PRE-CONGRESS COURSE 4

The fallopian tube and reproductive function

Special Interest Group Endometriosis / Endometrium
Munich - Germany, 29 June 2014
The fallopian tube and reproductive function

Munich, Germany
29 June 2014

Organised by
The ESHRE Special Interest Group Endometriosis/Endometrium
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Course coordinators

Hilary Critchley (United Kingdom; past SIGEE co-ordinator), Andrew Horne (United Kingdom; deputy SIGEE coordinator), Anneli Stavreus-Evers (Sweden; past deputy SIGEE coordinator), Antoine Watrelot (President, International Society for Fallopian tubes and Reproductive Surgery)

Course description

Basic science and clinical content addressing:
- what we know about normal Fallopian tube function
- what animal models we have available to study Fallopian tube biology
- emerging data about Fallopian tube origins of ovarian cancer
- the effects of environmental factors on Fallopian tube function – the Fallopian tube and pregnancy failure
- clinical approaches to the regulation of Fallopian tube function. Future research priorities will be proposed by each speaker for discussion at the end of each presentation

Target audience

Basic scientists and clinicians
Scientific programme

Chairmen: Antoine Watrelot – France and Hilary Critchley - United Kingdom

09:00 - 09:30 Normal fallopian tube function
Anneli Stavreus-Evers - Sweden

09:30 - 09:45 Discussion

09:45 - 10:15 Modelling the fallopian tube: lessons from animal models
Håkan Billig - Sweden

10:15 - 10:30 Discussion

10:30 - 11:00 Coffee break

11:00 - 11:30 The fallopian tube as the origin of ovarian cancer
Stephen G. Hillier - United Kingdom

11:30 - 11:45 Discussion

11:45 - 12:15 The effect of the environment on Fallopian tube function
Andrew Horne - United Kingdom

12:15 - 12:30 Discussion

12:30 - 13:30 Lunch

Chairmen: Ertan Saridogan - United Kingdom and Andrew Horne - United Kingdom

13:30 - 14:00 Tubal pregnancy
Stephen Tong - Australia

14:00 - 14:15 Discussion

14:15 - 14:45 Tubal hydrosalpinx and embryo implantation
Annika Strandell - Sweden

14:45 - 15:00 Discussion

15:00 - 15:30 Coffee break

15:30 - 16:00 Fertility control: laparoscopic versus hysteroscopic tubal obstruction
Justin Clark - United Kingdom

16:00 - 16:15 Discussion

16:15 - 16:45 Management of tubal pregnancy: salpingectomy versus salpingostomy
Femke Mol - The Netherlands

16:45 - 17:00 Discussion

17:00 - 18:00 Business meeting SIG Endometriosis and Endometrium
MANAGING ENDOMETRIOSIS: THE APP

AT YOUR FINGERTIPS
All you need to know about endometriosis is now at your fingertips:
• interactive decision-aid
• easy access to the guideline
• links to background information
Based on the ESHRE Guideline on the Management of Women with Endometriosis.

TRY THE APP NOW!
Download the app for free during the 2014 ESHRE Annual Meeting (Access from 28 June to 6 July 2014), using the access code "ESHRE2014"
Visit www.eshre.eu/guideline/endometriosis or scan the QR code below.
The ESHRE endometriosis App is freely accessible for ESHRE members.

LAUNCH SESSION
Want to know everything about the endometriosis app?
Take part in the launch session with ESHRE: Monday 30 June - 12:00 to 13:00, room 2
Normal Fallopian tube function

Anneli Stavreus-Evers
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Department of Women’s and Children’s Health
Uppsala University
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Conflict of interest

• I declare no conflict of interest

Learning objectives

• Fallopian tube morphology
• Hormonal regulation of the Fallopian tube
• Function of the Fallopian tube
The Fallopian tube

- Fallopian tube, oviduct, uterine tubes, salpinx (salpinges, greek for trumpet)

Oviduct -- the non-mammalian equivalent

The Fallopian tube

- Gabrielle Fallopio
- 1561, Italy

Believed function:
Simple connection between the uterus and the ovary

The Fallopian tube

- Isthmus
- Ampulla
- Infundibulum
- Fimbriae
Cross section of the Fallopian tube

(A) infundibulum, (B) ampulla and (C) isthmus

Tubal transport

• Contractions by musculature
• Ciliary activity
• Flow of tubal secretion

Ciliated cells

• Cilia reach peak activity at the time of ovulation
• Estrogen increases cilia formation
• Cilia disrupt and remove cumulus mass
• Prostaglandins stimulate cilia beat frequency
Peg cells
- Peg cells produce follicular fluid
- Progesterone increases the number of peg cells

Tubal fluid
- Secreted towards fimbriae - against action of cilia
- Provide nutrients for spermatozoa, oocyte and zygotes
- Promote capacitation by removing glycoproteins from the plasma membrane of the sperm

Muscular layers (Subserosa)
- The outermost sheath has longitudinal muscular fibers
- The middle layer has circular muscular fibers
- The innermost layer has spirally arranged muscular fibers

http://legacy.owensboro.kctcs.edu/gcaplan/anat2/histology/histo%20c%20female%20reproductive.html
Estrogen receptors, progesterone receptors and prostaglandin receptors

