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The effectiveness of reproductive surgery in the treatment of female infertility: facts, views and vision

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Abstract

Background: The role of reproductive surgery is declining due to the widespread availability of assisted reproductive technology, but an evidence-based fundament for this decline is lacking. We therefore performed a systematic review of the literature.
Methods: We searched MEDLINE, EMBASE and the Cochrane Library for randomised trials evaluating laparoscopic or hysteroscopic interventions in subfertile women, studying pregnancy or live birth rates. We present an overview of the results and quality of the detected studies.
Results: The methodological quality of the 63 detected studies was mediocre. The laparoscopic treatment of minimal/ mild endometriosis might increase the pregnancy rate but the two major studies report conflicting results. Excision of the endometriotic cyst wall increases the spontaneous conception rate (RR 2.8, 95% CI 1.4-5.5). Laparoscopic ovarian drilling results at least in equal pregnancy rates as gonadotropin treatment (RR 1.0, 95% CI 0.83-1.2) but decreases the multiple pregnancy rate (RR 0.16, 95% CI 0.04-0.58). Laparoscopic tubal surgery for hydrosalpinx prior to IVF increases the pregnancy rate (RR 1.9, 95% CI 1.4-2.7). Removal of polyps prior to IUI increases the pregnancy rate (RR 2.2, 95% CI 1.6-3.1). Myomectomy for submucosal fibroids results in higher pregnancy rates (RR 2.2, 95% CI 1.6-2.9). The removal of intramural/ subserosal fibroids shows a beneficial trend, albeit not statistically significant (RR 1.2, 95% CI 0.75-1.9). Hysteroscopy in patients with recurrent IVF failure increases the pregnancy rates even in the absence of pathology (RR 1.6, 95% CI 1.3-1.9).
Conclusions: Although the limited evidence indicates a positive role for some surgical reproductive interventions, we should be very cautious in providing guidelines for clinical practice in reproductive surgery since more research is needed.

Key words: Laparoscopy, hysteroscopy, reproductive surgery, effectiveness, pregnancy rate, live birth rate.

Abbreviations

ART: assisted reproductive technology
CDSR: Cochrane Database of Systematic Reviews
CENTRAL: Cochrane Central Register of Controlled Trials
CI: confidence interval
DARE: Database of Abstracts of Reviews of Effects
HTA: Health Technology Assessment Database
IVF: in vitro fertilisation
IUI: intrauterine insemination
MH-F: Mantel-Haenszel, fixed effects model

mRCT: metaRegister of Controlled Trials
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR: risk ratio
RCT: randomised controlled trial

Introduction

Worldwide ART has replaced reproductive surgery for tubal factor infertility, limiting its role as first-line treatment (Bosteels *et al*., 2007). It is not clear whether this change in clinical practice is due to the higher cost-effectiveness of ART compared to reproductive surgery or caused by other factors such as a lack of surgical expertise, patient's desires to achieve results rapidly or the concern to protect patients from procedure-related complications. In moderate and severe endometriosis radical laparoscopic surgery is often delayed until several ART cycles have failed (Littman *et al*., 2005). Its surgical treatment necessitates a high level of expertise (Kennedy *et al*., 2005).

As a consequence, laparoscopy is increasingly bypassed in the diagnostic work-up of infertility (Fatum *et al*., 2002). Some authors report that the exploration by diagnostic laparoscopy in an infertile population either did not reveal any pathology or only minimal or mild endometriosis in 40-70% of cases (Forman *et al*., 1993). From a prognostic point of view, the test 'diagnostic laparoscopy' fails to be an ideal predictor for infertility (Collins *et al*., 1995; Mol *et al*., 1999). However, the shift away from reproductive laparoscopic surgery favoring ART is not supported by solid evidence.

The position of hysteroscopy in current fertility practice is similarly unclear. Used on an outpatient basis with small calibre hysteroscopes, its technical feasibility and high patient compliance in general gynaecological practice are demonstrated by numerous RCTs (Kremer *et al*., 2000; Soriano *et al*., 2000; Unfried *et al*., 2001; De Angelis *et al*., 2003; Guida *et al*., 2003; Litta *et al*., 2003; Pellicano *et al*., 2003; Marsh *et al*., 2004; Shankar *et al*., 2004; Campo *et al*., 2005; Sharma *et al*., 2005; Garbin *et al*., 2006; Guida *et al*., 2006; Sagiv *et al*., 2006; De Placido *et al*., 2007; Kabli and Tulandi, 2008). However, neither the ease of use nor the low costs should by themselves justify the widespread application of a surgical procedure. Indeed, the number of RCTs demonstrating the effectiveness of hysteroscopy in treating female infertility is limited (Bosteels *et al*., 2010).

Our aim is to study the effectiveness of reproductive surgery in treating female subfertility, by giving an overview of all published randomised trials measuring pregnancy or live birth rates.

Methods

Literature search methodology

For the current systematic review no written protocol was registered.

We aimed to identify randomised clinical trials (RCTs) or systematic reviews of such trials on reproductive surgery in infertile women with pregnancy or live birth rate as the primary outcome. To do so, we searched the Cochrane Library (1970 to June 1st 2010) for relevant trials in the CDSR, DARE, CENTRAL or HTA databases. We also searched the National Library of Medicine's MEDLINE using a combination of textwords and MeSH terms for "laparoscopy", "hysteroscopy" ,"infertility", "pregnancy rate" and "live birth rate" (1966-June 1st 2010) and Excerpta Medica EMBASE (1974 to June 1st 2010). The search strategies in the appropriate thesaurus for each database were developed by a librarian at the University Biomedical Library Campus Gasthuisberg, Katholieke Universiteit Leuven and are described in the addendum. The search strategy included the filters from the Cochrane Collaboration website (Haynes *et al*., 1994; Dickersin *et al*., 1994), developed for the detection of randomised controlled trials with reported sensitivities of 95 and 99% (Shojania and Bero, 2001; Robinson and Dickersin, 2002; Glanville *et al*., 2006). We also searched the Current Controlled Trials (metaRegister) at http://www.controlled-trials.com/ for registered relevant trials. The last up-dated search was done on June 1st 2010.

Language restrictions were not applied, and the searches were done simultaneously and independently by two authors (JB and TD).The reference lists of all known primary articles were examined independently by the same two authors (JB and TD). We also used the 'related articles' function of PubMed, as well as the reference lists of detected articles to look for relevant studies.

Study selection

We included RCTs reporting on pregnancy or live birth rates, but excluded non-randomised trials, studies not reporting on reproductive outcome or done in a population with gynaecological problems other than infertility as well as trials on diagnostic accuracy, technical feasibility, patient compliance and cost-effectiveness. Study selection was done by two authors independently based on reviewing the full text article (JB and TD). The κ-value of inter-reviewer agreement on the final inclusion of the relevant RCTs was 0.82. In case of disagreement, the opinion of a third author was asked (SW) until consensus was reached.

Data extraction and critical appraisal

For data extraction and critical appraisal of the methodology, the PRISMA Statement was followed (Moher *et al*., 2009). The characteristics of the different study populations, the control and study intervention as well as other relevant study characteristics were extracted from the full text articles. The corresponding authors were contacted in case of unclear study methodology or to obtain missing data. Two authors (JB and TD) independently extracted relevant study data. The critical appraisal based on the internal validity, the magnitude of the treatment effect and the general applicability was done by using standardised work sheets for quality assessment of randomised controlled trials from the website of the Dutch Cochrane Centre (http://dcc.cochrane.org/sites/dcc.cochrane.org/files/uploads/RCT.pdf). The internal validity was based on the description of the randomisation sequence generation, allocation concealment, blinding of physicians/patients and outcome assessors, the assessment of incomplete data and whether selective reporting or other forms of bias were likely or not.

Data synthesis and statistical analysis

Statistical analysis was done using the latest updated software provided by the Cochrane Collaboration (Rev Man 5 version 5.0.24, April 16th 2010). Dichotomous data were extracted in 2x2 tables. After consulting with a biostatistician we decided to express the results of individual trials and of the meta-analyses as risk ratios (RR) with 95% confidence limits (95% CI) using a fixed effects model (Mantel-Haenszel method). A sensitivity analysis comparing the use of odds ratios (OR) to risk ratios did not yield differences in the direction of the observed treatment effect, but in general the estimations of the treatment effect were more conservative with the use of RR. To facilitate clinical interpretation, results were re-expressed as numbers needed-to-treat (NNT) with 95% confidence intervals (CI). The NNTs were calculated from the RR in the meta-analyses using appropriate mathemical formulae available from the Cochrane Handbook for Systematic Reviews of Interventions. Statistical heterogeneity was assessed with the Chi-square test and the I^2 test.

We estimated the risk of bias at the study level and across studies using the risk of bias tool provided by the Cochrane Collaboration based on the randomisation sequence generation, concealment of allocation, blinding of patients/ physicians and outcome assessors, selective reporting of outcomes, whether or not incomplete data were addressed and the probability of other forms of bias.

We assessed the quality of the included trials by providing levels of evidence using the software provided by the Cochrane Collaboration (GRADE profiler version 3.2.2.20090501). An alternative grading system was used by allocating a 'level E' for 'evidence of an effect' when there was evidence of a significant difference between the interventions studied for the pregnancy or live birth rate or a'level G' for 'gap in evidence' when there was insufficient evidence of effectiveness or harm. A label 'E&G' was allocated when there was some evidence of a significant effect along with some gaps for the primary outcomes.

