997 to April 2002) or the Department of Obstetrics and Gynaecology of the Groene Hart Hospital, Gouda, The Netherlands (April 1999 to April 2000)

were eligible for inclusion in the trial.

Exclusion criteria were subfertility less than 1 year, woman older than 37 years at the time of first visit, anovulation despite clomiphene citrate or bromocriptine use, abnormal semen analysis according to World Health Organization (WHO)¹¹ criteria or testing of tubal patency performed in the past. The institutional review boards of each of the three hospitals approved the study protocol. Women were asked to participate in the study by their treating gynaecologist at the time that HSG would normally be planned, and informed consent was obtained. The treating gynaecologist telephoned the secretariat of Medical Center Haaglanden at The Hague to perform randomisation. A computer-based 1 : 1 ratio randomisation procedure was used to allocate the women into two groups. Randomisation was stratified for each participating hospital. All women routinely received vaginal ultrasound before randomisation. The intervention group underwent HSG first, and if the HSG showed normal uterine cavity and no tubal pathology and if the woman did not conceive within 6 months, a laparoscopy and dye followed after 6 months. When tubal pathology was assumed, laparoscopy was performed within 1–2 months after the HSG. The control group received a laparoscopy and dye immediately. If pathology of the uterine cavity was presumed by HSG or by vaginal ultrasound, hysteroscopy could be performed together with the laparoscopy. Moreover, a history of recurrent miscarriages or diethylstilboestrol (DES) exposure was an additional reason to perform a hysteroscopy during laparoscopy.

Because our trial was designed to determine the effectiveness of HSG in the routine fertility workup, we ensured that HSG and laparoscopy results were uniformly interpreted in all participating hospitals. At the same time, the study protocol intentionally allowed normal clinical freedom and a variety of choices and protocols after HSG and laparoscopy. Hence, the participating hospitals used their own protocol for therapeutic reproductive surgery and assisted reproductive treatments [e.g. intrauterine insemination (IUI) or IVF]. The primary analysis was conducted on an intention-to-treat basis. The primary outcome parameter in our study was occurrence of pregnancy within 18 months after randomisation. The diagnosis of pregnancy was based on a positive urine or serum pregnancy test in association with the presence of an intrauterine gestation sac on ultrasound scan.

HSG and laparoscopy and dye

All hysterosalpingographies were performed in the outpatient clinic of the department of radiology shortly after the menstrual period. A water-soluble contrast medium (Omnipaque 300®) was used. One photograph was taken of the phase when the cavity and tubes were just filled and one when there was overflow at both sides or when there was maximal filling of the tubes without overflow. After 30 min, a late

film was made to detect contrast depots. Findings of tubal pathology at HSG were classified according to², as normal, one-sided abnormality or two-sided abnormality. Additional intracavity abnormalities were scored separately. The results of HSG were interpreted in a weekly meeting by staff members specialized in reproductive medicine, who also decided whether laparoscopy and dye should be performed with or without delay.

Laparoscopy and dye was performed in the follicular phase and under general anaesthesia. After making pneumoperitoneum, a thorough inspection of the pelvis, internal genitalia, appendix and liver region was performed, followed by testing the patency of the Fallopian tubes using dye. A dilute solution of Methylene Blue was injected through the cervix. During laparoscopy, we determined adhesions, structural abnormalities of the uterus, endometriosis, periadnexal disease and Fallopian tube occlusion. Tubal pathology at laparoscopy was defined according to Mol *et al.*², as normal, one-sided abnormality or two-sided abnormality. Furthermore, endometriosis detected at laparoscopy was classified according to the classification of the American Fertility Society¹². Therapeutic reproductive surgery could be applied during laparoscopy, such as coagulation of endometriosis grade I/II, laparoscopic adhesiolysis or laparoscopic cystectomy.