ERα (red) and ERβ (green)

PR

Tubal contractility after treatment

Functions of the Fallopian tube

- Transport the sperm from the uterus to the site of fertilization
- Facilitate optimal milieu for the sperm and aid in capacitation
- Moving the embryo using muscular contractions and movement of the cilia
- A period of residence in the tube seem to be a requisite for full development of the embryo
- Signaling between the embryo and the maternal side
Sperm binding to the Fallopian tube

- Sperm reach the Fallopian tube in one hour
- The reservoir in the isthmus is receptor mediated
- The binding makes the sperm viable for longer time
- The binding might delay sperm transport
- Capacitation is promoted

Fertilisation and transport of the embryo to the uterine cavity

Leukaemia inhibitory factor (LIF)

- Maternal LIF is essential for implantation in mice
- LIF and its receptors are expressed in the human embryo, endometrium, and Fallopian tube
Expression of LIF in the human Fallopian tube

Expression of LIFR and gp130 in human Fallopian tube

LIF receptors in Human embryo
Signaling in the Fallopian tube

Embryo
Ovary
Endometrium

hCG
P

HER1/HER4

HB-EGF

LIFR

YHLR

PR

TNF

α(-)

P

COX(+)

hCG/LH receptor

P

(-)

hCG

PR

(+)

Thank you

References

- Holt and Fazeli Molecular Reproduction and Development 2010, 77 934-943
- Suarez and Pacey, Hum Rep Update, 2006 12, 23-37
- Holt and Fazeli Molecular Reproduction and Development 2010, 77 934-943
Modelling the fallopian tube: lessons from animal models – Håkan Billig (Sweden)

Contribution not submitted by the speaker
Learning Objectives

At the conclusion of the lecture, the audience should be aware of the incidence and lethality of epithelial ovarian cancer and be able to:

- Discuss theories of ovarian cancer pathogenesis.
- Summarize evidence for fallopian tube as a source of serous ovarian and peritoneal cancers.
- Appraise controversies linking reproductive factors and ovarian cancer.

Conflict of Interest Statement

The presenter has no conflict of interest to declare concerning the subject or content of this lecture.
Ovarian Cancer

• Metrics
• Mechanisms
• Mysteries
Ovarian cancer metrics

- 5th most common cause of cancer death
- 30% cure rate
- Life-time risk 1:65 (1.5%) by age 75
- Approx. 10-15% cases associated with identified hereditary abnormality
- BRCA1 or BRCA2 mutations are most common

EOC Risk Factors

- Age
- Family history
- Reproductive factors
- Lifestyle
- Height and body weight
- Diet
- Medical conditions, procedures and medications
- Talcum powder
- Asbestos
EOC Risk Factors

- Reproductive factors
  - Pregnancy: reduced
  - Breastfeeding: conflicting
  - Infertility: increased
  - Oral Contraceptive: reduced
- Medical conditions
  - Breast density: increased
  - HRT: increased
  - Endometriosis: increased
  - Ovarian cysts: increased
  - Hysterectomy: reduced
  - Tubal sterilisation: reduced
  - NSAIDs: conflicting
  - Paracetamol: conflicting
  - Diabetes: increased

Ovarian Cancer

- Metrics
- Mechanisms
- Mysteries

Ovarian cancer pathogenesis

- Incessant ovulation hypothesis: Fathalla, 1971
  - Ovulation traumatises the OSE such that chance of error occurring during cell division increase

- Gonadotrophin hypothesis: Cramer & Welch, 1983
  - Excessive gonadotrophin exposure increases oestrogenic stimulation of OSE

- Hormonal hypothesis: Risch 1998
  - Excessive androgen stimulation of the OSE increases OC risk while progesterone is protective
Ovulation as Injury

Ovulation as Inflammation

From ovulation to cancer:

Okamura et al 2003
Familial ovarian cancer history

Ovarian cancer characterised by ultrasound

Ovarian Cancer [Cancer Research UK]
- 4th most common cancer among women in UK
- 7,000 cases each year
- 90% cases arise in the ovarian surface epithelium
- Incidence correlates with duration/frequency of ovulation
- Prolonged use of fertility drugs might be adverse
68% serous
13% clear cell
9% endometrioid
3% mucinous
Soslow (2008); McCluggage (2011)

The distal fallopian tube is emerging as an established source of many early serous carcinomas in women with BRCA mutations (BRCA-+). Protocols examining the fimbrial (SEE-FIM) end have revealed a noninvasive but potentially lethal form of tubal carcinoma, designated tubal intraepithelial carcinoma. Tubal intraepithelial carcinoma is present in many women with presumed ovarian or peritoneal serous cancer. A candidate precursor to tubal intraepithelial carcinoma, entitled the 'p53 signature', suggests that molecular events associated with serous cancer (p53 mutations) may be detected in benign mucosa.

Origins of ovarian cancer

Origins of ovarian cancer

Origins of ovarian cancer
Inflammation-associated gene expression in human peritoneal cells


Fallopian tube (FT) origin of ovarian cancer?

