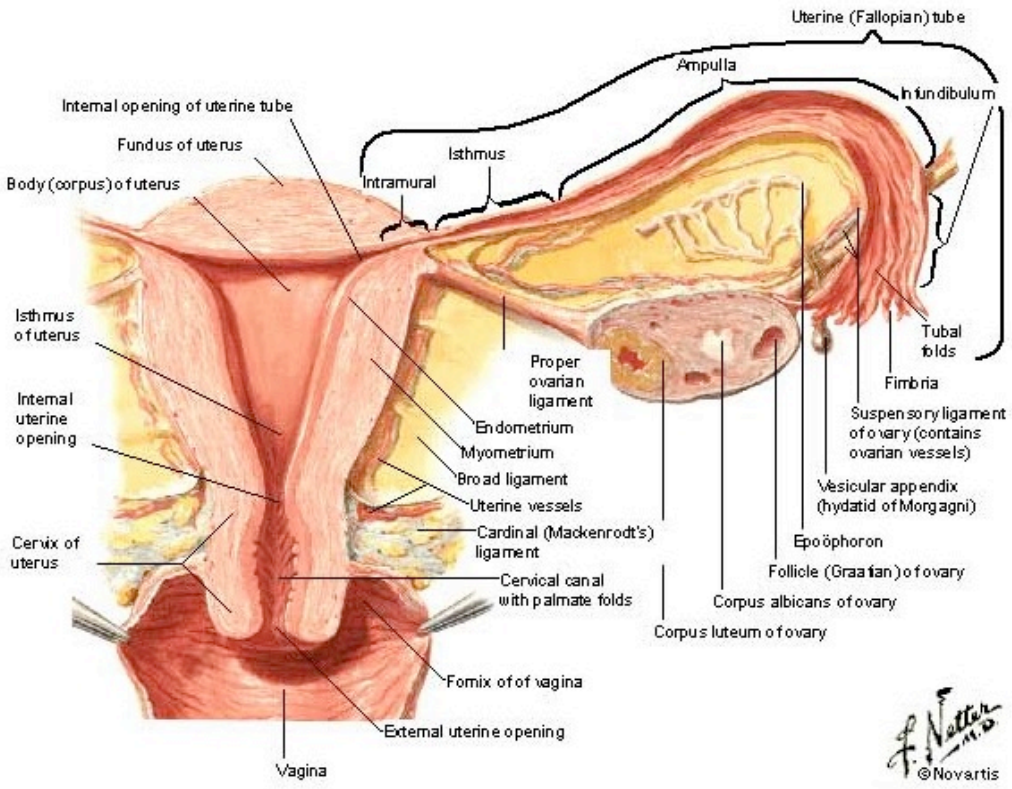
Tubal disease and Infertility

Tim Chang **April 2009**



The fallopian tube is 7-14cm in length connecting the ovary/peritoneal cavity to the uterus.

Functions:

- Mechanical conduit for sperm and egg and zygote transport
- Functional secretion of nutrients, "fertility" factors for egg, sperm interaction, fertiltization and early embryo support

Tubal factor infertility accounts for 30% female factor infertiltiy

Aetiology:

- Infection
  - ascending (Chlamydia/GC anerobes)
    - PID 1-2% females 15-39
    - Incidence chlamydia infection increasing since 1984
    - 2/3 tubal infertility related chlamydia
    - <50% tubal infertility patients have history PID
    - each episode PID increases risk infertility from 10%-20%-40% after 1-2 -3 attacks PID.
  - appendix
- endometriosis
- inflammatory lesions e.g.
  - SIN
  - endometriosis
  - polyps
  - mucous plugs (proximal tubes)
- fibroids especially uterotubal junction

Prognosis depends on:

- location damage
  - proximal 20%
  - distal 80%
- extent of damage
- nature damage eg inflammatory vs iatrogenic
- treatment techniques: microsurgery vs IVF

Classification of tubal disease severity

Variety classifications of tubal disease, but there is no simple system which can give accurate prognosis

Most classifications combine HSG with laparoscopy to give score

Internal architecture of tubes and physiology of the tube is not widely available

Most classifications look at:

- size tube / hydrosalpinx (normal < 15mm)
- rugal pattern on HSG
- adhesions
- state of fimbria
- muscular thickness of tube

	PR	EP
mild	70% vs 10-20% with no treatment	10%
moderate	30-50%	25%
severe	0-15%	>50%

Natural fertility without treatment overall 2-10% after 12 months.

NB:

- large thick walled hydrosalpinx <15% pregnancy rate after tubal surgery therefore IVF better.
- Thin walled hydrosalpinx without mucosal damage at Salpingoscopy 60 -70 % PR cumulative.

Diagnosis of tubal disease

Anatomy vs Function

Laparoscopic chromotubation

- Assess other pathology eg endometriosis
- Good for distal tubal disease and peri adnexal disease
- Current gold standard:
  Prognosis → fecundity rate ratio (FFR):

FRR is a specific form of pregnancy rate ratio, in which the follow-up time is short and equal for both compared groups. FRR of less than one for an item points to a decreased probability of pregnancy for patients with that item

  - 1 side obstructed 0.5
  - 2 sides 0.15

- invasive
- cannot assess intraluminal pathology

HSG

- Good
- Therapeutic effect (tubal flushing):
    - Oil based media have therapeutic effect vs no Rx (RR3 LBR)

Analysis 1.1. Comparison 1 OSCM versus no treatment, Outcome 1 Live birth.