Statistical methods

Descriptive statistics were used to assess the similarity of the groups. Categorical data were assessed by the chi-square test and continuous variables by Student's *t*-test. CPRs were calculated using standard time-to-event analysis (Kaplan–Meier survival analysis). For comparison of the different CPR curves, the log-rank statistic was used. On the basis of local unpublished data of Leiden University Medical Center, we calculated that for a subfertile couple the probability of getting pregnant after 1 year from intake, including artificial interference, is about 45%. With a smallest difference in CPR arbitrarily set at 10% (55% in the intervention group and 45% in the control group), an alpha error of 0.05 and a beta error of 0.20 (power of the study set at 80%), we calculated that at least 375 women should be included in each arm (a total of 750 women).

Results

A total of 344 women were randomised, 169 to the intervention group and 175 to the control group. Follow-up either to pregnancy or for 18 months was complete for all subjects in both groups. Figure 1 shows the flow chart of participants. At the end of the study, HSG had been performed in 152 of the 169 (90%) women in the

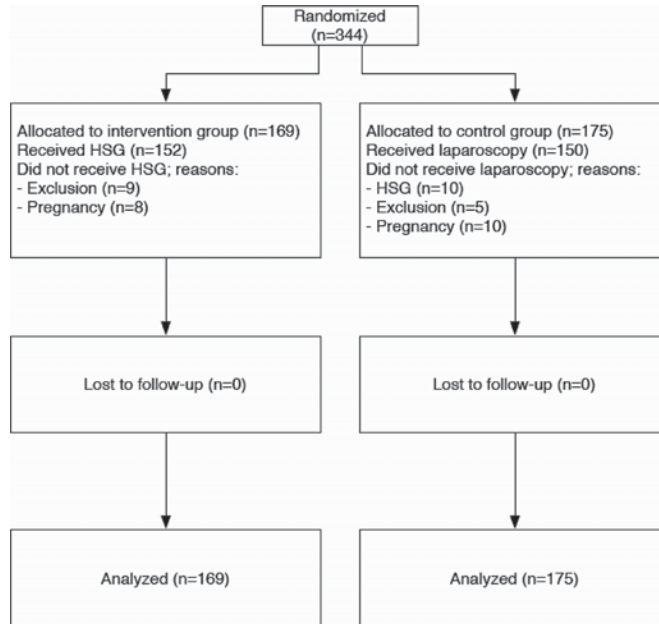


Figure 1.
Flow chart of participants.

intervention group. In the control group, 10 of the 175 (6%) women had undergone an HSG. Laparoscopies had been performed on 94 of the 169 (56%) women in the intervention group and on 150 of the 175 (86%) women in the control group. To deal with this, our analysis was based on the groups as randomised, following the intention-to-treat principle.

Table I summarizes the baseline characteristics of the women participating in the study. When comparing the women in the intervention and control groups, there were no significant differences between the groups regarding age, duration of subfertility, parity, history of pelvic inflammatory disease, intrauterine device, sexually transmitted disease or tubal surgery.

A total of 152 women in the intervention group underwent HSG, and in 58 women no additional laparoscopy was performed. In 40 of these 58 women, this was due to occurrence of pregnancy within 6 months after HSG. Hence, the pregnancy rate within 6 months after performing HSG was 26%. Of the other 18 women, no laparoscopy was performed for unknown reasons.

At HSG, 23 (15%) showed one-sided abnormalities and 23 (15%) showed two-sided abnormalities. In 10 of 152 women, HSG showed intracavity abnormalities, a reason why hysteroscopy was performed during laparoscopy.

Ninety-four laparoscopies were performed in the intervention group. At laparoscopy, 12 (13%) showed one-sided abnormalities and 15 (16%) showed two-sided abnormalities. Endometriosis was detected in 21 women (22%). The laparoscopic

Table I. Baseline characteristics of women participating in the study

Characteristics	Intervention group (<i>n</i> = 169)	Control group (<i>n</i> = 175)
Age (years) (mean ± SD)	30 ± 4.0	30 ± 4.0
Duration of subfertility (years) (mean ± SD)	2.0 ± 1.1	2.0 ± 0.8
Nulliparous	138 (82)	145 (83)
History of		
Pelvic inflammatory disease	5 (3)	5 (3)
Intrauterine device	4 (2)	5 (3)
Sexually transmitted disease	6 (4)	7 (4)
Tubal surgery	2 (1)	1 (1)
Ovulatory disorder	31 (18)	25 (14)

Values are expressed as number (percentage) unless otherwise specified.

