The capacity of hysterosalpingography and laparoscopy to predict natural conception

Human Reproduction, Vol.26, No.1 pp. 134–142, 2011

Present by R5郭恬妮

Introduction

- The prevalence of **tubal pathology** in subfertile populations varies between 11 and 30%
- **Chlamydia Trachomatis** is a major cause for tubal pathology
  - often asymptomatic
  - untreated can progress to PID, infertility, ectopic pregnancy and chronic pelvic pain.

- diagnostic tests to assess tubal patency :
  - hysterosalpingography (HSG)
  - Diagnostic laparoscopy (DLS): adhesions and the presence of endometriosis
  - Chlamydia Antibody Titer test (CAT): screening tests for the presence of tubal pathology
- The findings at these diagnostic tests should translate into a **prognosis** of natural pregnancy chances → to counsel patients on whether their pregnancy chances can be improved by surgery, IUI or IVF.

- The relative merits of HSG and laparoscopy for assessing tubal status have been discussed for many years
  - reflecting a **lack of agreement** among fertility subspecialists on which diagnostic tests have to be performed and their prognostic utility

- (Mol et al., 1997): **unilateral** tubal pathology at HSG **do not have reduced** chances of a treatment-independent pregnancy, in contrast to those with bilateral tubal pathology
- (Mol et al., 1999a): DLS and dye, a moderate reduction of natural pregnancy chances in case of unilateral tubal pathology and a **severe reduction in case of bilateral tubal pathology**

- (Mol et al., 1999b): **laparoscopy** was found to be a **better predictor** of future fertility than HSG
- The conclusion that laparoscopy is a better predictor of infertility than HSG was **weakened** by the fact that the **median interval** to laparoscopy after a normal HSG was 10 months, compared with 4.5 months for women in whom the HSG showed two-sided tubal abnormalities

- The purpose of the study presented here was to evaluate the impact of **unilateral and bilateral tubal pathology** at HSG and laparoscopy on treatment-independent pregnancy rates in a **large prospective cohort** of subfertile ovulatory women from mixed secondary and tertiary hospital populations

Materials and Methods

- January 2002 ~ February 2004,
- the fertility clinic of 38 centers in The Netherlands
- a prospective cohort study.

(Patients)

- limited to couples with a regular ovulatory cycle,
  - a cycle length between 23 and 35 days, with a within cycle variation of less than 8 days.
- None of the patients analysed used Clomiphene Citrate.
- Ovulation was detected by a basal body temperature chart, midluteal serum progesterone or by ultrasonographic monitoring of the cycle.

- Couples with a history of reversal of sterilization, tubal surgery, IVF or previous tubal patency testing were **excluded**

- Duration of subfertility: the period between the time the couple had started trying to conceive and the time of tubal testing.
- Male partners: at least one semen analysis was performed.
- The total motile sperm count (TMC) was calculated by multiplying semen volume, sperm concentration and percentage of motile spermatozoa.
- severe impairment of semen quality requiring IVF–ICSI (defined as a total motile count ,1×10^6) were also **excluded** from the present analysis.

(Tubal testing and follow-up)

- Three different protocols could be distinguished.
  - Routine HSG or DLS
  - CAT (+) → HSG or DLS
  - CAT (-) → HSG, CAT (+) → DLS
- HSG : in the follicular phase, spasmolytic drugs
- DLS: performed with a double puncture technique, methylene blue was injected at room temperature through a Foley catheter in the uterine cavity.

- HSG
  - no tubal occlusion
  - one sided tubal occlusion
  - two-sided tubal occlusion
  - impaired flow of contrast if contrast was not shown beyond the isthmic portion of the tube.

- Laparoscopy
  - Normal
  - one-sided tubal occlusion
  - two-sided tubal occlusion
  - proximal- or distal tubal occlusion.