Review: Tubal flushing for subfertility

Comparison: 1 OSCM versus no treatment

Outcome: 1 Live birth

Study or subgroup	OCSM n/N	No treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Johnson 2004	23/73	11/85		100.0 %	2.98 [1.40, 6.37]
Total (95% CI)	**73**	**85**		**100.0 %**	**2.98 [1.40, 6.37]**
Total events: 23 (OCSM), 11 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.82 (P = 0.0048)					

    - Water based media may have similar effect LBR (Oil v Water RR 1.49) but no RCT water vs control
- Water base media give better quality pictures and no granuloma formation
- F (+) up to 50% secondary to spasm
    - Sensitivity 60%
    - Specificity 80%
- fecundity rate ratio (FFR):
    - 1 side obstructed 0.8
    - 2 sides 0.4
- radiation
- pelvic infection rate 1-3%
- intravasation/granuloma/anaphylaxis

Ultrasound

- assess hydrosalpinx
    - sensitivity 80-90% PPV >90%
    - specificity 99% NPV 99%
    - variable accuracy for TOA/pyosalpinx
- other adnexal ovarian uterine pathology
- dating endometrium

Hy-Co-Sy

- Better tolerated HSG
    - Sensitivity 85%
    - Specificity 90%
- Assess other uterine adnexal pathology
- Requires more expertise but no studies inter observer variability
- good intra observer agreement R side > L side
- No evidence therapeutic effect

Salpingoscopy

- Scope through distal end tube to visualize distal tube and ampulla mucosa
- Grade I-V
- assess internal tubal anatomy → better prognostic indicator than laparoscopic assessment for PR outcome if minimal laparoscopic pathology (grade III-V no PR & all PR occur within 12 months procedure)

TABLE 2. Pregnancies According to Laparoscopic and Salpingoscopic Findings

	Grade I	Grade II	Grade III	Grade IV	Grade V
Regular	9	2	0	0	0
Convoluted	6	0	0	0	0
Hydrosalpinx	0	0	0	0	0

NS, χ^2 analysis.

N=91

from Marchino et. al. Salpingscopic and Laparoscopic investigations in relation to fertility outcome. JAAGL 2001: 8: 218-222

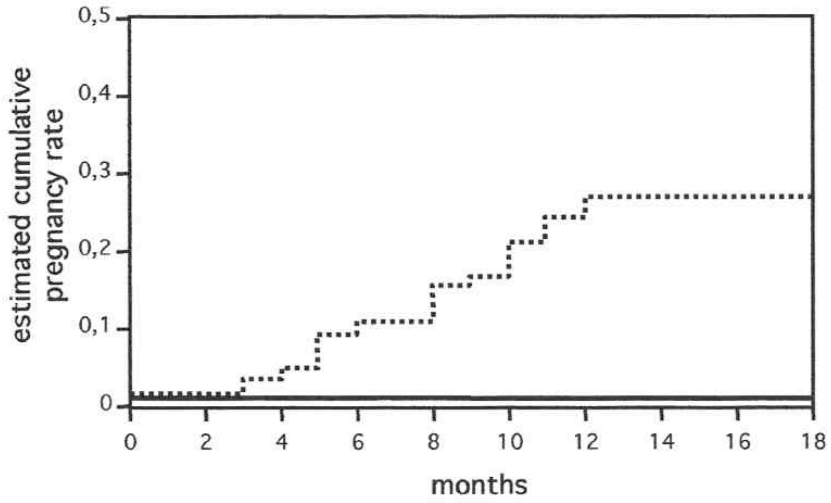


FIGURE 1. Estimated cumulative pregnancy rate in women with salpingoscopy classes I–II (dotted line) and III–V (solid line). Log rank test p <0.05.

Falloposcopy

- Uses hysteroscopy to introduce flexible scope through tubal ostia to assess proximal fallopian tube
- Finding may predict spontaneous pregnancy, but many abnormal findings are of uncertain/doubtful clinical significance
- Therapeutic with 50% recanalisation of blocked proximal tubes
- Successful cannulation 80-90% but good visualization from 30-90%
- Requires specialised instruments and expertise

Anti Chlamydia Abs testing (CAT)

- Non invasive

Sensitivity	60%	for tubal disease
Specificity	80%	vs laparoscopy

- False (-) not all tubal disease caused Chlamydia
- False (+) not all Chlamydia infection is STD related

Fertiloscopy

- Under sedation/?office setting hydrolaparoscopy via POD and hysteroscopy used assess uterus/tubes and ovaries.
- Minor therapeutic procedures can be performed e.g ovarian diathermy, adhesiolysis
- Good agreement for normal findings between fertiloscopy and laparoscopy
- Current role TBD

Selective salpingography and tubal catheterization (SSTC) recommended NICE

- Tubal catheter introduced via cervix into fallopian tubes and contrast agent injected to visualize fallopian tubes and measure tubal pressures
- More accurate than lap/dye in assessing proximal tubes
- 70%-90% procedural success
- Prognostic information with tubal insufflation pressures:
- Therapeutic effect with tubal catheterization (TC)

	good	mediocre	poor
Tubal pressures	<300mm Hg	300-500	>500
4 year cumulative non IVF PR	74%	56%	30%
Following TC 4 yr non IVF PR for initial poor prognosis patients	92%	45%	