- Occult FT cancers occur in 4.4% of BRCA1 and BRCA2 positive women – Finch et al 2006
- Fimbriae of distal FT are most common sites of serous adenocarcinoma in BRCA-positive women – Medeiros et al 2006
- Precursor lesions for HG pelvic serous cancers are present in FT of high-risk women – Lee et al 2007
- p53 mutation and dysfunction occurs in HGSOC and STIC – Ahmed et al 2010
- p53 'signatures' occur in morphologically normal FT – Crum et al 2007
- Identical p53 lesions in STIC and adjacent HGSOC – Kuhn et al 2012
- Distal FT has twice the no. stem-like epithelial cells than proximal FT – Paik et al 2012

Fallopian tube is the origin of high-grade serous carcinomas in Dicer-Pten DKO mice

Nonovarian origins of ovarian cancer

Hilar region of the ovary is an area of epithelial transition that is vulnerable to malignant transformation, very much like the transition zone of the cervix.

During ovulation, tubal epithelial cells from the fimbriae implant on the denuded surface of the ovary, resulting in the formation of inclusion cysts that become transformed in the ovarian microenvironment.

Both ovary and fallopian tube as potential sources of ovarian cancer?

- Hilar region of the ovary is an area of epithelial transition that is vulnerable to malignant transformation, very much like the transition zone of the cervix.

- During ovulation, tubal epithelial cells from the fimbriae implant on the denuded surface of the ovary, resulting in the formation of inclusion cysts that become transformed in the ovarian microenvironment.

Ovarian surface epithelium at the junction area contains a cancer-prone stem cell niche


Hilum cells show preferential transformation after conditional inactivation of Trp53 and Rb1


Ovarian Cancer

- Metrics
- Mechanisms
- Mysteries
## EOC Risk Factors

- Reproductive factors
- Medical conditions

<table>
<thead>
<tr>
<th>Factor/Condition</th>
<th>Effect on EOC risk</th>
</tr>
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<tbody>
<tr>
<td>Pregnancy</td>
<td>reduced</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>conflicting</td>
</tr>
<tr>
<td>Infertility</td>
<td>increased</td>
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<tr>
<td>Breast density</td>
<td>increased</td>
</tr>
<tr>
<td>Oral Contraceptive</td>
<td>reduced</td>
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<tr>
<td>HRT</td>
<td>increased</td>
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<tr>
<td>Endometriosis</td>
<td>increased</td>
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<tr>
<td>Ovarian cysts</td>
<td>increased</td>
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<tr>
<td>Hysterectomy</td>
<td>reduced</td>
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<td>reduced</td>
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<tr>
<td>NSAIDs</td>
<td>conflicting</td>
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<td>Paracetamol</td>
<td>conflicting</td>
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<tr>
<td>Diabetes</td>
<td>increased</td>
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### Fallopian tube as the origin of ovarian cancer

- Tubal ligation reduces ovarian cancer risk  

- How?  
DNA damage is enhanced in FT epithelium exposed to follicular fluid (FF)

Model for ovarian cancer origination in distal fallopian tube

How could tubal ligation reduce ovarian cancer risk?

(a) screening effect
(b) alteration of ovarian function
(c) a mechanical barrier against ascending carcinogenic agents
(d) prevention of endometrial and proximal Fallopian tube cell ascent
Conclusions:

• Distal fallopian tube epithelium is a likely source of ovarian carcinoma, as is ovarian surface epithelium.

• Ovarian carcinoma, fallopian tube carcinoma, peritoneal carcinoma could be a single disease entity.

• "Tackle one, tackle them all".

Acknowledgements

Mick Rae          Hilary Critchley          Peter Ghazal
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Chris Harlow      Alistair Williams       Catherine Murray
Oliver Gubbay     Sharon McPherson        Joo Thong
Wei Guo           Scott Fegan

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Medical Research Council
European Commission FPV
Learning objectives

• Understand what biological factors are important for normal tubal function
• Understand the potential mechanisms explaining how environmental factors interfere with normal tubal function
Cigarette smoking

• 19% (23% in Scotland) of adult women are regular cigarette smokers
• Smoking has been identified as a major risk factor for ectopic pregnancy
• Majority of published studies support a dose dependent increase in ectopic pregnancy in women who smoke
• The biological mechanisms through which cigarette smoke increases the likelihood of ectopic pregnancy remain unclear

Endocannabinoids are multifunctional fatty acid amides that are thought to play a pivotal role in regulating embryo-tubal transport. In the mouse, silencing of cannabinoid receptor 1 (CB1) results in tubal embryo retention. CB1 is expressed in human Fallopian tube smooth muscle and epithelium. Ectopic pregnancy is associated with reduced expression of CB1 in human Fallopian tube.


Endocannabinoid system (ECS)

- CB1 expression is largely restricted to ciliated epithelial cells.

- Smoking is associated with a reduction in percentage of Fallopian tube epithelial cells that express CB1.
**Prokineticins**

- Prokineticin 1 (PROK1) signalling via prokineticin receptor 1 (PROKR1) regulates the expression of several genes with important roles in endometrial receptivity and implantation.
- PROKR1 is expressed in the epithelium and smooth muscle of non-pregnant Fallopian tube.
- PROKR1 mRNA is altered in Fallopian tube of women with ectopic pregnancy.