Table II. Therapeutic reproductive surgery applied in the intervention and control groups

Surgery	Intervention group (<i>n</i> = 94)	Control group (<i>n</i> = 150)
None	65 (69)	102 (68)
Coagulation of endometriosis grade I/II	23 (25)	41 (27)
Laparoscopic adhesiolysis	5 (5)	5 (4)
Laparoscopic cystectomy	1 (1)	2 (1)

Values are expressed as number (percentage).

therapeutic interventions applied in the intervention group are summarized in Table II.

In 150 of 175 women in the control group, a laparoscopy and dye was performed. Seven of these 150 women also had a hysteroscopy performed during laparoscopy. At laparoscopy, 13 (9%) showed one-sided abnormalities and 16 (11%) showed two-sided abnormalities. Endometriosis was detected in 43 women (29%). Different laparoscopic therapeutic interventions could be applied when abnormal findings were seen (Table II). Table II shows that there were no significant differences in numbers of laparoscopic therapeutic interventions between both groups.

Table III shows the numbers of assisted reproductive treatments applied during the study in the intervention group and in the control group. There were no significant differences in numbers of applied assisted reproductive treatments between both groups.

In the intervention group, 83 pregnancies occurred in follow-up time of 2115 months, whereas in the control group 88 pregnancies occurred in 2257 months of follow-up. Therefore, the annualized pregnancy rate was 0.47 [95% confidence interval (CI)

Table III. Assisted reproductive treatment applied in the intervention and control groups

Treatment	Intervention group (<i>n</i> = 169)	Control group (<i>n</i> = 175)
None	94 (56)	101 (58)
Intrauterine insemination	60 (35)	61 (35)
IVF	15 (9)	13 (7)

Values are expressed as number (percentage).

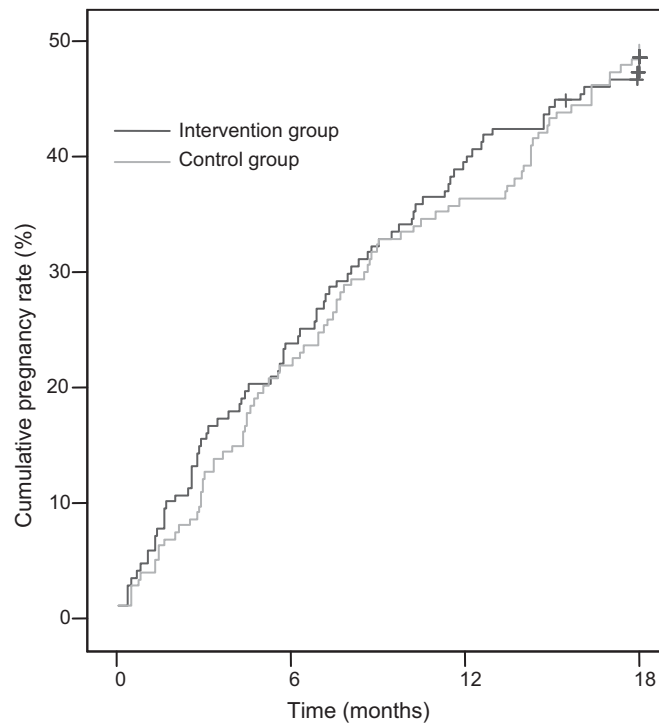


Figure 2. Cumulative pregnancy rates for the intervention group, which included hysterosalpingography (HSG), and control group, which excluded HSG.

0.37 to 0.57] in the intervention group and 0.47 (95% CI 0.37 to 0.57) in the control group. The CPR at 18 months was 49.1% (95% CI 41.6 to 56.6) in the intervention group and 50.3% (95% CI 42.8 to 57.8) in the control group, a difference of -1.2% (95% CI -11.8 to 9.5). Pregnancy rates at given times throughout the study were also not significantly different (Figure 2). No difference in primary or secondary subfertility was found. Of the 31 multiparous women in the intervention group, 15

were pregnant at the end of follow-up, compared with 17 of 30 multiparous women in the control group. Moreover, 69% of women in the intervention group who received assisted reproductive treatment were pregnant at the end of follow-up, compared with 63% in the control group. The 6% difference between study groups was not statistically significant (95% CI -8 to 21).