- No RCT but a number of observational studies conclude LBR after successful SSTC 10-40% (after 12 months)
- Complications:
    - Perforation up to 10% most require observation
    - Infection
    - Radiation exposure

Classifications of Tubal Disease

TABLE 1

Hull Rutherford AJ Classification 2002

1. Minor (favourable surgical prognosis:≥ 50% over 2 years)
   Tubal fibrosis absent even if occluded (proximally)
   Tubal distension absent even if occluded (distally)
   Mucosal appearances fabourable (e.g. folds evident on salpingography)
   Peritubal-ovarian adhesions flimsy

2. Intermediate (questionable surgical prognosis)
   Unilateral severe tubal damage with or without contralateral minor disease
   'Limited' dense adhesions of tubes otherwise surgically favourable tubes

3. Severe (unfavourable surgical prognosis: ≤ 10% over 2 years)
   Bilateral severe tubal damage
   Tubal fibrosis extensive
   Tubal distension > 1.5cm
   Mucosal appearance abnormal (e.g. folds absent or 'honeycomb' on salpingography)
   Bipolar disease
   'Extensive' dense adhesions (i.e. difficult surgery)

Boer-Meisel et al., 1986 (modified)

Four questions	Four answers	Factor score
1. Is the tube wall thin?	yes	1
	no	2
2. Is the gross condition of the endosalpinx normal?	yes	1
	no	2 or 3
3. Are there many adhesions?	yes	3
	no	1 or 2
4. Are the adhesions fixed?	yes	3
	no	1 or 2

Four "yes" answers – good prognosis (77% conception rate);
Three "yes" answers – intermediate prognosis (21%) conception rate);
Two "yes" answers – poor prognosis (3% conception rate)

Rock et al., 1978

Mild (80% pregnancy rate)
- Absent or small hydrosalpinx < 15mm diameter
- Inverted fimbria easily recognized when patency achieved
- No significant peritubal or periovarian adhesions
- Preopeerative hysterogram reveals a rugal pattern

Moderate (31% pregnancy rate)
- Hydrosalpinx 15-30mm diameter
- Fragments of fimbria not readily identified
- Periovarian or peritubular adhesions without fixation, minimal cul-de-sac adhesions

Severe (16% pregnancy rate)
- Large hydrosalpinx > 30mm diameter
- No fimbria
- Dense pelvic or adnexal adhesions with fixation of the ovary and tube to either the broad ligament, pelvic sidewall, omentum and/or bowel
- Obliteration of the cul-de-sac
- Frozen pelvis (adhesion formation so dense that limits of organs are difficult to define)

Mage et al; 1987

Factors	scoring
Tubal patency	None=0, parial=2, total occlusion=5
Tubal mucosa	Normal=0, decreased= 5, no folds honeycomb=10
Tubal wall (direct exam)	Normal=0, thin=5, thick/rigid=10
Grade 1, 2-5 Grade II 6-10 Grade III 11-15 Grade IV >15	60% pregnancy 40% 9.5% 0%

Surgery for tubal disease

There is NO RCT comparing efficacy of surgery for tubal infertility vs IVF (Cochrane 2007there) and difficult to mount such trials. Despite this, there is evidence tubal surgery is effective in selected cases. Ideally surgery should be performed at the

primary operation and therefore should be performed by surgeons experienced with tubal surgery.

Success of tubal surgery depends on:
- Accurate diagnosis
- Careful selection of patients
- Meticulous microsurgical techniques

Currently tubal surgery cannot correct intratubal damage therefore careful selection of patients is critical in the success of surgery.

Most studies tubal surgery performed before IVF and there is no RCT IVF vs tubal surgery.

Microsurgical techniques from nonRCT show improved outcomes vs macrosurgical techniques especially proximal tubal surgery

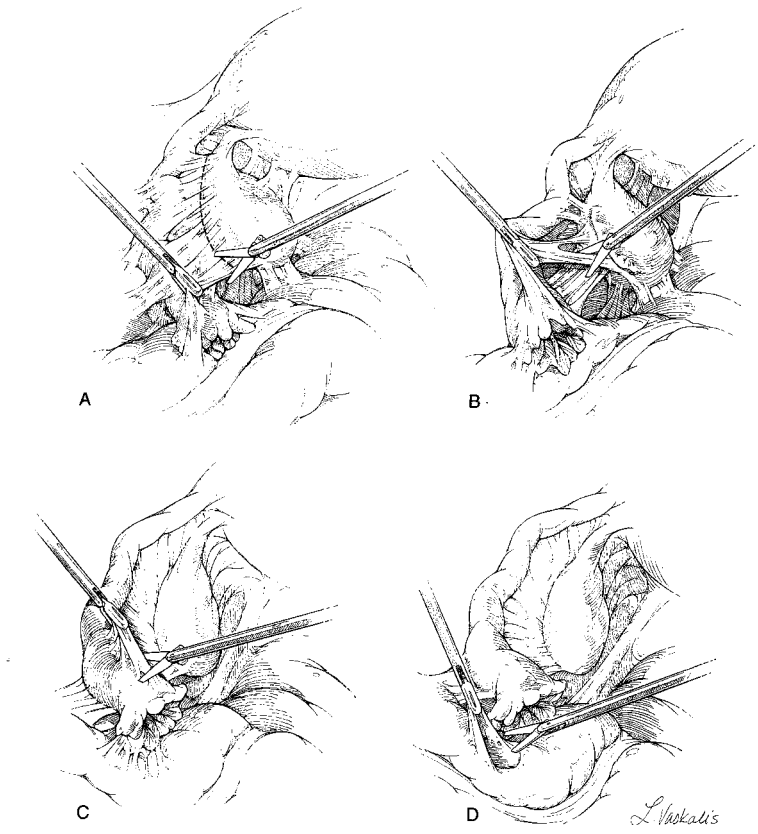
No Evidence open microsurgery vs laparoscopy for treatment tubal disease. Some surgeries eg salpingolysis, are easily adopted, but others e.g cornual anastomosis, are more difficult to perform.