**Tubal PROKR1 expression and smoking**

- Graph showing the relative expression levels of PROKR1 in non-smokers and smokers.
- Bar graph showing the effect of different nicotine treatments on PROKR1 expression.

*Shaw et al., Am J Path 2010*
Nicotinic acetylcholine receptor (-7 expression in human Fallopian tube

Cotinine increases tubal PROKR1 via nAChR-7

Cotinine increases tubal PROKR1 via nAChR-7
Dysregulated smooth muscle activity
Increased receptivity to embryo
Impaired tubal transport
Ectopic pregnancy
Cigarette smoking
Cotinine
PROKR1
AChR α7
Dysregulated ciliary activity
Impaired tubal transport
Ectopic pregnancy
"omics technology"
The role of BAD

CELL DEATH

Cleavage of substrates

Procaspsase 3 → Caspase 3

Caspase 9

Procaspsase 9

BAD

Bcl-2

BAD and Bcl-2 expression in Fallopian tube

BAD and Bcl-2 expression in Fallopian tube of smokers
Caspase expression in Fallopian tube of smokers

Expression of proliferation markers in Fallopian tube of smokers

Structural changes in the Fallopian tube of smokers
Chlamydia trachomatis infection

- Most common bacterial sexually transmitted infection worldwide
- Epidemiological studies indicate that pelvic C. trachomatis infection is a major risk factor for ectopic pregnancy
- The delineation of role of C. trachomatis infection in ectopic pregnancy has significant public health implications, particularly in relation to the screening programmes
- The mechanism by which past C. trachomatis infection leads to tubal implantation is not understood and does not appear to be a direct consequence of tissue destruction by the organism


Life cycle of Chlamydia trachomatis

http://blacksad.immunology.org/pathogens-disease/chlamydia-trachomatis
**Prokineticins and *Chlamydia***

* PROKR2 mRNA expression levels were significantly increased in OE-E6/E7 cells treated with live *C. trachomatis* and UV-killed *C. trachomatis* after 8 hours of treatment.

Shaw et al. Am J Path 2011

**TLR2**

Fallopian tube

OE-E6/E7 cells

* Toll-like receptors are expressed in Fallopian tube epithelium and oviductal epithelial cells.

Shaw et al. Am J Path 2011

**PROKR2 mRNA expression in OE-E6/E7 cells can be induced by TLR2 activation**

Shaw et al. Am J Path 2011
C. trachomatis infection increases Fallopian tube PROKR2 via TLR2 and NFκB activation resulting in a microenvironment predisposed to ectopic pregnancy

Integrins

*Family of widely-expressed heterodimeric cell surface receptors that mediate cell – cell and cell – extracellular matrix adhesion

*Integrins (α1β1, α4β1, αvβ3) are markers of receptivity to the presenting embryo in the uterus

*Functional data limited as homozygous β1 and α4 mutations are embryonic lethal and 80% of αv-/- mice die in-utero

*Unlike the uterus, all five integrin receptivity markers (α1, β1, α4, αv, and β3) are constitutively expressed throughout the menstrual cycle in the Fallopian tube epithelium
Mouse model mimicking past exposure to *Chlamydia trachomatis* infection

![Graph showing infection levels over time](image)

In-vitro model of embryo attachment

- Trophoblast spheroids
- Tubal epithelial cells

*Kodithuwakku et al Lab Invest 2012*
In-vitro model of embryo attachment

+/- neutralising antibody to β1

Trophoblast spheroids

Tubal epithelial cells

Kodithuwakku et al. Lab Invest 2012
References


http://bitesized.immunology.org/pathogens-disease/chlamydia-trachomatis

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Medical management of tubal ectopic pregnancy

Professor Stephen Tong, MBBS, PhD
Translational Obstetrics Group
Department of Obstetrics & Gynaecology
The University of Melbourne
Mercy Hospital for Women, Melbourne AUSTRALIA

ESHRE Pre-congress Course, Munich 2014

Disclosure slide:
I am a named inventor of a patent covering the use of Epidermal Growth Factor Receptor Inhibitors to treat ectopic pregnancies

Learning Objectives:
1. Understand methotrexate, its mechanism of action, side effects and how it evolved to become used to treat ectopic pregnancies
2. Detailed review of commonly used protocols for medical management of ectopic pregnancies
3. Know the rationale behind the upper serum hCG cut-offs recommended by RCOG and ACOG
4. Review the option of conservative management for ectopic pregnancy
Learning Objectives:

5. Be aware of the prognostic significance of an early fall in serum hCG levels with medical management

6. Suggested future research directions for medical therapeutics

An ectopic pregnancy may be suitable for medical management if

- The mother is medically stable
- And is able to take methotrexate
- The ectopic pregnancy is not too big
- Based on serum hCG levels and ultrasound examination

Methotrexate:
History of Methotrexate

Lucy Wills  Sidney Farber

Development of Methotrexate to treat ectopic pregnancy

1956: Methotrexate used to cure choriocarcinoma
   - First cure of a solid tumour