- Follow-up started after tubal testing and ended 12 months thereafter.
- A model was used to calculate the chances of natural conception (Hunault et al., 2004) → **treatment was generally advised to those with a probability below 30%.**
- For all women lost to follow-up, the general practitioner was sent a questionnaire and asked about the fertility status of the couple.

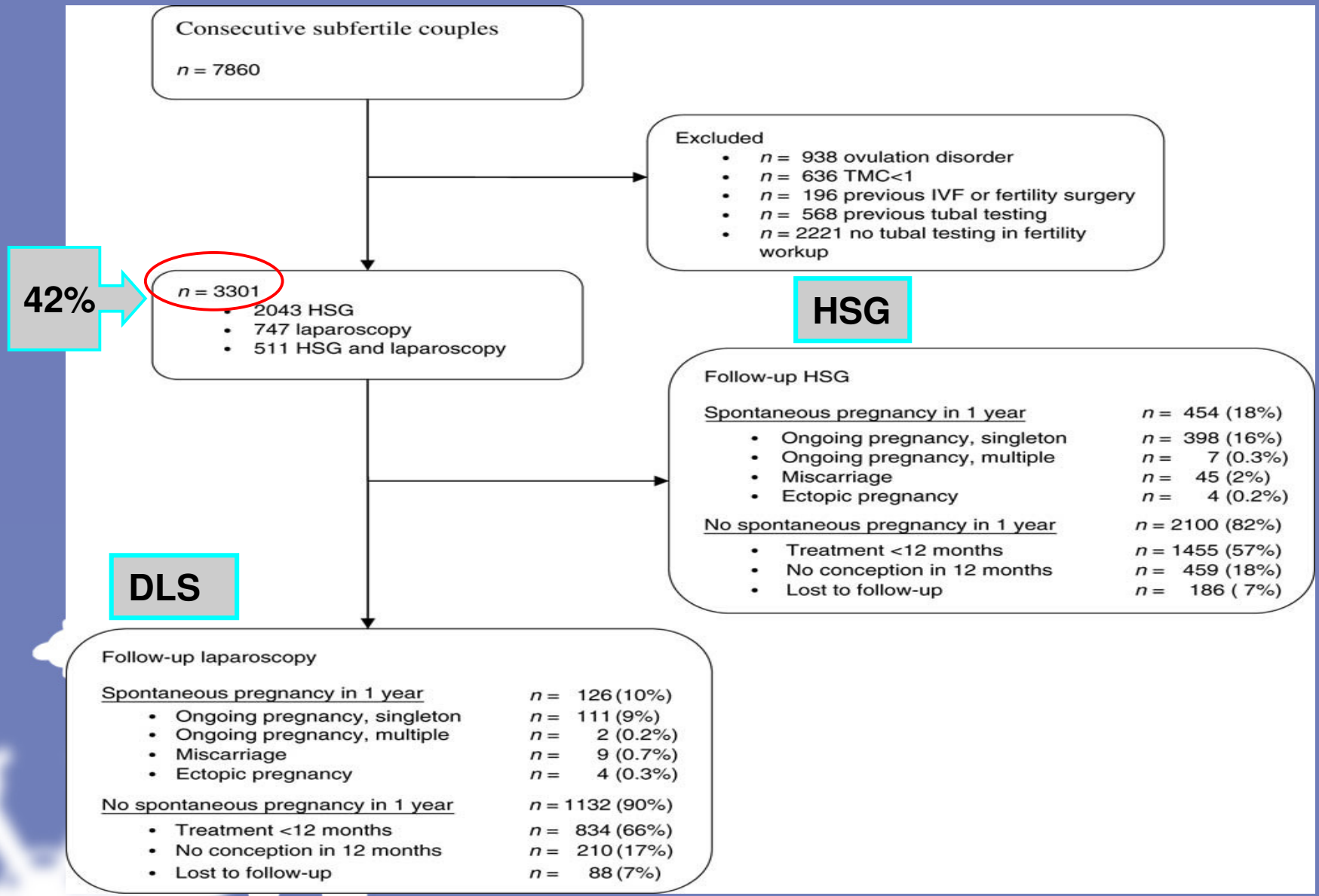
(Analysis)

- The primary end-point: a spontaneous ongoing pregnancy at 12 weeks of gestational age, confirmed by ultrasonography.
- Time to pregnancy was censored at the moment treatment (IUI, IVF or tubal surgery) started within 12 months after counseling, or at the last date of contact during follow-up, when the couple had no ongoing pregnancy.