Directly after randomisation, it appeared that 14 couples were inappropriately randomised. The reasons were as follows: abnormal semen analysis ($n=9$), maternal age ($n=2$) and immediate withdrawal of women from participation in the trial but they agreed to be followed up for pregnancy ($n=3$). In the remaining 330 women, the CPR at 18 months was 50% (95% CI 42 to 58) in 160 women in the intervention group and 51% (95% CI 43 to 59) in 170 women in the control group. This difference of -1% was not significant (95% CI -12 to 10).

When excluding all women who did not receive the allocated intervention, 17 in the intervention group and 25 in the control group, the CPR at 18 months was 46% (95% CI 38 to 54) in the 152 women in the intervention group and 45% (95% CI 37 to 53) in the 150 women in the control group.

Discussion

Here, we report results from a randomised controlled trial assessing the usefulness of HSG as a conventional diagnostic investigation in the subfertility workup prior to laparoscopy, the gold standard for detecting tubal pathology. There was no difference in CPRs at 18 months between the intervention group (49.1%) and the control group (50.3%). We demonstrated that routine use of HSG prior to laparoscopy and dye in the fertility workup did not result in a significant effect on the incidence of pregnancy, compared with routine use of laparoscopy without HSG.

The distribution of laparoscopic therapeutic interventions and additional assisted reproductive treatments was equal between the intervention and control groups (Tables II and III). Hence, it is unlikely that these laparoscopic therapeutic interventions and additional assisted reproductive treatments affected the difference between both groups. Where early laparoscopy is not routine, the trial results also show that a protocol that begins with HSG and proceeds to laparoscopy when indicated has a similar yield to that of early routine laparoscopy.

A flaw of this study is the limited number of women who entered the trial. Our original power calculation envisaged 375 women in each group. We ended enrolment of women after 5 years because of difficulties in recruitment, thereby accepting a lower power for the study. By that time, 344 women were participating, each group containing about 200 less than the original power calculations required. Given the

absolute equality of a close to 50% pregnancy rate in both groups, a pregnancy rate of about 65% would have been required in the next 200 women in the intervention group to achieve overall significance at the 5% level. The chances of this happening were very small, given a success rate of about 50% in the first 169 women. As the binomial probability of such an occurrence is less than 1 in 100, it is extremely unlikely that continuing the study would have altered the conclusions that can be drawn from it.

The additional value of HSG compared with laparoscopy in the fertility workup is particularly the assessment of the uterine cavity. Uterine cavity malformations with a frequency of about 10–15% in subfertile women can be visualized by HSG, although the effectiveness of surgical treatment at enhancing pregnancy rates is not established⁹. The endovaginal ultrasound has been demonstrated as a reliable alternative for detecting uterine cavity pathology¹³. It can also be used in the visualization of pelvic pathology such as endometriosis or ovarian pathology. Ultrasonography in comparison with HSG is less invasive and easily performed in a short period without roentgen radiation. HSG, though, remains the only trustworthy method for examining tubal mucosal fold configuration, especially when tubal microsurgery (e.g. salpingostomy) is considered¹⁴, albeit that HSG then can be better carried out after laparoscopy. The reason that HSG is performed early in the fertility workup is based more on tradition and personal preference, rather than on the demonstrated usefulness of its components¹. In these circumstances, oil-soluble contrast medium can be used to improve pregnancy rates, although HSG with oil-soluble contrast medium is associated with an increased risk of granuloma formation and embolism; mortality in connection with embolism has been reported¹⁵.

Chlamydia antibody testing (CAT) may replace HSG as screening test that can be used for estimating the risk of tubal pathology prior to laparoscopy. Several studies have shown that CAT might be as accurate as HSG in diagnosing tubal pathology¹⁶⁻¹⁹.

In conclusion, this study shows that routine use of HSG at an early stage in the fertility workup prior to laparoscopy and dye does not influence cumulative pregnancy rate.