1960s: Reported use of methotrexate to aid safe removal of placenta from an abdominal implantation site

1982: First reported use of methotrexate for ectopic pregnancy

1991: Publication of the first trial using the single dose methotrexate protocol
   - Stovall et al (1991)

Methotrexate – Mechanism of action

Skubisz and Tong ISRN O and G 2012
Side effects of methotrexate

Methotrexate affects cells that are rapidly turning over

Side effects
- Vomiting, diarrhea, mouth ulcers
- Skin dryness, sensitivity to the sun
- Hair thinning
- Headaches / Malaise / cognitive effects

Serious side effects
- Suppressed blood counts: anaemia/neutropenia/thrombocytopenia
- Liver / Renal dysfunction
- Lung – interstitial pneumonitis

Medical Management of Ectopic Pregnancy

Initial work up

Clinical assessment
- Is the mother stable?

Ultrasound
- Confirm diagnosis (exclude heterotopic pregnancy)
- Size of gestational sac, fetal cardiac activity, blood in the maternal abdomen

Blood tests
- Serum hCG (assess suitability for medical management)
- Rhesus status (give Anti-D)
- Haematological blood counts, and liver, renal function tests
Contra-indications for medical management

Related to the ectopic pregnancy itself
• Suspicions of ruptured ectopic pregnancy, or haemodynamic instability
• Serum hCG >3000-5000 IU/L
• Relative contra-indications: Large ectopic size >3.5 cm; presence of fetal cardiac activity

Related to the patient
• Haemodynamic instability
• Abnormalities in renal, haematologic or liver laboratory tests
• Immunodeficiency, pulmonary, liver or peptic ulcer disease
• Breastfeeding or co-existent intrauterine pregnancy
• Sensitivity to methotrexate
• Unlikely to be compliant with monitoring, or does not have timely access to medical care

Methotrexate protocol – single dose regimen

**Day 1**
- Measure serum hCG
- 50 mg/m² methotrexate

**Day 4**
- Measure serum hCG

**Day 7**
- Measure serum hCG
- Serum hCG drops >15% between days 4 and 7:
  - Monitor hCG weekly until resolution
- Serum hCG has NOT dropped >15% between days 4 and 7:
  - Give second dose of methotrexate, redo this protocol (‘new’ day 4 and 7)

Methotrexate protocol – two dose regimen

**Day 1**
- Measure serum hCG
- 50 mg/m² methotrexate

**Day 4**
- Measure serum hCG
- 50 mg/m² methotrexate

**Day 7**
- Measure serum hCG
- Serum hCG drops >15% between days 4 and 7:
  - Monitor hCG weekly until resolution
- Serum hCG has NOT dropped >15% between days 4 and 7:
  - Give second dose of methotrexate, redo this protocol (‘new’ day 4 and 7)
Methotrexate protocol – multi dose regimen

Day 1
- Measure serum hCG
- 50 mg/m² methotrexate

Day 3
- Measure serum hCG
- 50 mg/m² methotrexate

Day 5
- Measure serum hCG
- 50 mg/m² methotrexate

Day 7
- Measure serum hCG
- 50 mg/m² methotrexate

Leucovorin 0.1 mg/kg
- Days 2, 4, 6, 8

Cease methotrexate when serum hCG drops >15% between days 4 and 7.
Monitor hCG weekly until resolution

Follow-up
During treatment, AVOID the following:
- Intercourse, or pelvic examinations
- Sun exposure (methotrexate dermatitis)
- Folic acid
- Anti-inflammatory drugs (interactions with methotrexate can cause bone marrow suppression)

After the ectopic pregnancy has resolved:
- Avoid falling pregnant 3 months
  (There is little evidence to support this)
- Take folate for future pregnancies
  (especially if within 6 months of methotrexate treatment)

A closer look at aspects of medical management using methotrexate
1. Proposed starting serum hCG cut-off for single dose protocol

Pretreatment serum hCG of <5000 IU/L:

Supported by:
- NICE Guidelines (updated 2012)

Menon et al (2007) often cited to justify this cut-off
- Meta-analysis of 5 observational studies (n=503 in total)
  - Pretreatment hCG 2000-5000 IU/L, only 3.7% risk of failure (n=106)
  - Risk of failure increases 3 fold if pretreatment hCG 5000-10,000 IU/L

However, these may be optimistic rates:
  e.g. In a clinical trial, of 51 who had methotrexate, 4 tubal ruptures occurred with pretreatment hCG levels between 2000-5000 IU/L (Hajenius et al 1997)

2. Evidence comparing methotrexate regimens

Very little evidence directly comparing regimens

Single vs multiple doses
- 2 direct comparison trials, collectively n=159
  - No difference in outcomes (Klauser et al 2005; Alleyassin A et al 2006; Mol et al 2008)

Review of single vs multi-dose (Barnhart et al 2003)
- N=1327, but a mix of data from trials, observational studies
  - Single dose greater chance of failure (88% vs 93% for multi-dose)
  - Single dose less side effects
3. The two dose protocol