Results

The process of literature search and selection is described in Figure 1. We retrieved 106 possibly relevant articles in MEDLINE, 334 possibly relevant articles in EMBASE and 170 relevant reviews, clinical trials and abstracts of reviews from the Cochrane Library. We identified 37 possibly relevant trials in the Current Controlled Trials Register. After screening of the abstracts or titles of non duplicate 592 possibly relevant publications, 97 full text articles were assessed for eligibility. Finally, we included 63 randomised trials on reproductive surgical techniques and pregnancy outcome. An overview of these trials and a summary of their findings grouped according to the specific pathology or clinical setting are presented in table 1.

How effective is reproductive surgery by laparoscopy in subfertile women compared to alternative treatments?

Minimal and mild endometriosis

There are two RCTs on the effectiveness of laparoscopic surgery for minimal or mild endometriosis in women with otherwise unexplained subfertility (Marcoux *et al*., 1997; Gruppo Italiano, 1999). The larger Canadian trial (n = 341) showed a treatment effect of the laparoscopic excision/ablation of minimal or mild endometriosis for the ongoing pregnancy rate at 9 months compared to diagnostic laparoscopy (RR 1.7, 95% CI 1.1-2.5). For every eight women with unexplained subfertility and associated minimal or mild endometriosis treated by laparoscopic excision or ablation, it is expected that one additional person will have an ongoing pregnancy (NNT = 8, 95% CI 5 to 32). The beneficial treatment effect was still present in patients without endometriotic adhesions (n = 284) as demonstrated by a subgroup analysis (cumulative incidence ratio 1.6, 95% CI 1.2-2.5).

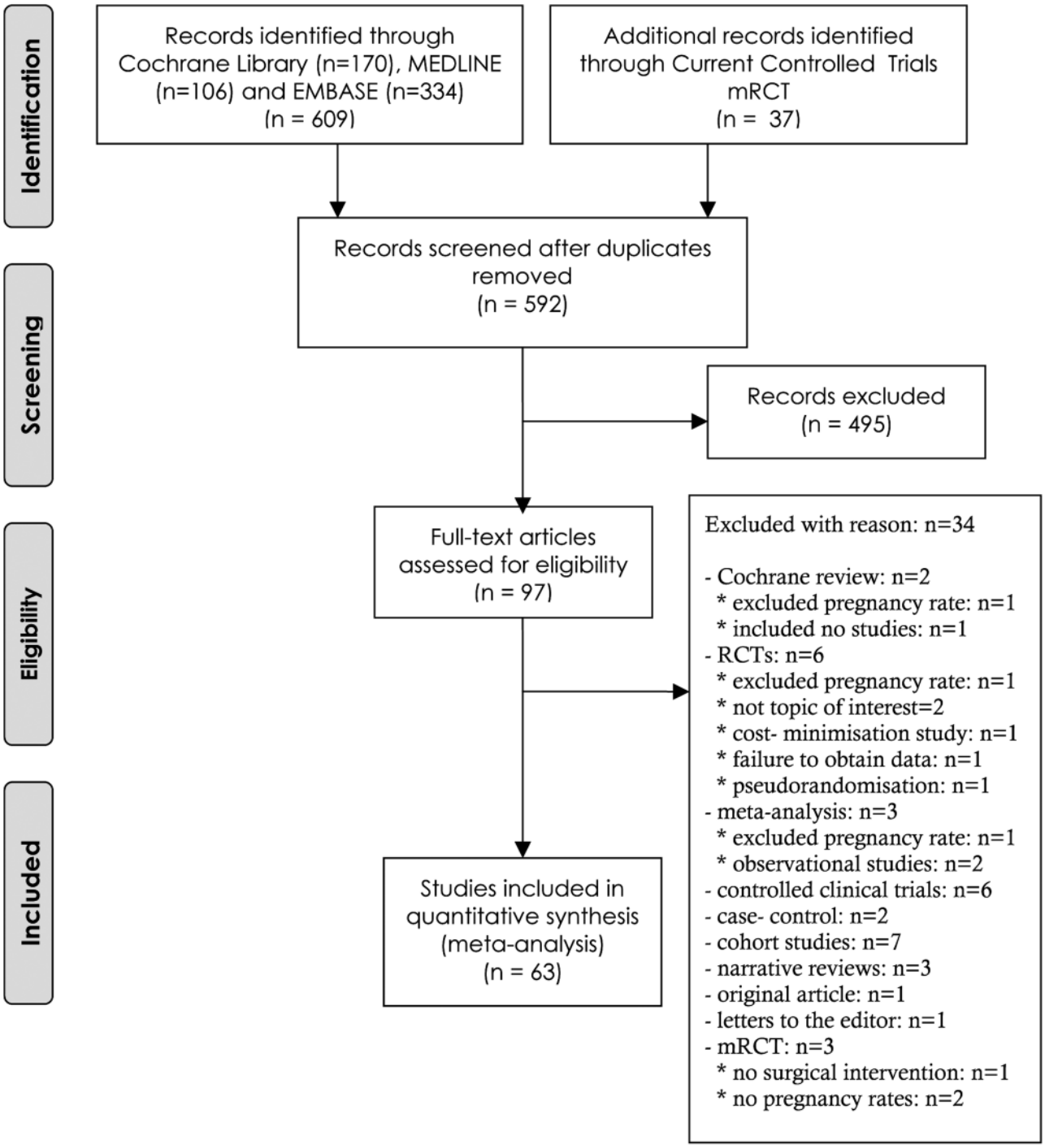

Fig. 1. — PRISMA 2009 Flow Diagram: Systematic Review of benefit after reproductive surgery

The smaller Italian study (n = 101) failed to demonstrate a statistically significant difference, but more important did not even show a trend to a higher number of pregnancies (RR 0.81, 95% CI 0.41-1.6) or an increase in the live-birth rate (OR 0.88, 95% CI 0.40-1.9). Despite the conflicting results, the data of both trials were pooled in a Cochrane review (Jacobson *et al*., 2010). The laparoscopic treatment of minimal or mild endometriosis shows a trend in increasing the ongoing pregnancy or live birth rate which is marginally significant (RR 1.5, 95% CI 1.0-2.1). By doing a re-analysis of the primary data of the Italian trial, we found that data from 5 women in the intervention group and 3 women in the control group were missing. This discrepancy could not be clarified after contacting the authors. A post hoc sensitivity analysis aimed at examining whether the missing data could have had an impact on the results, did not demonstrate statistically significant differences between the intervention and control groups

Table 1. — Summary of findings of included studies.

reference	population	intervention	comparison	outcome	RR (95%CI)
Laparoscopic treatment of minimal and mild endometriosis in women with otherwise unexplained infertility					
Gruppo Italiano 1999	101 women aged 20-39 y with unexplained infertility > 12m and r-AFS I endometriosis	resection/ ablation (n = 54)	diagnostic laparoscopy only (n = 47)	TDR PR (unclear)	0.88 (0.40, 1.9) 0.81 (0.41, 1.6)
Marcoux 1997	341women < 37 y with unexplained infertility > 2 y and r-AFS I endometriosis	excision/ ablation and adhesiolysis (n = 172)	diagnostic laparoscopy only (n = 169)	CPR 9 m FR	1.7 (1.1, 2.5) 1.9 (1.2, 3.1)
Laparoscopic treatment of endometriotic cysts in infertile women					
Alborzi 2004	100 women with a mean age of 28 y and the presence of an endometrioma > 3 cm on US	excision (n = 32)	drainage and ablation (n = 30)	CPR 12 m	2.5 (1.2, 5.2)
Beretta 1998	64 women aged 20-40 y with endometrioma > 3 cm on US	excision (n = 9)	bipolar ablation (n = 17)	CPR 24 m	5.7 (0.68, 47)
Demirol 2006	99 women with mean age 35 y and endomtriomas ≥ 3 and < 6 cm on TVUS	drainage and dissection of the pseudocapsule (n = 49)	ICSI (n = 50)	PR/P	0.91 (0.54, 1.5)
Laparoscopic ovarian drilling for ovulation induction in infertile women with PCOS					
Al- Mizyen 2007	21 women aged 20-38 ywith CC-resistant PCOS	bilateral LOD +/- CC (n = 10)	unilateral LOD +/- CC (n = 10)	PR/P? unclear	0.83 (0.37, 1.8)
Amer 2009	72 anovulatory women aged 18-39 y with PCOS	LOD (+/_ CC) (n = 33)	clomiphene citrate 12 c (+/-LOD). (n = 32)	PR LBR/P	0.87 (0.59, 1.3) 0.81 (0.50, 1.3)
Balen 1994	10 patients mean age 29.5 y with refractory PCOS	unilateral LOD (n = 4)	bilateral LOD (n = 6)	PR/P? unclear	not estimable
Bayram 2004	168 women mean age 29 y with CC-resistant PCOS	LOD +/-CC - rFSH (n = 83)	gonadotropin (rFSH) max 6 c (n = 85)	OPR/P LBR/P	1.01 (0.81, 1.2) 1.04 (0.82, 1.3)
Farquhar 2002	50 women aged 20-38 y with CC-resistant PCOS	LOD (n = 29)	gonadotropin (HMG or rFSH) 3 cycles (n = 21)	OPR/P LBR/P	0.72 (0.24, 2.2) 0.72 (0.20, 2.6)
Ghafarnegad 2010	100 women with CC-resistant PCOS	LOD (n = 50)	gonadotropin (n = 50)	OPR/P	0.80 (0.34, 1.9)
Hamed 2010	110 women aged 20-35 y with CC- and insuline-resistant PCOS	diagnostic laparoscopy + metformin (n = 55)	LOD (n = 55)	PR/C PR/P	2.1 (1.02, 4.2) 1.9 (1.02, 3.6)
Kaya 2005	35 women with CC-resistant PCOS	bilateral LOD (n = 17)	3 cycles of gonadotropin + IUI (n = 18)	PR/P	1.1 (0.42, 1.6)
Lazoviz 1998	57 women with CC-resistant PCOS	LOD (n = 29)	6 cycles of gonadotropin (n = 28)	PR/P	1.8 (0.98, 3.4)
Palomba 2010	50 infertile women with CC-resistant PCOS	LOD + observation (n = 25)	CC + metformin (n = 25)	LBR/C	1.1 (0.62, 1.9)
Roy 2009	44 women mean age 29 y with CC-resistant PCOS	bilateral LOD +/- CC (n = 22)	unilateral LOD +/- CC (n = 22)	PR THBR	1.0 (0.52, 1.9) 0.89 (0.42, 1.9)
Roy 2010	43 women aged 20-40 y with CC-resistant PCOS	rosiglitazone 4 mg bd + CC (n = 22)	unilateral LOD with multi-vitamins bd + CC (n = 21)	CPR 6m	0.82 (0.43, 1.6)
Sharma 2006	20 women with CC-res. PCO	bipolar LOD (n = 10)	unipolar LOD (n = 10)	PR/P	0.75 (0.41, 1.4)
Vegetti 1998	29 women with CC-res. PCO	LOD (n = 16)	gonadotropin (FSH) 6 c (n = 13)	PR/P	0.33 (0.07, 1.4)
Youssef 2007	87 women with PCOS	uni.LOD +/-CC (n = 43)	bil.LOD +/-CC (n = 44)	PR/P	1.1 (0.75, 1.5)
Zakherah 2010	150 women with CC-resistant PCOS	clomiphene + tamoxifen (n = 75)	LOD without ovulation induction (n = 75)	LBR/P	0.89 (0.63, 1.3)
Pre and postoperative medical therapy for endometriosis surgery					
Alborzi 2007	88 infertile women with endometriosis all stages	pentoxifylline 800 mg (n = 43)	placebo (n = 45)	PR/P	1.1 (0.65, 1.9)
Balasch 1997	60 infertile women with r-AFS I/ II endometriosis	pentoxifylline 800 mg (n = 30)	placebo (n = 30)	CPR 12 m	1.7 (0.64, 4.4)
Batioglu 1997	25 women with uni- or bilateral endometriomas > 3 cm	postsurgical treatment with triptorelin 3.75 mg im x 4 weekly 6 m (n = 13)	presurgical treatment with triptorelin 3.75 mg im x 4 weekly 6 m (n = 13)	CPR 12 m	0.46 (0.15, 1.4)