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References

1. Helmerhorst FM, Oei SG, Bloemenkamp KW and Keirse MJHC (1995) Consistency and variation in fertility investigations in Europe. *Hum Reprod* 10,2027–2030.
2. Mol BW, Collins JA, Van Der Veen F and Bossuyt PM (2001) Cost-effectiveness of hysterosalpingography, laparoscopy, and Chlamydia antibody testing in subfertile couples. *Fertil Steril* 75,571–580.
3. Rowe PJ, Comhaire FH, Hargreave TB and Mellows HJ (1993) *WHO Manual for the Standardized Investigation and the Diagnosis of the Infertile Couple*. Cambridge University Press, Cambridge, UK, p. 4.
4. Swart P, Mol BW, van der Veen F, van Beurden M, Redekop WK and Bossuyt PM (1995) The accuracy of hysterosalpingography in the diagnosis of tubal pathology: a meta-analysis. *Fertil Steril* 64,486–491.
5. Mol BW, Swart P, Bossuyt PM, van Beurden M and van der Veen F (1996) Reproducibility of the interpretation of hysterosalpingography in the diagnosis of tubal pathology. *Hum Reprod* 11,1204–1208.
6. Glatstein IZ, Sleeper LA, Lavy Y, Simon A, Adoni A, Palti Z, Hurwitz A and Laufer N (1997) Observer variability in the diagnosis and management of the hysterosalpingogram. *Fertil Steril* 67,233–237.
7. Johnson N, Vandekerckhove P, Watson A, Lilford R, Harada T and Hughes E (2005) Tubal flushing for subfertility. *Cochrane Database Syst Rev* 18,CD003718.
8. Glatstein IZ, Harlow BL and Hornstein MD (1998) Practice patterns among reproductive endocrinologists: further aspects of the infertility evaluation. *Fertil Steril* 70,263–269.
9. National Institute for Clinical Excellence (2004) *Fertility: Assessment and Treatment for People with Fertility Problems—Full Guideline*. RCOG Press, London.
10. Haynes B (1999) Can it work? Does it work? Is it worth it? The testing of healthcare interventions is evolving. *BMJ* 319,652–653.
11. World Health Organization (1999) *WHO Laboratory Manual for the Examination of Human Semen and Semen–Cervical Mucus Interaction*, 4th edn. Cambridge University Press, Cambridge, UK.
12. American Fertility Society (1985) Revised American Fertility Society classification of endometriosis: 1985. *Fertil Steril* 43,351–352.
13. Braun P, Grau FV, Pons RM and Enguix DP (2005) Is hysterosalpingography able to diagnose all uterine malformations correctly? A retrospective study. *Eur J Radiol* 53,274–279.
14. te Velde ER, Boer-Meisel ME, Meisner J, Schoemaker J and Habbema JD (1989) The significance of preoperative hysterosalpingography and laparoscopy for predicting the pregnancy outcome in patients with a bilateral hydrosalpinx. *Eur J Obstet Gynecol Reprod Biol* 31,33–45.
15. Lindequist S, Justesen P, Larsen C and Rasmussen F (1991) Diagnostic quality and complications of hysterosalpingography: oil-versus water-soluble contrast media – a randomised prospective study. *Radiology* 179,69–74.

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16. Dabekausen YA, Evers JL, Land JA and Stals FS (1994) Chlamydia trachomatis antibody testing is more accurate than hysterosalpingography in predicting tubal factor infertility. *Fertil Steril* 61,833–837.
17. Mol BW, Dijkman B, Wertheim P, Lijmer J, van der Veen F and Bossuyt PM (1997) The accuracy of serum chlamydial antibodies in the diagnosis of tubal pathology: a meta-analysis. *Fertil Steril* 67,1031–1037.
18. Land JA, Evers JL and Goossens VJ (1998) How to use Chlamydia antibody testing in subfertility patients. *Hum Reprod* 13,1094–1098.
19. Veenemans LM and van der Linden PJ (2002) The value of Chlamydia trachomatis antibody testing in predicting tubal factor infertility. *Hum Reprod* 17,695–698.