- proximal occlusions (HSG or DLS) VS. distal occlusion /hydrosalpinx → had a different prognostic effect on treatment-independent pregnancy?

- classified the findings at HSG and laparoscopy into **three groups** (without tubal pathology, with one-sided, with two-sided tubal pathology) and constructed Kaplan–Meier curves for each
- adjusted fecundity rate ratios **(FRRs)** and 95% confidence intervals (CIs) were calculated through multivariable Cox regression modelling.

Results


Consecutive subfertile couples
n = 7860
Excluded
n = 938 ovulation disorder
n = 636 TMC<1
n = 196 previous IVF or fertility surgery
n = 568 previous tubal testing
n = 2221 no tubal testing in fertility workup
42%
n = 3301
2043 HSG
747 laparoscopy
511 HSG and laparoscopy
HSG
Follow-up HSG
Spontaneous pregnancy in 1 year n = 454 (18%)
Ongoing pregnancy, singleton n = 398 (16%)
Ongoing pregnancy, multiple n = 7 (0.3%)
Miscarriage n = 45 (2%)
Ectopic pregnancy n = 4 (0.2%)
No spontaneous pregnancy in 1 year n = 2100 (82%)
Treatment <12 months n = 1455 (57%)
No conception in 12 months n = 459 (18%)
Lost to follow-up n = 186 (7%)
DLS
Follow-up laparoscopy
Spontaneous pregnancy in 1 year n = 126 (10%)
Ongoing pregnancy, singleton n = 111 (9%)
Ongoing pregnancy, multiple n = 2 (0.2%)
Miscarriage n = 9 (0.7%)
Ectopic pregnancy n = 4 (0.3%)
No spontaneous pregnancy in 1 year n = 1132 (90%)
Treatment <12 months n = 834 (66%)
No conception in 12 months n = 210 (17%)
Lost to follow-up n = 88 (7%)