Microsurgical technique principles
Surgical philosophy / attitude
(1) magnification
(2) constant irrigation to avoid desiccation
(3) meticulous haemostsis
(4) minimal tissue handling/injury
(5) complete excision of abnormal tissue and precise tissue alignment
microsurgical techniques equally applicable laparoscopy
- magnification
- closed environment with warmed humidified CO2
- delicate instruments

Operative procedures:
Distal tube disease
Microscopic techniques slightly improve PR (over variable timeframe)
Represents 80% tubal disease

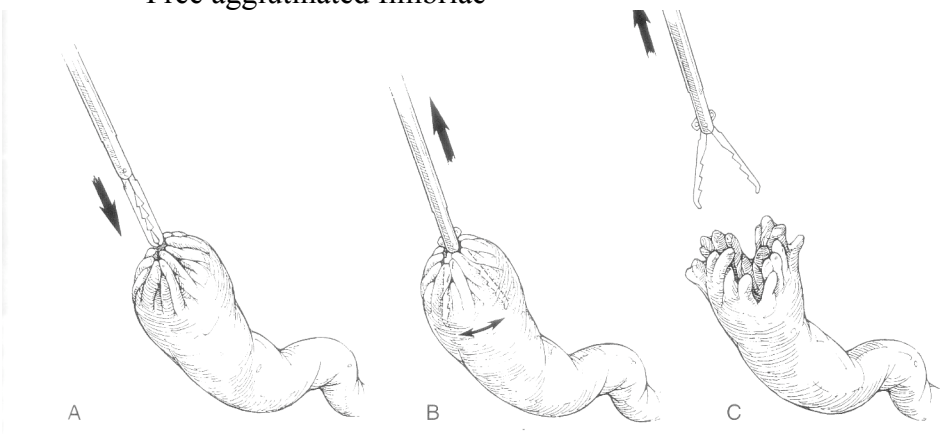
Salpingo-ovariolysis
Periadnexal adhesions often associated other tubal disease, but can be isolated
ideally performed at time of initial laparoscopy

- PR 50-60% vs 15%-20% PR without treatment (RRx3) non-RCT evidence
- EP 5-10%
- Laparoscopy leads to similar results but there are no RCTs
- No difference with/without use laser

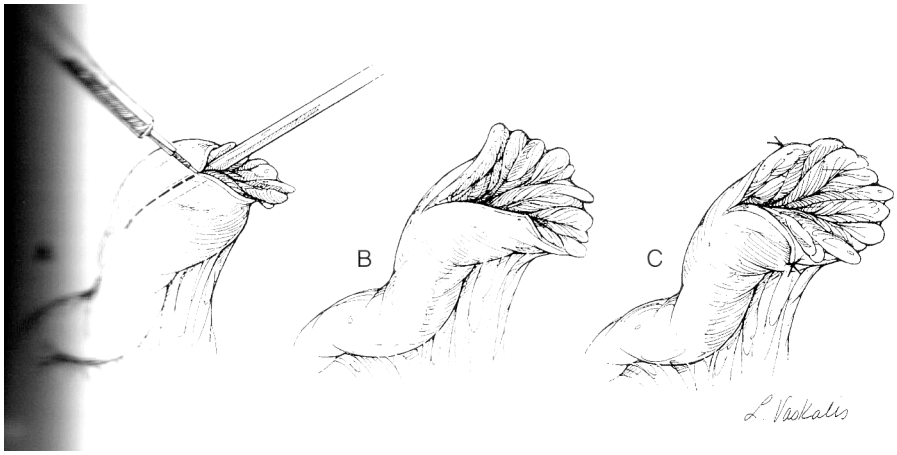


Fimbroplasty
Open microscopic
Reconstruction of fimbriae:

- Free agglutinated fimbriae



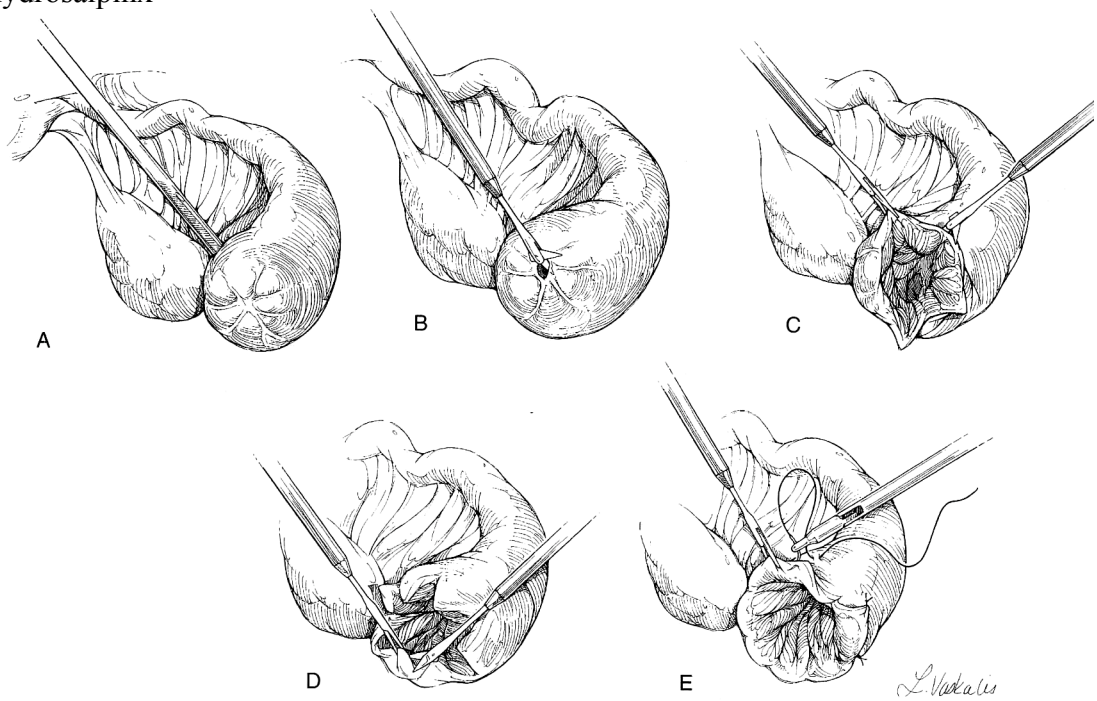
- Correction phimosis



Usually performed conjunction with salpingolysis and salpingostomy, therefore results of isolated fimbrioplasty performed independently are few:

- PR 60% vs 40% macroscopic techniques
- EP 5% vs 15%
- Laparoscopic techniques comparable to microscopic but EP up to 15%

Salpingostomy (terminal)
Creation of new stoma from completely occluded fallopian tube, often associated with hydrosalpinx



overall PR = 20-30% in selected cases from cases series of experienced fertility centres

For isolated distal occlusion (mild/moderate tubal disease only)
Success depends on:

- pre existing tubal damage
- Extent of adhesions

PR Mild 40-60%
Severe <20%
EP 10-20%

laparoscopic approach yields PR 15-30% but NO RCT open vs laparoscopic
Many opt IVF if severe distal damage as conception rate < 20%

Tubal re-anastomosis

- Reversal sterilization
- Distal tubal disease

Incidence reversal sterilization 1-2%

- Early age sterilization <30yrs
- Change marital status
- Death of child / lower SES etc

Success depends on:

- length of tube length (cm) = PRx10 (min 4 cm of tube: no PR <4cm)
- co existing pathology esp rule out male factor
- age female
- type of sterilization (Filshie clips vs bipolar diathermy)
- microsurgical approaches improve PR but no RCT

laparotomy selected cases PR 55-90%

TABLE 1. Outcomes of Tubal Ligation Reversals Performed by Laparotomy: Selected Large Patient Series

Authors	n*	Mean Age	Follow-up	Pregnancy Rate	Ongoing Pregnancy/Delivery Rate	Ectopic Rate†
SH Kim et al[8]	922	31.8	>5 yrs	55%	45%	5%
JD Kim et al[9]	364	32.4	≥1 year	90%	82%	2%
Dubuisson et al[10]	206	35.2	≥2 years	70%	NS	2%
DeCherney et al[11]	124	NS	≥18 mo	74%	58%	6%
Gomel[12]	118	NS	≥18 mo	64%	55%	1%

NS = not stated
* Includes only patients available for follow-up
† The denominator is the total number of women having tubal ligation reversal

laparoscopy yielded slightly lower PR 31-78% depending on technique

*TABLE 2. Outcomes of Laparoscopic Tubal Ligation Reversals**

Authors	n†	Mean Age	Length of Follow-up	PR	Ongoing/Delivery Rate	Ectopic Rate
Yoon et al[17]	49	33.5	≥1 yr	78%	73%	2%
Barjot et al[18]	16	35.5	≥6 mo	31%	25%	5%
Dubuisson et al[19]	32	NS	NS	59%	41%	6%
Bissonette et al[20]	98	NS	≥15 mo	70%	50%	7%
Stadtmauer & Sauer[21]	14	34	6 mo	43%	36%	0

NS = not stated; PR = pregnancy rate
* Published series of 10 or more patients
† Includes only patients available for follow-up

most pregnancies occur within 12 months
no successful delivery for women >43years
EP 1-7%
No RCT evidence tubal reversal vs IVF (Cochrane 2006)

Proximal tubal disease
20% tubal infertility
micro surgical techniques significantly improve conception rate
interstitial obstruction causes:

- infection/inflammatory
- SIN
- Mucous plugs/polyps/synechiae
- Tubal endometriosis

Tubo cornual anastomosis
In selected cases by experienced centres

Microsurgical	PR 40-60%	with EP 5-10%
Macrosurgical	PR 15-25%	

Selective Salpingography with Transcervical Catheterization (SSTC)

- 90% cannulation of at least 1 tube
- 85% occlusions overcome
- 50% reocclusion rate
- 10-40% LBR
- 10% perforation rate

No role in tubal re-implantation (conception rate<20%)

If concomitant proximal + distal disease pregnancy rates extremely poor

Failed tubal surgery
Except in rare circumstances should microsurgical procedures be repeated in failed cases as the success<20% eg

- failure for technical reasons esp if initial surgery was done with non-microsurgical techniques.