Bianchi 1999	77 women < 40 y with advanced endometriosis	danazol 600 mg/d during 3 months (n = 36)	no treatment (n = 41)	PR/P	1.1 (0.53, 2.3)
Busacca 2001	women < 40 y with r-AFS III/ IV endometriosis	GnRHa (n = 15)	no treatment (n = 15)	CPR 18 m	0.83 (0.32, 2.1)
Creus 2008	104 women with r-AFS I/II endometriosis	pentoxifylline 800 mg (n = 51)	placebo (n = 53)	CPR 6 m	2.02 (0.88, 4.6)
Loverro 2001	62 women with r-AFS III/IV endometriosis	GnRHa (n = 33)	no treatment (n = 29)	PR/P	0.73 (0.25, 2.1)
Parazzini 1994	75 women < 38 y with r-AFS III/ IV endometriosis	nafarelin nasal 400 μg daily during 3 months (n = 36)	placebo (n = 39)	PR/P	1.1 (0.42, 2.8)
Telimaa 1987	60 women with advanced endometriosis	danazol 600 mg daily (n = 20) or MPA 100 mg dialy (n = 20)	placebo (n = 20)	PR/P	0.89 (0.09, 8.4)
Vercellini 1999	269 premenopausal women with endometriosisscore ≥ 4	goserelin sc 3.6 mg /4w 6m (n = 133)	no treatment (n = 134)	PR/P	0.63 (0.28, 1.4)
Surgical treatment for tubal disease in women due to undergo in vitro fertilisation					
Dechaud 1998	60 women mean age with tubal infertility only	bilateral salpingectomy (n = 30)	laparoscopic adhesiolysis (n = 30)	LBR/P	2.2 (0.95, 4.9)
Goldstein 1998	35 infertile women aged 22-38 y	salpingostomy/ -ectomy (n = 15)	no surgery (n = 16)	LBR /P	4.3 (0.54, 33)
Hammadieh 2008	66 women with uni- or bilateral hydrosalpinx	aspiration (n = 32)	no aspiration (n = 34)	CPR/P	1.7 (0.69, 4.0)
Kontoravdis 2006	115 women with uni- or bilateral tubal block	tubal occlusion (n = 50)	salpingectomy (n = 50)	OPR/P	0.77 (0.48, 1.2)
Moshin 2006	204 women with ultrasound visible hydrosalpinges	1. salpingectomy (n = 60) 2. tubal occlusion (n = 78)	1. no treatment (n = 66) 2. no treatment (n = 66)	CPR/P CPR/P	3.2 (1.5, 6.5) 3.3 (1.6, 6.7)
Strandell 1999	204 infertile women < 39 y prior to first IVF treatment; no fibroids present.	salpingectomy (n = 116)	no surgery (n = 88)	LBR/P	1.6 (0.90, 2.7)
Laparoscopic treatment of fibroids for subfertility					
Campo 1999	60 women mean aged 25-42 y with intramural/ subserosal fibroids	surgery preceded by GnRHa (n = 30)	surgery without GnRHa (n = 30)	PR/P	1.4 (0.66, 2.9)
Casini 2005	87 women < 35 y with unexplained infertility and one intramural/subserosal fibroid < 4 cm	surgery (n = 40)	no surgery (n = 47)	PR/P	1.2 (0.75, 1.9)
Palomba 2007	136 women with symptomatic fibroids or unexplained infertility	laparoscopic myomectomy (n = 68)	myomectomy by minilaparotomy (n = 68)	LBR/P	1.4 (0.95, 2.2)
Seracchioli 2000	131 infertile women with at least 2 myomas ≥ 5 cm	abdominal myomectomy (n = 65)	laparoscopic myomectomy (n = 66)	LBR/P	1.1 (0.80, 1.5)
Hysteroscopic treatment of fibroids for subfertility					
Casini 2005	181 women < 35 y with unexplained infertility and one submucosal with or without intramural fibroid < 4 cm	hysteroscopy and/or laparotomy (n = 52)	no surgery (n = 42)	PR/P	1.9 (0.97, 3.7)
Shokeir 2009	215 women with otherwise unexplained primary infertility and US diagnosed submucosal fibroids	hysteroscopic myomectomy (n = 101)	diagnostic hysteroscopy and myoma biopsy (n = 103)	PR/P	2.2 (1.6, 3.2)
Surgery by laparoscopy or hysteroscopy prior to IUI or IVF					
Demirol 2004	421 patients with primary infertility and at least 2 failed IVF attempts	5 mm hysteroscopy (n = 210)	no hysteroscopy (n = 211)	CPR/P	1.5 (1.1, 2.1)
Pérez-Medina 2005	215 infertile women planned for IUI with polyps on TVUS	hysteroscopic polypectomy (n = 107)	diagnostic hysteroscopy (n = 108)	CPR 6 c	2.2 (1.6, 3.1)
Rama Raju 2006	520 patients with primary infertility and at least 2 failed IVF attempts	5 mm hysteroscopy (n = 265)	no hysteroscopy (n = 255)	CPR/P	1.6 (1.3, 1.9)
Tanahatoe 2005	154 infertile women with medical ground for IUI	laparoscopy prior to IUI (n = 77)	IUI first (n = 77)	OPR/P	0.89 (0.64, 1.2)