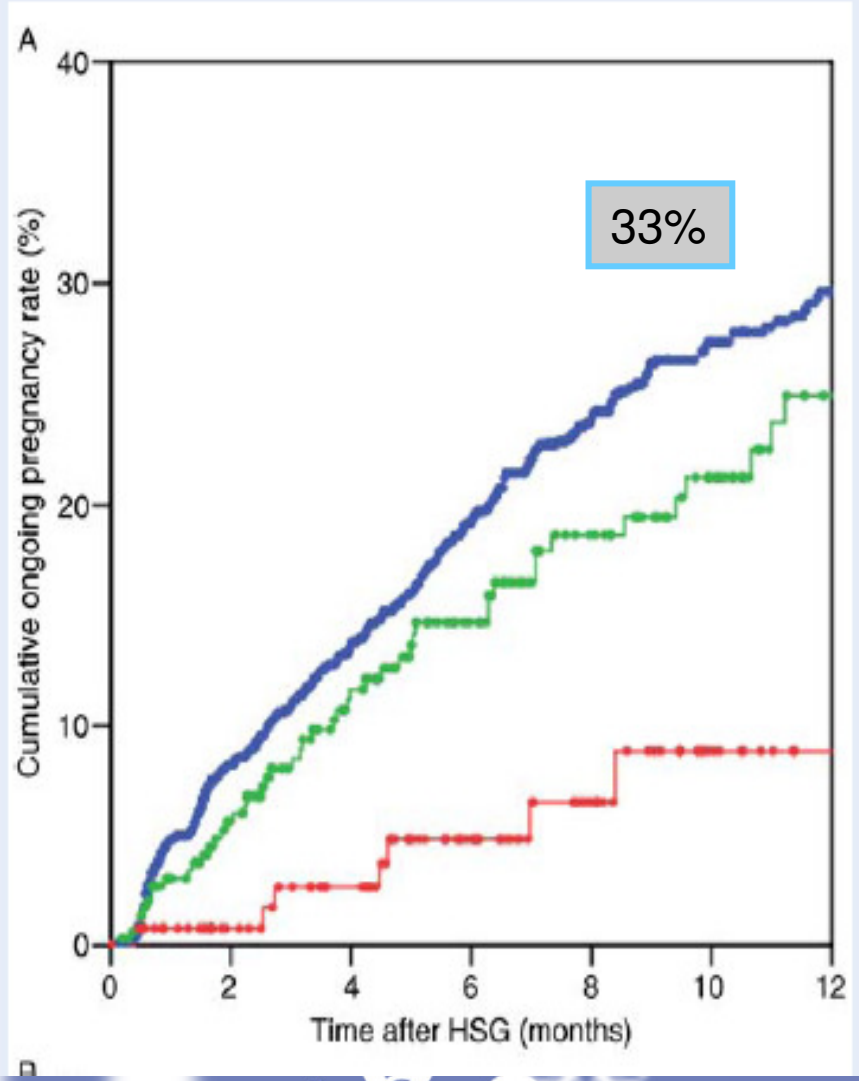
- The baseline characteristics of the 3301 couples are shown in Table I.

Table I Baseline characteristics of 3301 couples at time of procedure.

	HSG (n = 2554)		Diagnostic laparoscopy (n = 1258)	
	Mean/median[a]	5th–95th percentiles	Mean/median[a]	5th–95th percentiles
Female age (years)	32.8	25.6–39.5	32.7	25.9–39.0
Male age (years)	35.4	28.0–45.0	35.1	27.6–44.8
Duration of subfertility (years)	1.8[a]	1.0–4.3	2.2[a]	1.2–5.0
Semen analysis, TMC (10^6)	57.6[a]	4.0–308	59.5[a]	4.8–274
Subfertility, primary (n) (%)	1568	61.4	806	64.1
Time to tubal test (months)[b]	3.0[a]	1.0–11.4	5.9[a]	1.4–16.8

TMC, total motile sperm count.
[a]Value is the median.
[b]Time from first consultation to tubal testing.

- **HSG contrast medium:**
  - 1626 (64%) : water-based contrast medium
  - 359 (14%) : oil-based contrast medium
  - 569 (22%) : unknown which medium


A
Cumulative ongoing pregnancy rate (%)
40
30
20
10
0
0
2
4
6
8
10
12
Time after HSG (months)
33%