Two dose protocol
- Listed as a protocol option in ACOG guidelines
- One report: single arm trial (Barnhart et al, 2007)
- Methotrexate given day 0 and 4 (n=101)
- 88% success rate, remainder proceeding to surgery
- No comparisons with existing protocols

4. Early serum hCG fall and outcomes

Prognostic value of an early decrease in serum hCG levels
- Fall in serum hCG between days 1-4 is associated with an 85% chance the ectopic will be cured with no further treatment needed
- Fall in serum hCG between days 1-4 of >20% is associated with 93-97% chance of cure with no further treatment needed

The faster the early fall in serum hCG, the more promising the prognosis
(Skubisz et al 2012; Agostini et al 2007)

5. Conservative Management of ectopic Pregnancy

Recent interest in conservative management of ectopic pregnancy
- ACOG guidelines, pretreatment hCG <200 IU/L
- RCOG guidelines, pretreatment hCG <1000 IU/L, but:
  - <100 mls in Pouch of Douglas, greater than 50% fall in hCG within seven days, review twice weekly
- Recent RCT published (Van Mello et al 2013):
  - n=73, inclusion was plateauing hCG <2000 IU/L
    (plateau defined as <50% hCG rise between days 0 and 4)
  - methotrexate vs expectant management
  - Primary treatment success 31/41 (76% methotrexate)
    vs 19/32 (59%) expectant [No difference]
Areas for future research

Other treatments to increase the efficacy of methotrexate (or replace methotrexate)

Adding mifepristone to methotrexate
- Meta-analysis (Mol et al 2008):
  - Single dose methotrexate vs methotrexate + mifepristone
  - 2 studies (n= 262 total); RR 0.84 (0.71-1.00; p=0.05)
No subsequent trials found

Adding Gefitinib to methotrexate
- Gefitinib is an epidermal growth factor receptor inhibitor
- Phase I trial (n=12) Gefitinib + methotrexate induced rapid declines in serum hCG (Skubisz et al, 2013)
- Phase II trial (n=28) encouraging efficacy data (ESHRE Munich 2014)
- Successful treatment of 8 extra-tubal ectopics (Horne et al 2014)
Larger RCT evidence required

Other treatments to increase the efficacy of methotrexate (or replace methotrexate)

Can we devise other treatments?
- Combinations of very low dose chemotherapeutic agents?
- Nanoparticle delivery of cytotoxics direct to the ectopic pregnancy?

(Kaitu'u-Lino et al 2013)
Stable unruptured ectopic pregnancies can be treated with methotrexate instead of surgery.

The single dose methotrexate protocol is most commonly used, and studied.

The evidence justifying different thresholds of upper serum hCG levels is not strong.
- Generally, the higher the starting hCG, the increased risk of failure.

Summary

There is still no strong data comparing different methotrexate regimens.

Conservative management of ectopic pregnancy is now being increasingly considered.

There is scope to find better agents to resolve ectopic pregnancies medically.

References
References


Tubal hydrosalpinx and embryo implantation

Annika Strandell
Associate professor, MD, PhD

Sahlgrenska Academy
University of Gothenburg

Disclosures

• None

Learning objectives

• Be aware of possible mechanisms on how hydrosalpinx exerts negative effects on the endometrial environment.

• Be able to discuss the different treatment options for hydrosalpinx patients undergoing IVF, based on the treatments’ effectiveness and quality of evidence.
Meta-analysis of retrospective studies

12 studies, including 6,713 cycles

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<tbody>
<tr>
<td></td>
<td>OR 0.1 1.0</td>
<td>10.0</td>
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</tbody>
</table>

Zeyneloglu et al. 1998

Theories of mechanism

- Embryo toxic properties of the fluid
- Altered endometrial receptivity
- Mechanical hindrance
Main treatment options prior to IVF

- Salpingectomy
- Tubal occlusion
- Transvaginal aspiration

Additional suggested treatments

- Salpingostomy
- Tubal embolization
- Sclerotherapy
- Antibiotic treatment

Salpingectomy

- Scandinavian multicenter RCT
- Salpingectomy vs no surgery prior to IVF
- The importance of fluid
  Ultrasound visible
  Bilateral hydrosalpinges
Effect of salpingectomy on birth rates in patients with hydrosalpinx

Meta-analysis of randomized studies of salpingectomy prior to IVF

Outcome: Ongoing pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Salpingectomy</th>
<th>No surgery</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dechaud 1998</td>
<td>13/30</td>
<td>6/30</td>
<td>3.1 (0.97, 9.7)</td>
</tr>
<tr>
<td>Kontoravdis 2006</td>
<td>17/50</td>
<td>2/15</td>
<td>3.4 (0.7, 16.6)</td>
</tr>
<tr>
<td>Strandell 1999</td>
<td>31/116</td>
<td>15/88</td>
<td>1.8</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>2.2 (1.3, 3.8)</td>
</tr>
</tbody>
</table>

Meta-analysis of randomized studies of salpingectomy prior to IVF

Outcome: Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Salpingectomy</th>
<th>No surgery</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dechaud 1998</td>
<td>13/30</td>
<td>6/30</td>
<td>3.1 (0.97, 9.7)</td>
</tr>
<tr>
<td>Kontoravdis 21.3</td>
<td>20/50</td>
<td>2/15</td>
<td>4.3 (0.9, 18.3)</td>
</tr>
<tr>
<td>Moshin 2006</td>
<td>23/80</td>
<td>8/66</td>
<td>4.5 (1.8, 11.1)</td>
</tr>
<tr>
<td>Strandell 0.9, 2.9</td>
<td>40/116</td>
<td>22/88</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Johnson et al. Cochrane library 2010
### Ovarian function?