Hysteroscopic septoplasty					
Colacurci 2007	160 patients with infertility and/ or recurrent pregnancy loss	hysteroscopic septoplasty with the Versapoint needle (n = 80)	hysteroscopic septoplasty with the resectoscope (n = 80)	PR/P	0.71 (0.54, 0.93)
Techniques for pelvic surgery in subfertility					
Chong 1991	37 women with bilateral proximal tubal occlusion needing surgical treatment	Bruhat technique (n = 15)	cuff technique (n = 19)	TPR/P	1.1 (0.26, 4.6)
Comninos 1977	30 women with bilateral proximal tubal occlusion undergoing salpingostomy	1.hydrotubation (n = 15) 2. prosthesis use (n = 15)	1.no hydrotubation (n = 15) 2. no prosthesis (n = 15)	TPR/P TPR/P	0.60 (0.17, 2.1) 2.00 (0.20, 19)
Kamel 1999	240 women with bilateral tubo-ovarian adhesions and patency	thermocoagulation (n = 120)	electrocoagulation (n = 120)	PR/P	0.91 (0.66, 1.3)
Rock 1984b	72 patients requesting reversal of sterilisation	operating microscope (n = 36)	loupe (n = 36)	TPR/P	0.83 (0.56, 1.2)
Soihet 1974	258 women with tubal infertility needing tubal surgery	1. early hydrotubation (n = 67) 2. antibiotic (n = 91) 3. tubal stent (n = 100)	1. late hydrotubation (n = 100) 2. no antibiotic (n = 100) 3. no tubal stent (n = 67)	TDR/P TDR/P TDR/P	0.95 (0.39, 2.3) 2.1 (1.1, 4.1) 1.0 (0.43, 2.6)
Tulandi 1985	67 infertile women with bilateral distal tubal occlusion	salpingostomy by laser (n = 37)	unipolar needle (n = 30)	TPR/P	1.3 (0.56, 2.9)
Tulandi 1986	63 infertile women with periadnexal adhesions	adhesiolysis by laser (n = 30)	unipolar needle (n = 33)	TPR/P	1.0 (0.65, 1.7)
Postoperative procedures for improving fertility following pelvic reproductive surgery					
Comninos 1977	30 women with bilateral proximal tubal occlusion undergoing salpingostomy	1.hydrotubation (n = 15) 2. prosthesis use (n = 15)	1.no hydrotubation (n = 15) 2. no prosthesis (n = 15)	TPR/P TPR/P	0.60 (0.17, 2.1) 2.0 (0.20, 20)
Gurgan 1992	40 women with CC-resistant PCOS undergoing LOD	second-look (n = 20)	no second-look (n = 20)	LBR/P	0.78 (0.36, 1.7)
Rock 1984a	206 women with tubal infertility treated with neosalpingostomy or fimbrioplasty	hydrotubation with steroids (n = 86)	hydrotubation without steroids (n = 86)	LBR/P	1.1 (0.64, 1.9)
Soihet 1974	258 women with tubal infertility needing tubal surgery	1. early hydrotubation (n = 67) 2. antibiotic (n = 91) 3. tubal stent (n = 100)	1. late hydrotubation (n = 100) 2. no antibiotic (n = 100) 3. no tubal stent (n = 67)	TDR/P TDR/P TDR/P	0.95 (0.39, 2.3) 2.1 (1.1, 4.1) 1.0 (0.43, 2.6)
Tulandi 1989	74 women with failure to conceive within 1 year after tubal microsurgery	laparoscopic tubal patency testing +/- adhesiolysis (n = 36)	no laparoscopy (n = 38)	TPR/P	1.1 (0.66, 1.9)
Techniques for adhesion prevention in pelvic reproductive surgery					
Adhesion SG 1983	277 infertile women undergoing open pelvic surgery	dextran (n = 55)	normal saline (n = 47)	PR/P unclear	0.49 (0.15, 1.6)
Jansen 1985	103 infertile women undergoing open pelvic microsurgery	dextran (n = 50)	Hartmann solution (n = 53)	CPR/P LBR/P	0.87 (0.39, 1.9) 0.53 (0.17, 1.6)
Larsson 1985	109 infertile women undergoing open pelvic surgery	dextran (n = 51)	saline (n = 54)	CPR/P LBR/P	0.71 (0.38, 1.3) 0.91 (0.33, 2.5)
Querleu 1989	131 infertile women treated by open pelvic microsurgery	noxytioline (n = 63)	no treatment (n = 63)	PR/P unclear	0.74 (0.41, 1.3)
Rock 1984a	206 women with tubal infertility treated with neosalpingostomy or fimbrioplasty	hydrotubation with steroids (n = 86)	hydrotubation without steroids (n = 86)	LBR/P	1.1 (0.64, 1.9)
Pellicano 2005	36 infertile women with not more than 4 fibroids > 3cm but < 10 cm	hyaluronic acid gel after lap.myomectomy (n = 18)	no hyaluronic acid gel after lap. myomectomy (n = 18)	PR/P	2.0 (1.1, 3.7)

DR: delivery rate
FR: fecundity rate
PR: pregnancy rate
c: cycles
m: months

CPR: cumulative pregnancy rate
LBR: live-birth rate
OPR: ongoing pregnancy rate
THBR: take home baby rate
TPR: total pregnancy rate
TDR: term delivery rate

PR/P: pregnancy rate per patient
PR/C: pregnancy rate per cycle
CPR/P: clinical pregnancy rate per patient
LBR/C: live-birth rate per cycle
LBR/P: live-birth rate per patient

in either a worst case (RR 0.74, 95% CI 0.35-1.5) or a best case scenario (RR 1.3, 95% CI 0.66-2.6), similar to the adjusted data from the available case analysis (RR 0.88, 95% CI 0.40-1.9). By consequence, this discrepancy would not have had implications for the results and conclusions in the meta-analysis.

Endometriotic cysts in moderate and severe endometriosis

We retrieved two randomised trials on the effectiveness of two different techniques for the treatment of endometriotic cysts (Alborzi *et al*., 2004; Beretta *et al*., 1998). The first trial (n = 62) demonstrated a treatment effect favoring the excision of the endometriotic cyst wall compared to drainage and ablation for the cumulative pregnancy rate at 12 months (RR 2.5, 95% CI 1.2-5.2) (Alborzi *et al*., 2004). A second smaller trial (n = 26) showed a trend in favor of the excision technique in increasing the cumulative pregnancy rate at 24 months, but the difference between both techniques in this underpowered trial was not statistically significant (RR 5.7, 95% CI 0.68-47) (Beretta *et al*., 1998). Meta-analysis of the results of these two trials, published in a Cochrane review (Hart *et al*., 2007) demonstrated an important treatment effect of the excision technique compared to the ablation technique for the chance of spontaneous conception at 12 months(RR 2.8, 95% CI 1.4-5.5). For every three infertile women with endometriotic cysts greater than 3 cm treated by laparoscopic excision, it is expected that one additional person will have a spontaneous conception at 12 months compared to fenestration and ablation (NNT = 3, 95% CI 2 to 3). There is no evidence of significant statistical heterogeneity (Chi^2 = 0.22, I^2 = 0%). Another randomised trial (n = 99) studied the effectiveness of drainage, followed by dissection of the pseudocapsule of ovarian endometriomas between 3 and 6 cm on transvaginal ultrasound prior to ICSI compared to starting ART without prior surgical treatment (Demirol, 2006). There was a trend in lower pregnancy rates after the removal of endometriotic cysts prior to IVF compared to starting ICSI immediately without surgery, but the difference is not statistically significant (RR 0.91, 95% CI 0.54-1.5).

Deeply infiltrative endometriosis

We did not find randomised trials on the effectiveness of the laparoscopic treatment of deeply infiltrative endometriosis in subfertile women with or without pain compared to expectant management or IUI/ IVF.

Laparoscopic ovarian diathermy in PCOS patients

We detected six randomised trials with 439 patients on laparoscopic ovarian diathermy (LOD) with or without clomiphene citrate in clomiphene-resistant PCOS compared to gonadotropin treatment (Bayram *et al*., 2004; Farquhar *et al*., 2002; Ghafarnegad *et al*., 2010; Kaya *et al*., 2005; Lazoviz *et al*., 1998; Vegetti *et al*., 1998). There were no differences in ongoing pregnancy rate per couple between the two treatment strategies (RR 1.0, 95% CI 0.83-1.2) as presented in Figure 2. There were however less multiple pregnancies per ongoing pregnancy in the LOD group compared to the gonadotropin group (RR 0.16, 95% CI 0.04-0.58) as demonstrated by a meta-analysis of five randomised trials in 166 patients (Bayram *et al*., 2004; Farquhar *et al*., 2002; Kaya *et al*., 2005; Lazoviz *et al*., 1998; Vegetti *et al*., 1998) (Fig. 3). For every six infertile women with clomiphene-resistant PCOS treated by LOD, it is expected that one person less will have a multiple pregnancy compared to gonadotropin treatment (NNT = 6, 95% CI 4 to13). There is no evidence of significant statistical heterogeneity (Chi^2 = 0.41, I^2 = 0%).

We retrieved five randomised trials (n = 181) comparing unilateral versus bilateral LOD in clomiphene resistant PCOS patients (Al-Mizyen and Grudzinskas, 2007; Balen and Jacobs, 1994; Roy *et al*., 2009, Sharma *et al*., 2006; Youssef and Atallah, 2007). Meta-analysis did not indicate a treatment effect of bilateral LOD for the clinical pregnancy rate compared to unilateral LOD (RR 0.97, 95% CI 0.75-1.3) as illustrated by the forest plot in Figure 4.

Tubal infertility

We found five randomised trials on the surgical treatment of hydrosalpinx prior to IVF (Dechaud *et al*., 1998; Hammadieh *et al*., 2008; Kontoravdis *et al*., 2006; Moshin and Hotineanu, 2006; Strandell *et al*., 1999). Meta-analysis of four trials (n = 455) (Dechaud *et al*., 1998; Kontoravdis *et al*., 2006; Moshin and Hotineanu, 2006; Strandell *et al*., 1999) showed a treatment effect of laparoscopic tubal surgery (any type) compared to no surgical treatment (any type) for the pregnancy rate (any definition) as presented in Figure 5 (RR 1.9, 95% CI 1.4-2.7). For every seven infertile women with hydrosalpinx treated surgically prior to IVF, it is expected that one additional person will have a pregnancy (any definition) compared to starting IVF immediately (NNT = 7, 95% CI 5 to11). There is no evidence of significant statistical heterogeneity (Chi^2 = 0.69; I^2 = 0%). Meta-analysis of two RCTs (n = 209) (Kontoravdis *et al*., 2006; Moshin and Hotineanu, 2006) comparing tubal occlusion versus no treatment