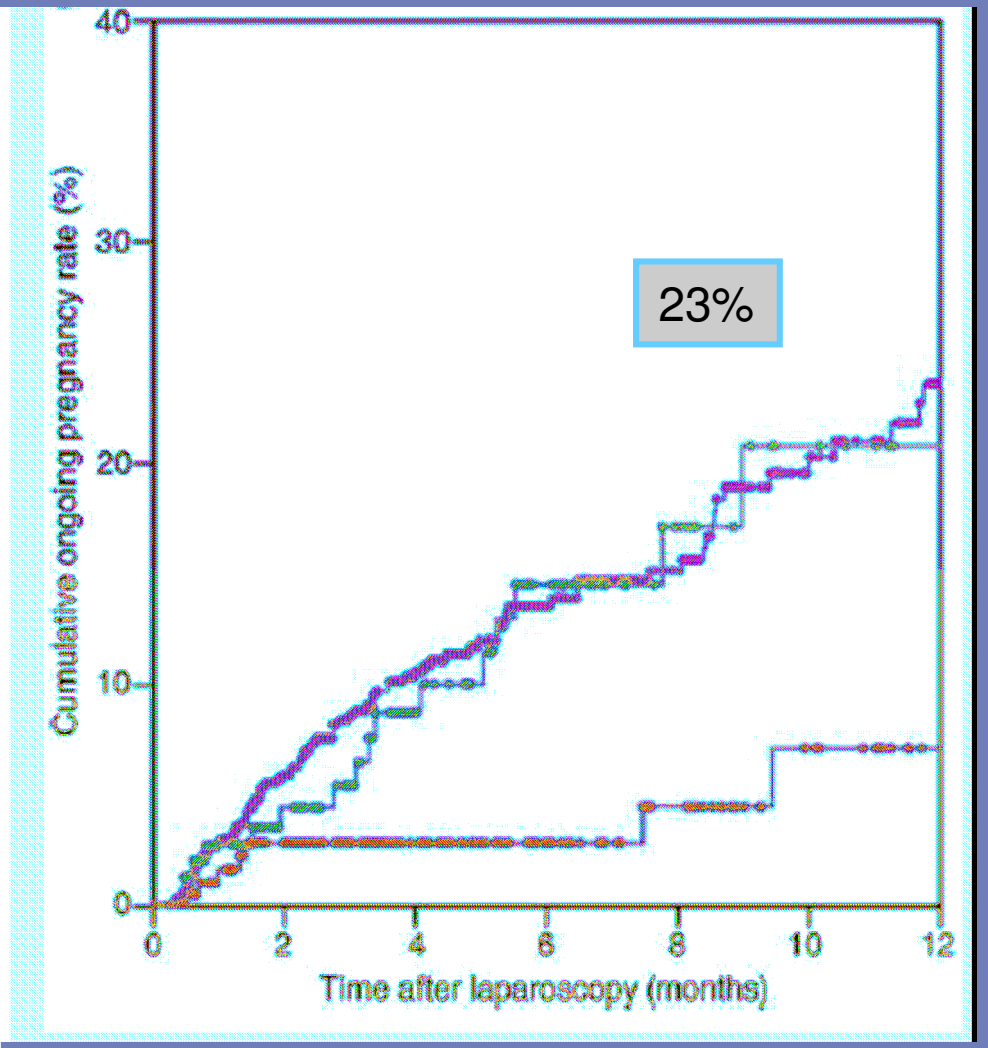

Cumulative ongoing pregnancy rate (%)
40
30
20
10
0
0
2
4
6
8
10
12
Time after laparoscopy (months)
23%

Table II Fertility outcome after HSG.

Findings at HSG	Frequency (%)	Number of ongoing pregnancies	FRR
Bilateral normal	2097 (82%)	350	1
Unilateral impaired flow of contrast[a]	84 (3%)	10	0.68 (0.36–1.3)
Unilateral occlusion	238 (9%)	38	0.89 (0.63–1.3)
Unilateral occlusion, contra-lateral impaired flow of contrast[a]	25 (1%)	2	0.36 (0.09–1.5)
Bilateral impaired flow of contrast[a]	51 (2%)	2	0.19 (0.05–0.80)
Bilateral occlusion	59 (2%)	3	0.26 (0.08–0.80)

FFR, fecundity rate ratio.

[a]Impaired flow meaning no flow of contrast beyond the isthmic portion of the tube.

Table III Fertility outcome after laparoscopy.