Adhesion prevention

No RCT looking at fertility as outcome in studies
Aim is to prevent fibrin bridges between healing tissues.
Endogenous fibrinolytic is plasminogen activator.

Injury → inflammatory exudates with fibrin → fibroblast invasion & collagen deposition then → 1 of 2 responses

a) plasminogen activation → lysis of adhesions and resolution
b) Release proinflammatory cytokines → inhibition plasminogen activation → adhesion formation

Modes to prevent adhesions

- Surgical technique
  Microsurgical principles
- Liquids to separate healing tissue
- Solid barriers to separate damaged / healing tissue
- Pharmacological agent to prevent/reduce inflammatory / cytokine response
  eg. NSAID Heparin Dipyridamole
- Products to stimulate fibrinolytic activity
  eg. t-PA
- Second look laparoscopy / surgery

liquid

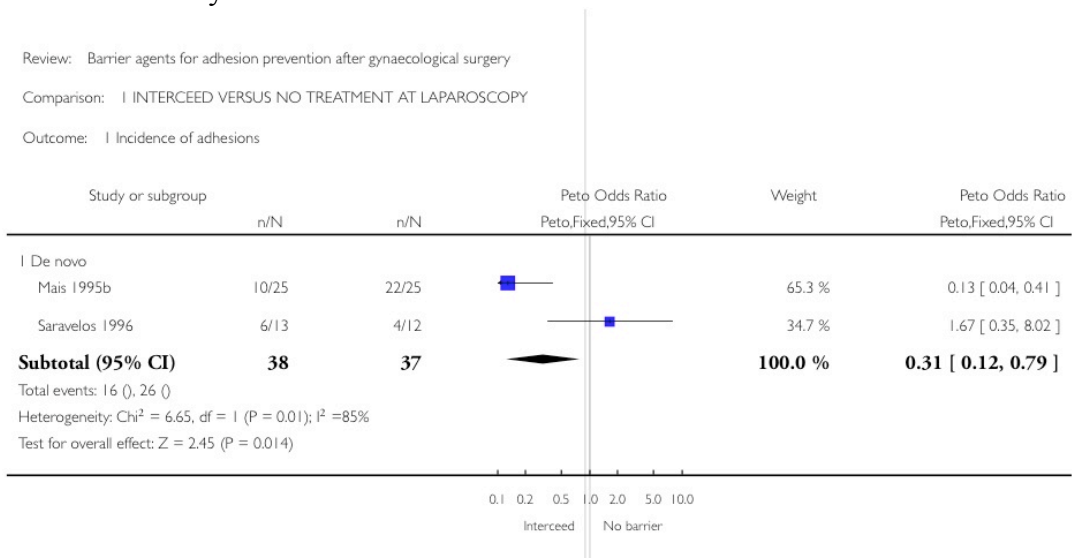
- crystalloid
  little use as fluid is reabsorbed within 24 hours.

- dextran 70
  some effect on decreasing adhesions in limited studies but SE:
  - oedema and increased fluid retention
  - abnormal LFTs
  - DIC and anaphylaxis
- hyaluronic acid
  human tissue oil
  commercial preparations:
  - intergel (withdrawn)
  - hyalobarrier
  - hybrid liquids

  limited evidence in reducing adhesions at second look laparoscopy (RR 0.31)
- icodextrin 4% (Adept)
  1 RCT vs Hartmanns showed reduction adhesion score
- Spraygel
  Hydrogel from 2 polyethylene based liquids are mixed
  No clinical data

Barriers

- oxidized regenerated cellulose (interceed)
  - ovarian surgery reduced adhesions in >50% vs controls (all types)
  - tubal surgery reduced adhesions in >50% vs controls
  - useful in reducing adhesion formation after endometriosis surgery and adhesiolysis



directions for use:

- complete haemostasis imperative (if interceed→black=>bleeding)
- remove all fluid
- large single layer that overlaps the desired area