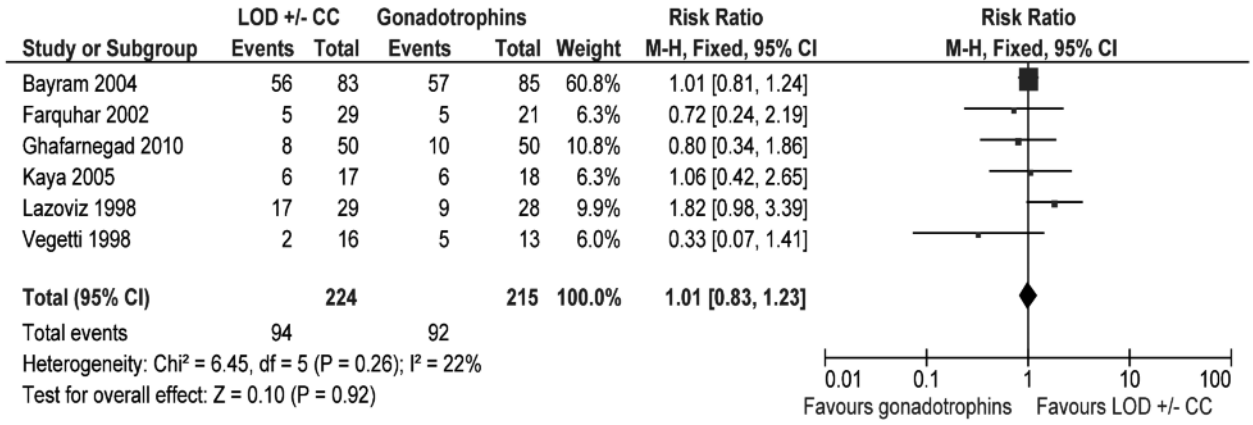

Fig. 2. — LOD with or without clomiphene versus gonadotrophins. Outcome: ongoing pregnancy rate per couple

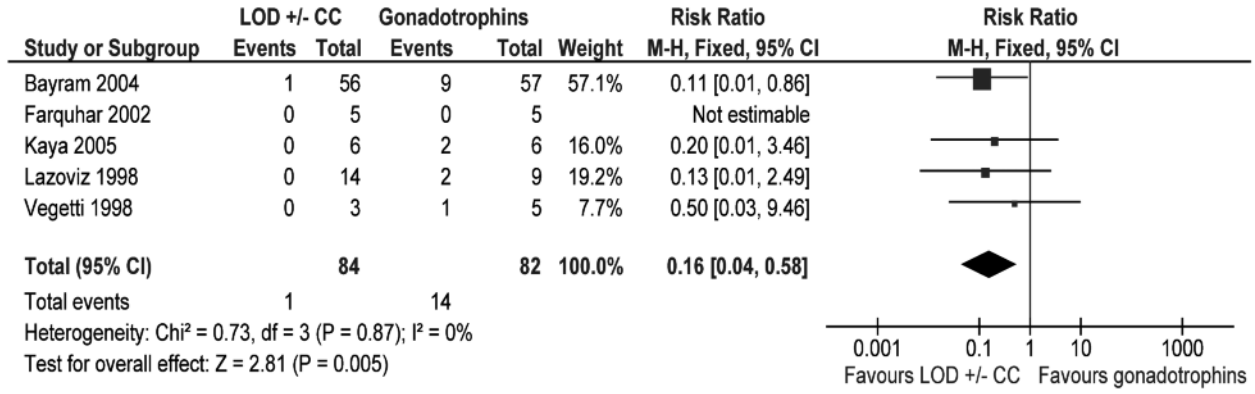

Fig. 3. — LOD with or without clomiphene versus gonadotrophins. Outcome: multiple pregnancy rate per couple

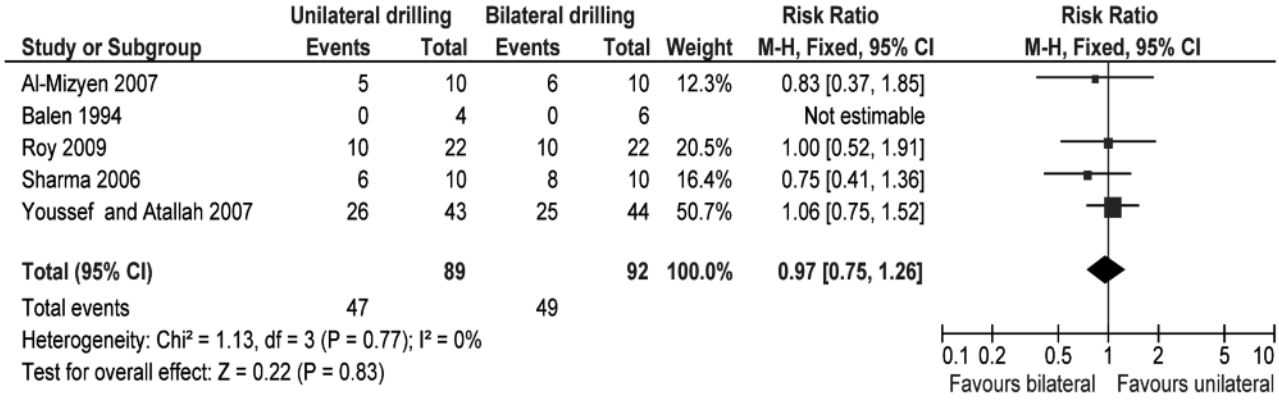

Fig. 4. — Unilateral versus bilateral laparoscopic ovarian diathermy in clomiphene-resistant PCOS patients. Outcome: clinical pregnancy rate per patient.

demonstrated a treatment effect of tubal occlusion for the clinical pregnancy rate (RR 3.2, 95% CI 1.7-6.0).There is no evidence of significant statistical heterogeneity ($Chi^2 = 0.01$, $I^2 = 0\%$). For every four women with hydrosalpinges treated by a tubal occlusion prior to IVF, it is expected that one additional person will have a clinical pregnancy (NNT = 4, 95% CI 3 to 6). The forest plot in Figure 6 graphically demonstrates that tubal occlusion is at least as effective as laparoscopic salpingectomy in improving the clinical pregnancy rate (RR 1.1, 95% CI 0.85-1.6). The transvaginal aspiration of fluid after oocyte pick-up (Hammadieh *et al*., 2008) showed a trend in increasing the clinical pregnancy rate com-

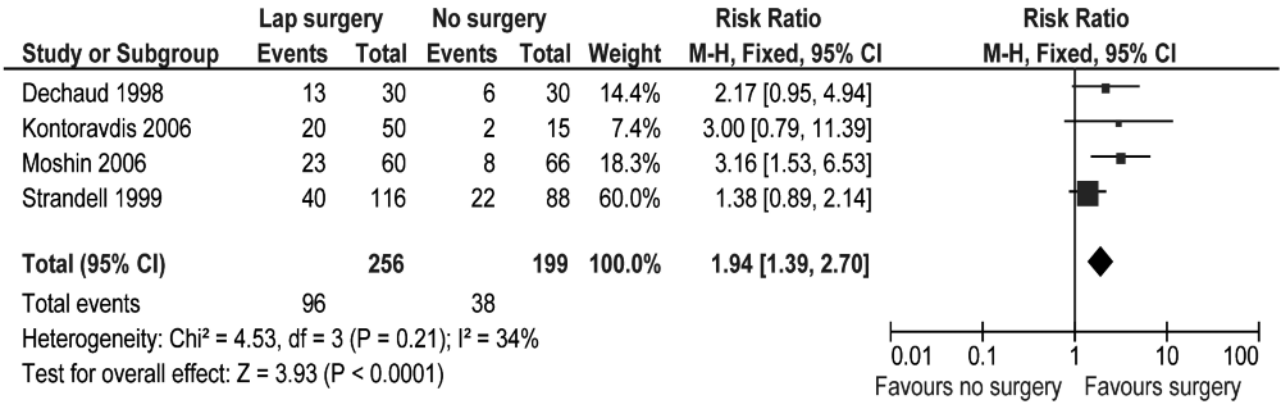

Fig. 5. — Laparoscopic surgery on the Fallopian tubes (all types) versus no surgery on the Fallopian tubes (all types). Outcome: pregnancy rate (any definition).

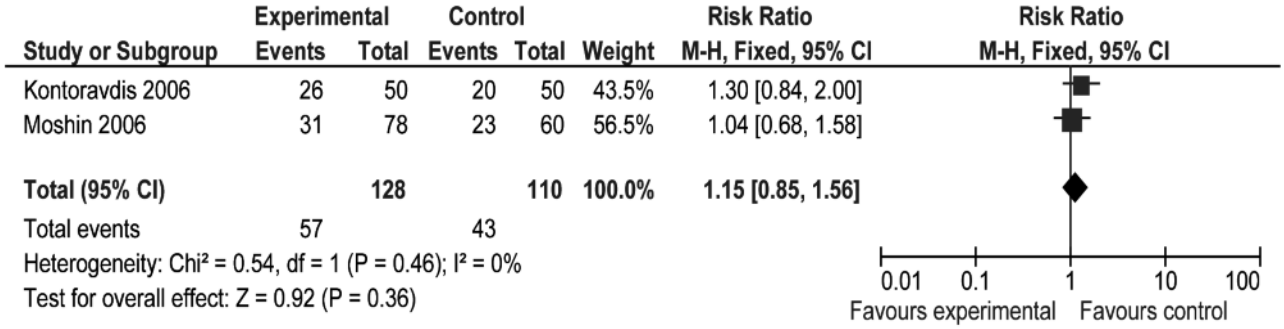

Fig. 6. — Tubal occlusion versus salpingectomy in subfertile women with hydrosalpinx prior to IVF. Outcome: clinical pregnancy rate.

pared to no treatment, but the difference was not statistically significant (RR 1.7, 95% CI 0.69- 4.0). We did not find randomised trials that compared the effectiveness of surgical reversal of tubal sterilisation with IVF in women with infertility due to sterilisation (Yossry *et al*., 2006). There are no randomised trials, to the best of our knowledge, comparing the effectiveness of reproductive surgery for tubal factor infertility to either expectant management or IVF treatment.