Findings at laparoscopy	Frequency (%)	Number of ongoing pregnancies	FRR
Bilateral normal	876 (70%)	90	1
Unilateral proximal occlusion	126 (10%)	12	0.58 (0.44–1.7)
Unilateral hydrosalpinx/ distal occlusion	25 (2%)	3	1.40 (0.43–4.5)
Unilateral proximal occlusion, contra-lateral hydrosalpinx/ distal occlusion	21 (2%)	3	1.83 (0.56–6.0)
Bilateral proximal occlusion	114 (9%)	3	0.19 (0.06–0.62)
Bilateral hydrosalpinx/ distal occlusion	23 (2%)	1	0.34 (0.05–2.5)
Unilateral proximal occlusion/ hydrosalpinx/ distal occlusion, contra-lateral adhesions	32 (3%)	1	0.58 (0.08–4.4)
Bilateral patent, unilateral adhesions	16 (1%)	0	0 (0–NE)
Bilateral patent, bilateral adhesions	25 (2%)	0	0 (0–NE)

FFR, fecundity rate ratio; NE, not estimable.

Table IV Tubal status detected at HSG when compared with the tubal status detected at laparoscopy.

Laparoscopy	Two-sided occlusion	One-sided occlusion	No occlusion	Total
HSG				
Two-sided occlusion	31	15	36	82
One-sided occlusion	12	47	94	153
No occlusion	13	17	246	276
Total	56	79	376	511

- HSG : one-sided occlusion → DLS revealed no occlusion in 60%,
- HSG : two-sided occlusion → DLS revealed no occlusion in 44%.
- DLS : one-sided occlusion → HSG revealed no occlusion in 22%
- DLS : two-sided occlusion → HSG showed no occlusion in 23%

Table II Fertility outcome after HSG.

Findings at HSG	Frequency (%)	Number of ongoing pregnancies	FRR
Bilateral normal	2097 (82%)	350	1
Unilateral impaired flow of contrast[a]	84 (3%)	10	0.68 (0.36–1.3)
Unilateral occlusion	238 (9%)	38	0.89 (0.63–1.3)
Unilateral occlusion, contra-lateral impaired flow of contrast[a]	25 (1%)	2	0.36 (0.09–1.5)
Bilateral impaired flow of contrast[a]	51 (2%)	2	0.19 (0.05–0.80)
Bilateral occlusion	59 (2%)	3	0.26 (0.08–0.80)

FFR, fecundity rate ratio.
[a]Impaired flow meaning no flow of contrast beyond the isthmic portion of the tube.

no significant difference in FRR

no significant difference in FRR

impaired flow of contrast was considered **as complete occlusion**, because this did not prove tubal patency

- DLS: we found **no differences** in prognostic outcome for **proximal** occlusions identified at laparoscopy compared with **distal** occlusion/hydrosalpinx or hydrosalpinges.
- therefore classified tubal pathology into three main categories
  - no tubal pathology
  - unilateral tubal pathology
  - bilateral tubal pathology

- Using this classification, the results of the uni- and multivariable Cox regression analysis are shown in Table V.

Table V Results of the uni- and multivariable Cox regression analysis.

	Univariable analysis				Multivariable analysis		
	HSG				HSG		
	n (%)	FRR	95% CI	*P*-value	FRR	95% CI	*P*-value
No tubal pathology	2097 (82)	1	–	–	1	–	–
Unilateral tubal pathology	322 (13)	0.83	0.61–1.13	0.25	0.81	0.59–1.11	0.19
Bilateral tubal Pathology	135 (5)	0.25	0.12–0.54	<0.001	0.28	0.13–0.59	0.001
Duration of subfertility (years)		0.89	0.80–0.99	0.02	0.90	0.90–1.00	0.05
Female age (years)[a]		0.95	0.93–0.98	<0.001	0.95	0.93–0.97	<0.001
Secondary subfertility		1.41	1.15–1.72	<0.001	1.53	1.24–1.88	<0.001
	Laparoscopy				Laparoscopy		
No tubal pathology	876 (70)	1	–	–	1	–	–
Unilateral tubal pathology	167 (13)	0.90	0.51–1.61	0.73	0.85	0.47–1.52	0.58
Bilateral tubal pathology	215 (17)	0.26	0.12–0.57	0.001	0.24	0.11–0.54	0.001
Duration of subfertility (years)		0.80	0.66–0.97	0.03	0.78	0.64–0.95	0.02
Female age (years)[a]		1.02	0.97–1.08	0.37	1.01	0.96–1.07	0.59
Secondary subfertility		1.66	1.13–2.46	0.01	1.78	1.19–2.66	0.005

[a]Per year older than 32.