more recent use of double layer surgical equally effective as interceed

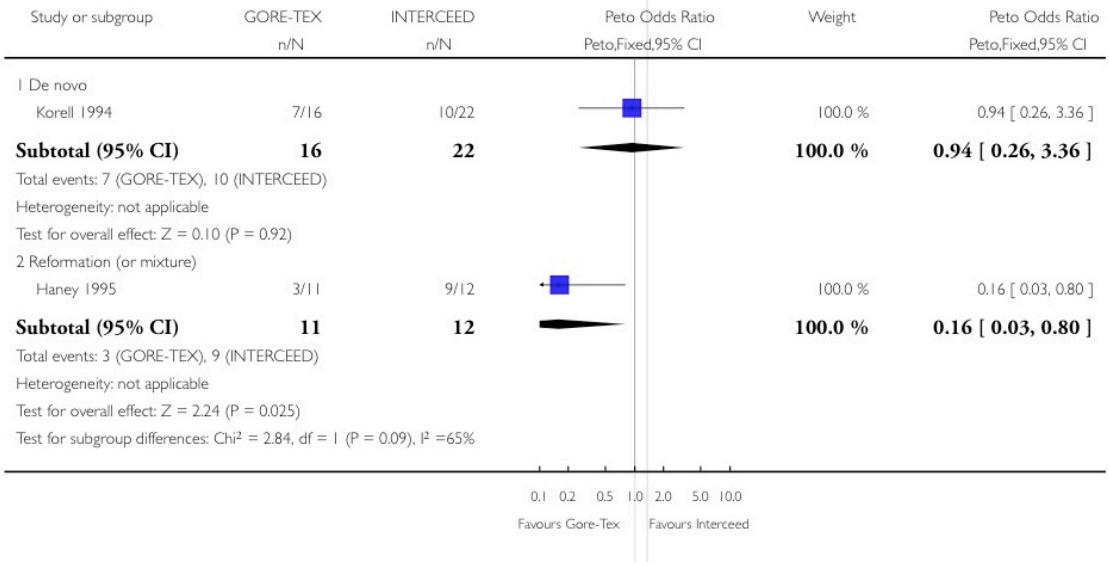
- polytetrafluoroethylene (Preclude or Gore-Tex)
    - non absorbable needs to be removed at second surgery
    - needs to be sutured
    - decrease adhesion formation and maybe better than interceed

Analysis 5.1. Comparison 5 GORE-TEX VERSUS INTERCEED, Outcome 1 Incidence of adhesions.

Review: Barrier agents for adhesion prevention after gynaecological surgery

Comparison: 5 GORE-TEX VERSUS INTERCEED

Outcome: 1 Incidence of adhesions



- seprafilm
  membrane of hyaluronic acid in carboxymethylcellulose which is bioresorbable up to 28 days, adheres to moist surfaces & turns into gel after 24 hours
  little evidence of efficacy and difficult to manipulate.

Anti inflammatory agents

Antibiotics / Steroids / Heparin / NSAIDs are often used but are not proven
Sildenafil and statins have been used in animal models

Second look laparoscopy

4 – 12 weeks post op to lyze soft adhesions
Exact role TBD but maybe useful if previously extensive adhesions or extensive surgery performed, however to date there is no evidence that it improves pregnancy rates or pain outcome.

Hydrosalpinx & ART

Hydrosalpinx does have negative impact on IVF success:

- reduced PR 50% vs controls
- Increase miscarriage x2

Mechanism: 1. mechanical flushing effect (most likely)
Treatment of unilateral hydrosalpinx can improve natural fertility
2. embryo toxic
3. inflammatory process damaged endometrium/tubal factors

Diagnosis & Assessment:

- U/S diagnose fluid filled tubes
- HSG
- Laparoscopy
- Salpingoscopy/falloposcopy → most accurate

Treatment of hydrosalpinx

Tubal Microsurgery

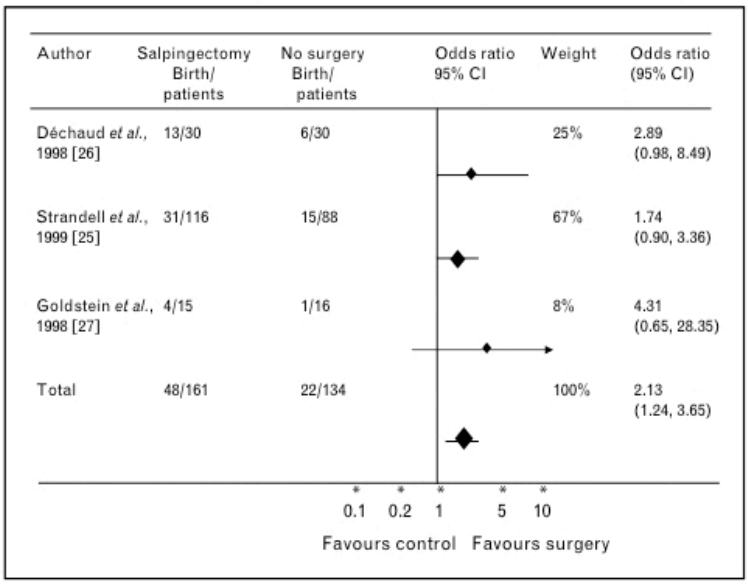
Salpingostomy/neosalpingostomy
Highly selected cases may yield 40-60%PR

IVF

need to block / remove HF prior to IVF

- **Salpingectomy**
  Evidence RCT Hydrosalpinx treated by
  Salpingectomy → delivery rate 40% vs 20%
  Cochrane 2006

Figure 1 Meta-analysis from a systematic review of randomized controlled trials, examining the effect on birth rates of pre-in-vitro fertilization salpingectomy compared with no surgery in patients with hydrosalpinx



CI, Confidence interval. Copyright Cochrane Collaboration, reproduced with permission.

Concern salpingectomy → negative impact ovarian function due to vascular compromise (study results mixed) but when performing salpingectomy → stay as close to tube as possible.