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Overall no. of oocytes contralateral</th>
<th>Ipsilateral vs.</th>
<th>ns</th>
<th>Prospective cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lass 1998</td>
<td>9.9 vs 9.1 ns</td>
<td>3.8 vs 6.0</td>
<td>p&lt;0.01</td>
<td>RCT</td>
</tr>
<tr>
<td>Strandell 1999</td>
<td>10.6 vs 10.6</td>
<td>6.1 vs 5.3 ns</td>
<td>-</td>
<td>Before and after surgery</td>
</tr>
<tr>
<td>Dar 2000</td>
<td>11.1 vs 9.7 ns</td>
<td>6.3 vs 6.2 ns</td>
<td>Matched controls</td>
<td></td>
</tr>
<tr>
<td>Strandell 2001</td>
<td>9.4 vs 8.7 ns</td>
<td>6.3 vs 6.2 ns</td>
<td>Matched controls</td>
<td></td>
</tr>
<tr>
<td>Tal 2002</td>
<td>8.6 vs 8.4 ns</td>
<td>6.3 vs 6.2 ns</td>
<td>Matched controls</td>
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</tr>
<tr>
<td>Gelbaya 2006</td>
<td>10.2 vs 13.7</td>
<td>3.6 vs 3.9</td>
<td>p&lt;0.05</td>
<td>Retrospective cohort</td>
</tr>
</tbody>
</table>

### Meta-analysis of randomized studies of salpingectomy vs. no surgery

#### Outcome: Number of oocytes

<table>
<thead>
<tr>
<th>Study</th>
<th>Salpingectomy mean (SD)</th>
<th>No surgery mean (SD)</th>
<th>Mean difference (95% CI)</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dechaud 1998</td>
<td>10.1 (5)</td>
<td>10.5 (6)</td>
<td>-0.4 (-3.2; 2.4)</td>
<td>N/A</td>
</tr>
<tr>
<td>Kontoravdis 2006</td>
<td>11.6 (5)</td>
<td>10.9 (5)</td>
<td>0.7 (-2.2; 3.6)</td>
<td>N/A</td>
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<tr>
<td>Moshin 2006</td>
<td>10.4 (6)</td>
<td>9.8 (6)</td>
<td>0.6 (-1.84; 2.6)</td>
<td>N/A</td>
</tr>
<tr>
<td>Strandell 1999</td>
<td>10.6 (6)</td>
<td>10.6 (6)</td>
<td>0.0 (-)</td>
<td>N/A</td>
</tr>
<tr>
<td>Total</td>
<td>0.2 (-0.9; 1.3)</td>
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</table>

### Tubal occlusion vs. no surgery

#### Outcome: Clinical pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Tubal occlusion</th>
<th>No surgery</th>
<th>OR (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kontoravdis 2006</td>
<td>20/50</td>
<td>2/15</td>
<td>4.3 (9.9; 21.3)</td>
<td>N/A</td>
</tr>
<tr>
<td>Moshin 2006</td>
<td>31/78</td>
<td>8/66</td>
<td>4.8 (2.0; 11.4)</td>
<td>N/A</td>
</tr>
<tr>
<td>Total</td>
<td>51/128</td>
<td>10/81</td>
<td>4.7 (2.2; 10.6)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Johnson et al. Cochrane Library 20
Tubal occlusion vs. Salpingectomy Outcome: Clinical pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Tubal occlusion</th>
<th>Salpingectomy</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kontoravdis 2006</td>
<td>26/50</td>
<td>20/50</td>
<td>1.6 (0.7; 3.6)</td>
</tr>
<tr>
<td>Moshin 2006</td>
<td>31/78</td>
<td>23/60</td>
<td>1.1 (0.5; 2.1)</td>
</tr>
<tr>
<td>Total</td>
<td>1.3 (0.8; 2.1)</td>
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<td></td>
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</tbody>
</table>

Salpingectomy vs. Tubal occlusion Outcome: Retrieved oocytes

<table>
<thead>
<tr>
<th></th>
<th>Salpingectomy mean (SD)</th>
<th>Tubal occlusion mean (SD)</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kontoravdis 2006</td>
<td>11.6 (5)</td>
<td>12.1 (5)</td>
<td>-0.5 (-2.5; 1.5)</td>
</tr>
<tr>
<td>Moshin 2006</td>
<td>10.4 (6)</td>
<td>10.2 (6)</td>
<td>0.2 (-1.8; 1.3)</td>
</tr>
<tr>
<td>Total</td>
<td>0.2 (-1.6; 1.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tubal occlusion by hysteroscopy

- Contraindication for laparoscopy
  - Obesity
  - Adhesions
- Mainly Essure, a spring device for tubal sterilization
- Out-patient setting, paracervical block / light sedation
- Other reported methods
  - Diathermy
  - Tubal embolization
Systematic review on Essure

- 115 patients in 11 studies reported
- No controlled studies
- Successful placement in 96% of women
- Tubal occlusion in 98%
- Complications reported
- Pregnancy rate per transfer 38%
- Live birth rate per transfer 28%
- Spontaneous pregnancy after unilateral placement.