Prevention of adhesions after reproductive surgery

With respect to peritubal adhesions, we found only one RCT (n = 74) on the effectiveness of salpingo-ovariolysis during a second-look laparoscopy after previous tubal microsurgery compared to no second-look procedure: there was a trend in increasing the cumulative probability of pregnancy (RR 1.1, 95% CI 0.66-1.9), albeit statistically not significant (Tulandi *et al*., 1989). We retrieved one small trial (n = 36) studying the effectiveness of hyaluronic acid gel application after laparoscopic myomectomy in infertile women with not more than 4 symptomatic fibroids larger than 3 but smaller than 10 cm (Pellicano *et al*., 2005). The chance of becoming pregnant was doubled in the group treated with hyaluronic acid gel application compared to no treatment with anti adhesion barrier (RR 2.0, 95% CI 1.1-3.7). Definitive conclusions cannot be made since this trial has several methodological flaws due to unclear methodology of allocation concealment and randomisation.

Intramural and subserosal fibroids

One randomised trial including 87 women with one intramural and/ or subserosal fibroid smaller than 4 cm and otherwise unexplained infertility studied the effectiveness of surgery by laparoscopy or laparotomy compared to no surgery (Casini *et al*., 2006). There was no statistically significant difference, although there was a trend in improving the pregnancy rate per patient at 12 months (RR 1.2, 95% CI 0.75-1.9).

Diagnostic and/or operative laparoscopy prior to IUI treatment

In a randomised trial including 154 infertile women with medical ground for IUI, there was no evidence of a treatment effect of laparoscopy prior to IUI for

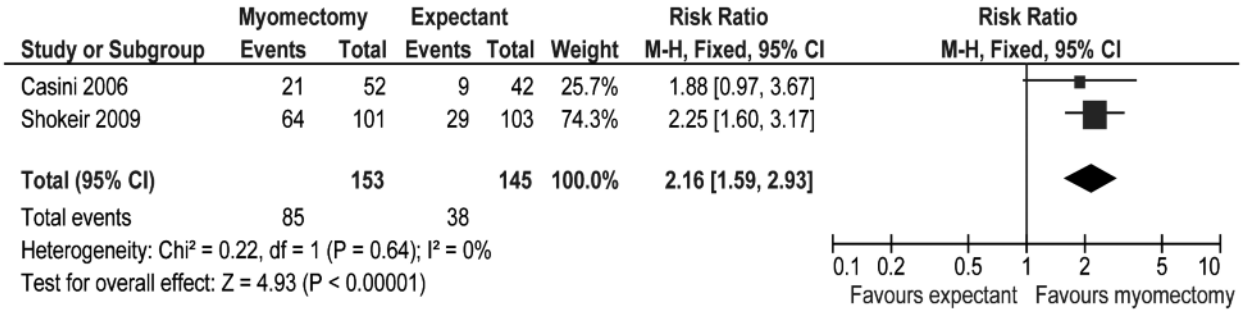

Fig. 7. — Hysteroscopic myomectomy versus expectant management in women with ultrasonographically diagnosed submucosal myomas and otherwise unexplained infertility. Outcome: clinical pregnancy rates.

the ongoing pregnancy rate per patient (RR 0.89, 95% CI 0.64-1.2) compared to immediate treatment with IUI (Tanahatoe *et al*., 2005).

How effective is reproductive surgery by hysteroscopy in subfertile patients compared to alternative treatments?

Endometrial polyps

Hysteroscopic removal of endometrial polyps detected by ultrasound significantly doubles the clinical pregnancy rate when compared to diagnostic hysteroscopy and polyp biopsy according to one randomised trial including 215 subfertile women with uterine polyps undergoing IUI (RR 2.2, 95%CI 1.6-3.1) (Pérez-Medina *et al*., 2005). For every three subfertile women with uterine polyps treated by hysteroscopic polypectomy, it is expected that one additional person will have a clinical pregnancy (NNT = 3, 95%CI 2 to 5).

Submucosal fibroids

In patients with submucosal fibroids with or without intramural fibroids and otherwise unexplained subfertility, hysteroscopic myomectomy doubles the pregnancy rate compared to expectant management (RR 2.2, 95% CI 1.6- 2.9) (Fig. 7) as demonstrated by a meta-analysis of two randomised trials in 298 patients (Casini *et al*., 2006; Shokeir *et al*., 2009). For every three women with submucosal fibroids and otherwise unexplained infertility treated by hysteroscopic myomectomy, it is expected that one additional person will have a pregnancy compared to expectant management (NNT 3, 95%CI 2 to5). There is no evidence of significant statistical heterogeneity ($Chi^2 = 0.22$; $I^2 = 0\%$).

Intrauterine septa

We did not find RCTs on the effectiveness of hysteroscopic septum resection compared to expectant management or alternative treatments in patients with otherwise unexplained primary subfertility. One randomised trial compared the effectiveness of two methods of hysteroscopic treatment of uterine septa (resectoscopy versus Versapoint electrode) in a mixed population of 160 patients with subfertility and recurrent pregnancy loss (Colacurci *et al*., 2007) and found no differences in outcome between both techniques. A randomised trial (http://www.studies-obsgyn.nl/trust NTR 1676) studying the effectiveness of hysteroscopic metroplasty in patients with recurrent pregnancy loss is ongoing.

Intrauterine adhesions

There are no randomised trials on the effectiveness of hysteroscopic synechiolysis with pregnancy or live birth rates as primary outcome. We excluded one pseudo-randomised trial on the effectiveness of hysteroscopy in treating intrauterine adhesions (Pabuccu *et al*., 2008). Furthermore we excluded two randomised trials on the effectiveness of autocross linked hyaluronic acid gel in the prevention of intra-uterine adhesions after hysteroscopic adhesiolysis (Acunzo *et al*., 2003) and after hysteroscopic surgery (Guida *et al*., 2004) since data on reproductive outcome are lacking.

Hysteroscopy in patients with recurrent IVF failure

A systematic review (El-Toukhy *et al*., 2008) with a meta-analysis of two randomised trials (n = 941) (Demirol and Gurgan, 2004; Rama Raju *et al*., 2006) demonstrated that office hysteroscopy in the cycle preceding a next IVF attempt nearly doubles the clinical pregnancy rate in infertile patients with at least two failed IVF attempts compared to starting IVF immediately (RR 1.6, 95% CI 1.3-1.9). For every seven infertile women with at least two failed IVF attempts treated by office hysteroscopy prior to a subsequent IVF cycle, it is expected that one additional person will have a clinical pregnancy compared to starting IVF immediately (NNT = 7, 95%CI

5 to12). There is no evidence of significant statistical heterogeneity ($Chi^2 = 0.16$; $I^2 = 0\%$). A subgroup analysis in the patients undergoing office hysteroscopy demonstrated no difference in clinical pregnancy rates irrespective whether pathology was detected and treated or not (RR 0.91, 95% CI 0.71-1.2).

Discussion

The laparoscopic treatment of all visible implants of minimal-mild endometriosis in women with otherwise unexplained subfertility is likely to be beneficial since it might increase the chance of a live birth or ongoing pregnancy. The two major trials do however report conflicting results. A beneficial effect of treating minimal-mild endometriosis is in accordance with the pooled data (Hughes *et al*., 1993; Adamson and Pasta, 1994) from one pseudo-randomised trial (Nowroozi *et al*., 1987) and two cohort studies (Fayez *et al*., 1988; Paulson *et al*., 1991) but is not confirmed by other observational studies (Seiler *et al*., 1986; Levinson, 1989; Chong *et al*., 1990). It should be noted that atypical endometriotic lesions have not been included in the earlier studies. The wider eligibility criteria in the Italian study, namely the longer duration of subfertility and the higher prevalence of more advanced endometriosis could have led to the unintentional inclusion of more patients with a less favourable prognosis, explaining the absent treatment effect in the Italian trial. The results of the Italian trial are more correctly interpreted if one accepts its division into two different subgroups based on whether co-treatment with GnRH agonists was given or not. A type II error due to low statistical power may therefore be responsible for the absence of statistically significant differences between the intervention and control groups. The wider eligibility criteria and the co-treatment with GnRH agonists have caused the substantial statistical heterogeneity in the meta-analysis of the two major trials. The underlying pathophysiological mechanism linking minimal-mild endometriosis to subfertility is still largely unknown. Therefore, controversy still exists whether there is a causal link between these lesions and subfertility (Olive and Schwartz, 1993; Vercellini and Crosignani, 1993). The excision of endometriotic cysts is superior to simple drainage and ablation for increasing the spontaneous conception rate. Some authors have observed that ovarian tissue may be inadvertently excised together with the endometrioma wall in the majority of patients (Muzii *et al*., 2005), which could lead to a reduction in ovarian volume (Exacoustos *et al*., 2004). There are many observational studies reporting conflicting results concerning the impact of ovarian cystectomy on the ovarian responsiveness (Yazbeck *et al*., 2006; Nargund *et al*., 1996; Loh *et al*., 1999, Ho *et al*., 2002; Marconi *et al*., 2002; Alborzi *et al*., 2007; Horikawa *et al*., 2008; Canis *et al*., 2001; Donnez *et al*., 2001; Wyns and Donnez, 2003). As a consequence there is uncertainty whether ovarian cystectomy of endometriotic cysts despite its favourable effect in the short term, could have a deleterious impact on the ovarian reserve in the longer term. The absence of a treatment effect in favour of the excision of endometriotic cysts smaller than 6 cm prior to IVF on the pregnancy rates compared to starting IVF immediately is in accordance with the results of an earlier observational study (Garcia-Velasco *et al*., 2004). In the randomised trial (Demirol, 2006) the trend of lower pregnancy rates after ICSI in the patients who were treated with cystectomy could be explained by the longer stimulation period, a higher gonadotropin requirement and a lower oocyte number: the absence of statistically significant differences due to the low number of included patients cannot enable at the present time to draw definitive conclusions on the need to perform an ovarian cystectomy prior to IVF.