Studies also show cost effectiveness of Bilateral salpingectomy prior to IVF

- **Tubal ligation ± distal fenestration**
  Small amount retrospective evidence to support this treatment
  Maybe indicated if dense adhesions or laparoscopy CI
  Distended tubes may become symptomatic

Table 2 Clinical pregnancy rates per embryo transfer in three retrospective studies comparing tubal ligation and salpingectomy with no surgery in hydrosalpinx patients, before in-vitro fertilization

Authors, publication year	Salpingectomy *n/n* (%)	Tubal ligation *n/n* (%)	No surgery *n/n* (%)
Murray *et al.*, 1998 [45]	9/23 (39)	9/15 (60)	4/47 (8.5) $P < 0.05$
Stadtmauer *et al.*, 2000 [37]	7/15 (47)	22/30 (73)	2/15 (13) $P < 0.05$
Surrey and Schoolcraft, 2001 [39]	16/28 (57)	7/15 (47)	–

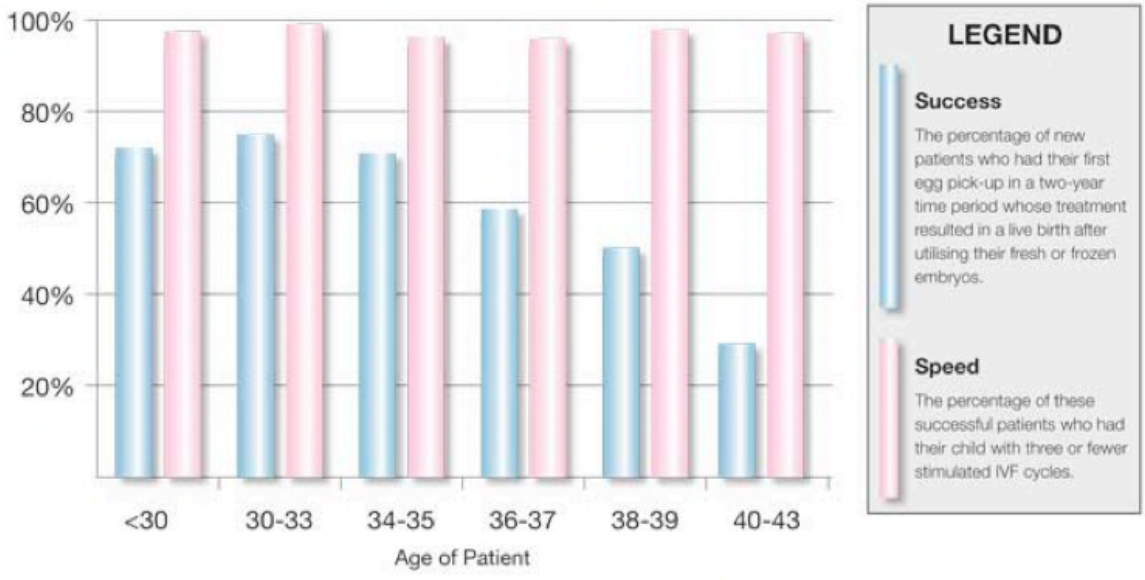
- **Aspiration of fluid**
  HF usually re-accumulates
  If hydrosalpinx noted at time of OPU, probably better to freeze all embryos and treat hydrosalpinx, then do CET

Table 3 Clinical pregnancy rates per embryo transfer in two retrospective studies on transvaginal aspiration of hydrosalpingeal fluid before in-vitro fertilization, including only first cycle

	Treatment group		
Authors, publication year	Aspiration *n/n* (%)	No aspiration *n/n* (%)	*P* value
Sowter *et al.*, 1997 [48]	6/30 (20.0)	3/18 (16.7)	1.0
Van Voorhis *et al.*, 1998 [49]	5/16 (31.3)	1/18 (5.6)	0.13

IVF vs tubal surgery

IVF becoming more successful, tubal surgery has been relegated.



from SIVF website 2009

Cochrane review 2008 no RCT IVF vs tubal surgery and difficult to mount RCT because:

- no simplified classification tubal disease accurately reflects prognosis
- improving IVF success rates
- outcomes depends on:
    - surgical expertise, which is diminishing
    - difficulty in blinding
    - poor financial support

(1) Age
Majority of pregnancies occur within 24 months after surgery
In the older female IVF probably a better option

(2) Other infertility factors
IVF more successful if multiple infertility factors are present

(3) Extent tubal disease
If success of surgery ≥ conception after 3 cycles IVF, then surgery is worthwhile e.g <35 years delivery rate after 3 cycles IVF is 80-90%

(4) Cost

(5) Patient desires and philosophy esp concern adverse obstetric outcome with IVF

Combined approach may be feasible with tubal surgery in good prognosis patients (most PR occur within 12 months of surgery) supplemented by cycles of IVF esp hydrosalpinx

Salpingitis Isthmica Nodosa (SIN)
Incidence 0.5 – 10%
↑ blacks
inflammatory lesions in the proximal tube (isthmic)
Characterized by:

- isthmic diverticula
- outpouching tubal epithelium
- hypertrophy surrounding muscle

Aetiology: (not proven)

- congenital mesonephric duct cells (evidence not strong)
- infection
- adenomyosis – like process
- neoplastic
- chronic tubal spasm

Diagnosis

- histopath (gold standard)
- HSG → characteristic tubal out pouching
- falloposcopy

It is a progressive disease

Associated with:

- E/P
- infertility

Treatment

- microsurgery resection + tubocornual anastomosis
- IVF

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