Discussion

- patients with **two-sided tubal pathology had significantly worse fertility prospects (HSG or DLS)**
- Because proximal tubal pathology (occlusion as well as impaired flow) is more likely to be due to artefacts (tubal spasm or ‘steal effect’)
  - analysed whether there was a difference in FRR between proximal and distal tubal pathology for the detection of natural pregnancy → **unable to detect such a difference.**

- The fertility rate ratios for two-sided tubal pathology are in accordance with results from our previous small retrospective Dutch cohort study
- However, in the present study we found a **lower FRR** in case of bilateral tubal pathology at compared with the Canadian cohort.
- This could be due to the **lower prevalence of bilateral tubal pathology at HSG** (5% compared with 24% in the Canadian study), whereas the prevalence of unilateral tubal pathology at HSG was comparable (13 versus 14%).

- Although the present study showed a similarly low FRR for bilateral tubal pathology at laparoscopy, the prognostic value of unilateral tubal pathology identified at laparoscopy (FRR 0.85) differed markedly from that in our previous two studies, which showed a FRR of 0.65 and 0.51, respectively (Mol et al., 1999a,b)
- The **longer delay between HSG and laparoscopy** in the Canadian study resulted in a higher proportion of patients with poor prognosis, which could have **negatively influenced the FRR**.

- **Selection bias** may have influenced the outcome of these previous studies, overestimating the detection rate of tubal pathology at laparoscopy in comparison to patients who only undergo HSG or a laparoscopy without a previous HSG.

- Of notice is the **lack of agreement between HSG and laparoscopy** in those patients who underwent both imaging tests.
- At laparoscopy bilateral tubal occlusion was diagnosed in 5% of the patients where previously HSG showed no occlusion.
- However, in 60% of the patients where HSG showed one-sided occlusion, and in 44% where HSG showed two-sided occlusion, **laparoscopy did not show any tubal occlusion.**

- Our finding that the presence of tubal pathology at HSG and laparoscopy has a **similar FRR is of interest**.
- Unilateral tubal pathology reduced the probability of a natural conception by 20% and bilateral tubal pathology reduced pregnancy chances by 75%, whether diagnosed at HSG or at laparoscopy.
- our findings suggest that the prognostic capacity of HSG and that of laparoscopy do not differ much.
- In contrast with previous studies: laparoscopy is a better predictor of treatment-independent pregnancy (Mol et al., 1999b).

- The results of our study are in support of the recommendation of the fertility guidelines of the National Institute for Clinical Excellence to use **HSG to test for tubal pathology** in women who are not known to have co-morbidities (NICE, 2004).
- A normal HSG reduces the probability that tubal pathology plays a role in future fertility chances
- oil-soluble contrast medium is used for tubal flushing → a positive effect on pregnancy rates (Luttjeboer et al., 2007).

•A randomized trial did not show an improved pregnancy outcome if DLS was routinely performed after normal HSG and before treatment with IUI (Tanahatoe et al., 2005).

- An important limitation of our study: not every patient HSG as well as laparoscopy was performed.
- Patients at low risk for tubal pathology → HSG
- with co-morbidities and considered to be at risk for tubal pathology → laparoscopy.
- the interpretation of this study is hampered by **selection bias** caused by a **difference in timing** of the imaging tests.
- Correction for these requires a study in which women are offered CAT, HSG and laparoscopy as part of their subfertility work-up.

- The **most important prognostic factors** are age of the woman, duration of subfertility and whether or not the couple have ever had a pregnancy before consultation.
- If the chances for natural conception are **above 30%,** expectant management is generally recommended.
- **Below 30%,** treatment is advised

Thanks for your listening!