Laparoscopic ovarian diathermy as a second-line treatment in women with clomiphene-resistant PCOS results at least in equal pregnancy rates and decreases the risk for multiple pregnancy compared to gonadotropin treatment, irrespective whether the technique is used uni- or bilaterally . The underlying physiological mechanism of action might be due to both local and systemic effects, resulting in follicular recruitment, maturation and ovulation (Aakvaag 1985; Armar *et al*., 1990; Balen *et al*., 1993; Greenblatt and Casper, 1987). It is however unknown how long the treatment effect of LOD lasts, although repeated spontaneous ovulations and subsequent pregnancies after a first pregnancy or miscarriage have been reported (Farquhar *et al*., 2002). Ovarian adhesions after the LOD procedure have been described, but their clinical relevance is unclear (Greenblatt and Casper, 1993). The theoretical risk of inducing premature ovarian failure needs to be addressed since some observational studies have described a significant reduction of the ovarian reserve after LOD (Weerakiet *et al*., 2007).

Prior to IVF treatment, the laparoscopic removal of an ultrasonographically visible hydrosalpinx doubles the live birth rate compared to starting IVF immediately. This supports the observed negative impact of tubal infertility due to hydrosalpinx on the implantation rates in IVF treatment (Camus *et al*., 1999). At the present, there is no evidence to support performing bilateral salpingectomy whether or not bilateral hydrosalpinges are present. The pooled data from two RCTs (Dechaud *et al*., 1998; Strandell *et*

al., 1999) confirm that salpingectomy for hydrosalpinx prior to IVF is effective before a first IVF treatment cycle. Some observational studies have studied the effect of salpingectomy on the ovarian reserve. One clinical controlled trial demonstrated significantly higher baseline FSH levels after salpingectomy as well as a lower ovarian response to stimulation but the pregnancy rates were similar in both groups (Gelbaya *et al*., 2006). Another clinical controlled trial equally found higher baseline FSH levels after laparoscopic salpingectomy compared to proximal tubal division but pregnancy rates per patient did not differ between both groups (Nakagawa *et al*., 2008). The possible long term negative impact of salpingectomy on female fertility should be addressed by future RCTs. Alternatively, the occlusion of a hydrosalpinx is as effective as salpingectomy (Kontoravdis *et al*., 2006; Moshin and Hotineanu, 2006) whereas the ultrasound-guided transvaginal needle aspiration shows a trend in doubling the clinical pregnancy rate (Hammadieh *et al*., 2008) but its effect was statistically not significant. The negative impact of a hydrosalpinx on the outcome of IVF is hypothetically explained by the intermittent bathing of the uterine cavity with toxic fluid within the hydrosalpinx, which may lower the endometrial receptivity (Akman *et al*., 1996; Fleming and Hull, 1996; Freeman *et al*., 1996; Katz *et al*., 1996; Strandell *et al*., 1994) possibly by reducing the endometrial expression of β- integrin (Meyer *et al*., 1997). Alternative hypothetical mechanisms of action include direct embryo toxicity as demonstrated in a murine model (Mukherjee *et al*., 1996) or a negative impact on oocyte growth and development during early follicular recruitment (Freeman *et al*., 1996). Randomised trials studying the effectiveness of tubal surgery compared to expectant management and IVF in terms of livebirth rates are lacking, as has been reported by other authors (Pandian *et al*., 2008).

The impact of fibroids on fertility remains controversial (Pritts, 2001; Lefebvre *et al*., 2003; Vilos, 2003; Griffiths *et al*., 2006; Somigliana *et al*., 2007; Vimercati *et al*., 2007; Somigliana *et al*., 2008; Klatsky *et al*., 2008; Pritts *et al*., 2009) despite an abundancy of observational studies (Seoud *et al*., 1992; Narayan and Goswamy, 1994; Farhi *et al*., 1995; Lumbiganon *et al*., 1996; Eldar-Geva *et al*., 1998; Marshall *et al*., 1998; Ramzy *et al*., 1998; Stovall *et al*., 1998; Bulletti *et al*., 1999; Bajekal and Li, 2000; Dietterich *et al*., 2000; Healy, 2000; Hart et al, 2001; Jun *et al*., 2001; Surrey *et al*., 2001; Wang *et al*., 2001; Check *et al*., 2002; Donnez and Jadoul, 2002; Ng and Ho, 2002; Yarali and Bukulmez, 2002; Bulletti *et al*., 2004; Manyonda *et al*., 2004; Oliveira *et al*., 2004; Parazzini *et al*., 2004; Wang and Check, 2004; Wise *et al*., 2004; Benecke *et al*., 2005; Gianaroli *et al*., 2005; Ng *et al*., 2005; Rackow and Arici, 2005; Surrey *et al*., 2005; Khalaf *et al*., 2006; Klatsky *et al*., 2007). Some observational data suggest that submucosal, intramural and subserosal fibroids interfere with female fertility in decreasing order of importance (Somigliana *et al*., 2007) whereas other non-controlled studies have suggested that the number, size and distorsion effect of fibroids on the uterine cavity may be more important (Bulletti *et al*., 1999; Varasteh *et al*., 1999; Bernard *et al*., 2000; Fernandez *et al*., 2001; Oliveira *et al*., 2005, Khalaf *et al*., 2006; Mukhopadhaya *et al*., 2007). Fibroids are believed to interfere with sperm migration, ovum transport and embryo implantation (Richards *et al*., 1998), which may explain why the hysteroscopic removal of submucosal fibroids doubles the clinical pregnancy rates compared to expectant management in women with otherwise unexplained subfertility. Many hypothetical mechanisms have been put forward such as altered contours of the uterine cavity resulting in altered mechanical pressure or abnormal uterine contractility (Bettocchi *et al*., 2002; Farrugia *et al*., 2002; Oliveira *et al*., 2004), local inflammation, focal endometrial vascular disturbances, chronic endometritis, secretion of vasoactive substances or an enhanced intrauterine androgen environment(Richards *et al*., 1998).

Hysteroscopic polypectomy prior to IUI doubles the pregnancy rates but at the present we cannot recommend the systematic removal of all polyps in subfertile women based on one RCT. Observational studies have suggested a possibly higher impact of tubocornual polyps on female fertility (Venturini *et al*., 1987; Brooks *et al*., 1990; Lee *et al*., 1997; Shokeir *et al*., 2004; Yanaihara *et al*., 2008). The effect of the size, number and the localisation of endometrial polyps on fertility should be examined as well as possible association between endometrial polyps and endometriosis (Mc Bean *et al*., 1996; Kim *et al*., 2003).

Two randomised trials have confirmed the effectiveness of auto-cross linked hyaluronic acid gel in the prevention of intra-uterine adhesions after hysteroscopic adhesiolysis (Acunzo et al, 2003) and after hysteroscopic surgery (Guida *et al*., 2004) but have unfortunately failed to present data on the fertility outcome.

The higher pregnancy rates after hysteroscopy even in the absence of intrauterine pathology in women with recurrent IVF failure is an unexpected observation which nevertheless could be explained by the cervical dilatation and/or direct hysteroscopic visualisation of the uterine cavity facilitating embryo transfer (Mc Manus *et al*., 2000; Mansour and Aboulghar, 2002) or alternatively by an immunological mechanism triggered by the hysteroscopic

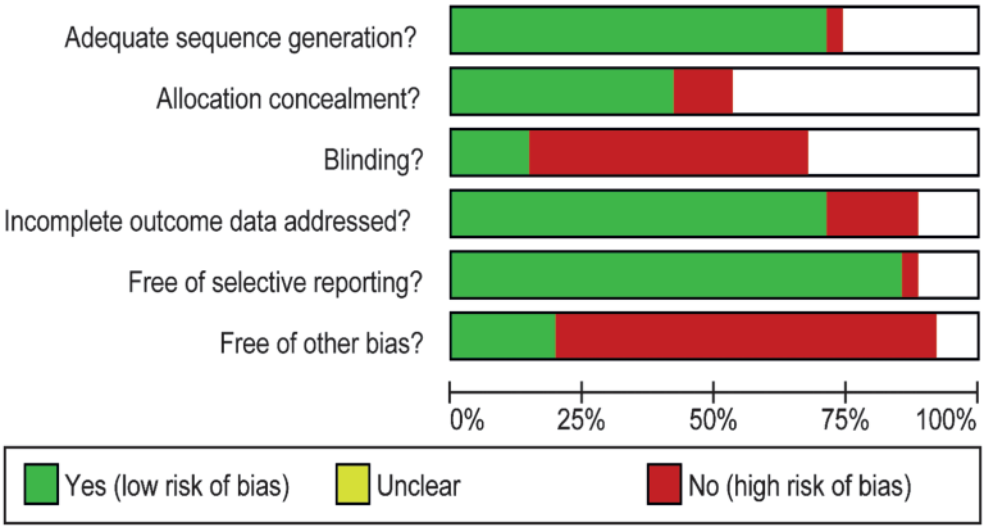

Fig. 8. — Risk of bias graph of all included studies

Table 2. — Review of the effectiveness of reproductive surgery: levels of evidence.

topic under review	RCTs	number of participants	conclusions for primary outcomes (evidence category)
Laparoscopic treatment for subfertility associated with rAFS I/II endometriosis	2	437	Laparoscopic excision/ ablation and adhesiolysis improves the chance for live birth and ongoing pregnancy (E)
Treatment of endometriomata by excision or ablation.	2	88	The excision of endometriotic cysts significantly improves the chance for spontaneous conception at 12 months (EG)
Treatment of endometriomata prior to IVF	1	99	There is no evidence of an effect in favor of removing endometriomata prior to IVF (G).
Laparoscopic drilling for induction of ovulation in PCOS.	6	439	There is no evidence of a treatment effect of LOD (6-12 months follow-up) versus gonadotropin injections (3-6 cycles) for the ongoing pregnancy rates (EG).
	5	166	There are significantly fewer multiple pregnancies with LOD (E)
	5	181	There is no evidence of an effect of bilateral compared to unilateral LOD (EG).
Surgical treatment for tubal disease in women with hydrosalpinx due to undergo IVF	4	455	Laparoscopic salpingectomy for hydrosalpinges prior to IVF significantly improves the chances for pregnancy (all definitions) (E).
	2	209	Tubal occlusion is at least as effective as an alternative (EG)
Prevention of adhesions after previous reproductive surgery	1	74	There is no evidence of a treatment effect for second-look laparoscopy with adhesiolysis in improving pregnancy rates after failed tubal microsurgery(E).
	1	36	There is some benefit for the use of hyaluronic acid gel after laparoscopic myomectomy (G).
Surgical treatment of fibroids for sub-fertility	2	309	Hysteroscopic myomectomy doubles the pregnancy rate compared to expectant management in subfertile women with submucosal fibroids (EG).
	1	87	The removal of intramural or subserosal fibroids tends to increase the pregnancy rate, but the effect is not statistically significant (G).
Laparoscopy prior to IUI	1	154	There is no evidence of a treatment effect of laparoscopy prior to IUI (E).
Hysteroscopic removal of polyps	1	215	Hysteroscopic removal of polyps visible on ultrasound increases the pregnancy rates in women undergoing IUI (E)
Hysteroscopy in women with IVF failure	2	941	Hysteroscopy prior to IVF doubles the clinical pregnancy rates in patients with 2 failed IVF attempts (E).

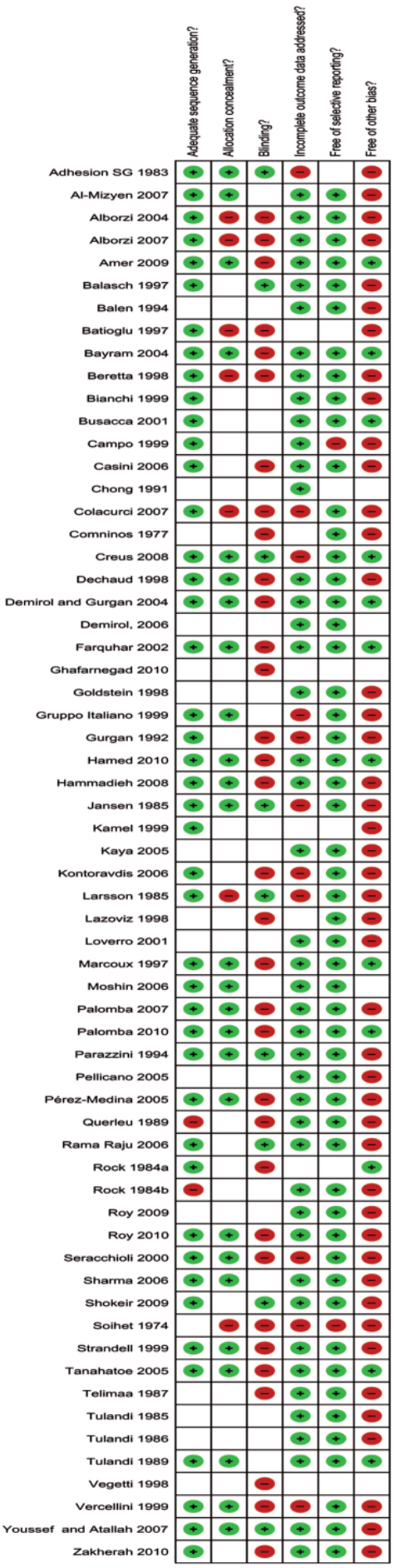

Fig. 9. — Summary of the risk of bias of individual studies

manipulation or by the effect of the distension medium on the endometrium. The hypothecical immunological mechanism which may similarly explain the increased odds of spontaneous pregnancy after hysterosalpingography (Luttjeboer *et al*., 2007) is currently under study in an ongoing randomised trial (NCT 00367367) (Geslevich *et al*., 2006). The results of a registered randomised trial on the effectiveness of hysteroscopy before a first ICSI treatment cycle have not been published yet to the best of our knowledge (NCT 00830401).

We included only randomised trials in this systematic review because this provides the least biased measure of the effectiveness of interventions (Benson and Hartz, 2000; Britton *et al*., 1998; Concato *et al*., 2000; McKee *et al*., 1999; Kunz *et al*., 2001; Johnson *et al*., 2008). A recent systematic review of Cochrane reviews on gynaecological surgery demonstrated that the treatment effects tended to be overestimated systematically in trials without allocation concealment, although the difference was not statistically significant (Selman *et al*., 2008). This finding is consistent with the current understanding of the mechanisms of allocation concealment bias (Kunz and Oxman, 1998). A graphical presentation of the risk of bias of all the included studies is presented in Figure 8. A summary of the risk of bias of all the individual trials included in this systematic review is given in Figure 9. Nearly 75% of all studies have an adequate randomisation sequence generation, while nearly 50% have adequate allocation concealment and less than 20% have adequate blinding. The overall quality of the included trials in the present systematic review is by consequence mediocre. Therefore, we should be cautious in making definitive conclusions. At the present we should refrain from providing guidelines for clinical practice in reproductive surgery. It seems more appropriate to present levels of evidence for the different clinical interventions as illustrated in the summary of the effectiveness of the interventions in Table 2.

Most surgical trials will inevitably be at high risk for performance bias resulting from the difficulties with blinding surgeons and patients. Moreover, variation in expertise of surgeons with different surgical procedures is an almost unavoidable confounding variable (Johnson *et al*., 2008), as well as variation in techniques such as the routine use of anti-adhesive barriers. Nevertheless the future holds promise since gynaecological surgery, in contrast to other surgical specialities is being exposed to the scrutiny of RCTs, following the pioneering pathway of reproductive medicine (Johnson *et al*., 2003, 2008; Vandekerckhove *et al*., 1993). Despite the difficulty with the methodology and conduct of RCTs in reproductive surgery, we need to set up adequately

powered and pragmatic multicentre randomised trials studying the effectiveness of reproductive surgery versus no treatment or alternative treatment.

Two possible sources of bias in this systematic review should be addressed. Firstly, the filters for the systematic literature search did not include textwords or MeSH terms for endometriosis, fibroids, polyps and tubal pathology. This might have decreased the sensitivity of our search due to the unintentional omission of smaller trials. A second possible source of detection bias is the fact that our group has already published a narrative review on laparoscopy and a systematic review on hysteroscopy in the treatment of infertility (Bosteels *et al*., 2007, 2010).

An important limitation in the majority of the included trials concerns the choice by the authors to use pregnancy and live birth rates as outcome measures. This is a crude way to assess fertility compared to other parameters such as monthly fecundity rate, cumulative pregnancy rate and time to pregnancy by life table analysis. Future randomised trials on reproductive surgery should not neglect the importance of the time factor in the choice of the most appropriate outcome measure. Moreover, in some clinical settings an 'expectant management' group should be used as a control to study the effectiveness of a surgical procedure as proposed by some authors (Hull *et al*., 1987; Olive *et al*., 1985).

Summary conclusions and future perspectives

Compared to IVF, reproductive surgery has the potential to restore the natural procreation of the subfertile couple leading to several conceptions after one successful intervention. Repeated success can however only be achieved by effective interventions. A randomised controlled trial is the current gold standard of examining the effectiveness of interventions By consequence, clinical research in the field of reproductive surgery should ideally be guided by high quality randomised trials whenever there is uncertainty about effectiveness of a specific surgical intervention.

The evidence provided by the meta-analysis on treating minimal or mild endometriosis in women with unexplained infertility shows a beneficial effect in favour of the excision/ ablation and adhesiolysis, despite the fact that the two major trials show different results. The long term risks versus benefits ratio in treating infertile patients with endometriotic cysts by the excision technique should be addressed, whether or not in the IVF setting.

The use of IVF for tubal pathology at the expense of reproductive surgery should not be continued without adequate randomised trials studying the harms and benefits of both treatments head-to-head.

We need randomised trials studying the effectiveness of the laparoscopic and/ or hysteroscopic removal of intramural fibroids close to the junctional layer of the myometrium or with impression on the uterine cavity in patients with unexplained subfertility and prior to IUI or IVF treatment.

A trial on the effectiveness of hysteroscopic removal of uterine septa in patients with recurrent pregnancy loss is currently ongoing.

The effectiveness of the anti-adhesion barriers in restoring the normal fertility potential in patients with severe intra-uterine adhesions should be studied by randomised trials.

Before promoting hysteroscopy as a screening tool in the infertile population undergoing ART, we should wait for the results of the randomised trial on the effectiveness of hysteroscopy before a first IVF or IUI attempt.

All future RCTs should focus not only on the beneficial short term effects of the intervention, but should address the possible detrimental long term effects on female fertility. This is the only sound way to measure the 'true' effectiveness of a reproductive surgical intervention.

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Contributions of the authors

Jan Bosteels was responsible for coordinating research and writing of this manuscript.

Steven Weyers and Thomas D'Hooghe were involved in the selection of studies and the data extraction process.

Chantal Mathieu, Steven Weyers, Thomas D'Hooghe and Ben Willem Mol critically reviewed this systematic review.

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