Transvaginal aspiration

- Cycle time – oocyte retrieval
- Re-occurrence
- 2 RCT

Transvaginal aspiration vs. no aspiration

Outcome: Clinical pregnancy rate

<table>
<thead>
<tr>
<th>Aspiration</th>
<th>No aspiration</th>
<th>OR (95% CI)</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammadieh 2008</td>
<td>10/32</td>
<td>6/34</td>
<td>2.1 (0.7, 6.7)</td>
<td></td>
<td></td>
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<tr>
<td>Fouda &amp; Sayed 2006</td>
<td>17/54</td>
<td>7/53</td>
<td>3.0 (1.1, 8.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>26/86</td>
<td>13/87</td>
<td>2.6 (1.2, 5.5)</td>
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</tr>
</tbody>
</table>
Summary estimates for interventions for hydrosalpinx prior to IVF

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic salpingectomy</td>
<td>OR 2.31</td>
<td>(1.48, 3.62)</td>
</tr>
<tr>
<td>Laparoscopic tubal occlusion</td>
<td>OR 4.78</td>
<td>(2.01, 11.38)</td>
</tr>
<tr>
<td>Transvaginal aspiration</td>
<td>OR 2.61</td>
<td>(1.24, 5.51)</td>
</tr>
</tbody>
</table>

Odds ratio for clinical pregnancy rate

Quality of evidence for effect

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Quality of Evidence</th>
<th>Reason for downgrading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salpingectomy</td>
<td>High</td>
<td>High risk of bias</td>
</tr>
<tr>
<td>Tubal occlusion</td>
<td>Low?</td>
<td>Precision</td>
</tr>
<tr>
<td>Transvaginal aspiration</td>
<td>Moderate</td>
<td></td>
</tr>
</tbody>
</table>

Hydrosalpinx and IVF: A treatment protocol

- Hydrosalpinx ultrasound-visible before start
- Accessible HSX
- Evaluate mucosa if indicated
- Salpingostomy
- Salpingectomy
- Laparoscopy
- Extensive adhesions
- Proximal occlusion + distal drainage
- Patient wishes no surgery
- Transvaginal aspiration at ovum pick-up + antibiotics
- Contraindication to laparoscopy
- Consider hysteroscopy and tubal occlusion
Hydrosalpinx and IVF: A treatment protocol

Hydrosalpinx NOT ultrasound-visible before start

Visible during stimulation
Transvaginal aspiration at ovum pick-up + antibiotics

Unilateral hydrosalpinx

- Chance of spontaneous conception if treated
- Described for salpingectomy and tubal occlusion
- Strong recommendation for surgery
- Young enough to wait for spontaneous conception.

Conclusion

- Don’t do nothing prior to IVF!
- Inform
- Discuss
- Suggest
References

Fertility control: laparoscopic versus hysteroscopic tubal obstruction

T. Justin Clark MD(Hons)
Consultant Obstetrician and Gynaecologist & Honorary Reader
Birmingham Women’s Hospital & University of Birmingham
United Kingdom

Declaration of Interest
T. Justin Clark MD (Hons) MRCOG

Conceptus (manufacturer of Essure®)
- Consultant to Conceptus (2008-2012)
- Received funding from Conceptus for travel and accommodation (ESGE conference, Strasbourg, France, 2001)
- Trained clinicians in the Essure® technique from 2004 - present

Hologic (manufacturer of Adiana®)
- Member of the Hologic European Advisory Board (2008 - present)
- Received funding from Hologic for travel and accommodation (AAGL conferences Chicago (2001) and Washington (2007))

Femcare-Nikomed (manufacturer of Filshie Clip)
- Received one-off honoraria for attending an expert panel (2007)

Learning objectives
Fertility control: laparoscopic versus hysteroscopic tubal obstruction

For laparoscopic and hysteroscopic methods of tubal occlusion:

- Understand their mechanisms of action
- Understand how to counsel, perform and follow up the procedures
- Appreciate their relative advantages and disadvantages in terms of
  - Preferences
  - Feasibility
  - Feeding
  - Efficiency
  - Cost-Effectiveness
  - Adverse effects
- Gain an insight into the current evidence base, recent developments and the direction of future research
UNDERSTANDING THEIR MECHANISMS OF ACTION

Fertility control: laparoscopic versus hysteroscopic tubal obstruction

**Laparoscopic tubal occlusion:**
Mechanisms of action

- Mechanical occlusion
  - Later fibrosis
  - Clips may migrate

![Image of laparoscopic tubal occlusion](image)

**Laparoscopic tubal occlusion:**
Mechanisms of action cont.

- Filshie Clip
  - titanium-silicone clip
  - uses the pressure exerted by the applicator to close the clip

- Hulka-Clemens clip
  - plastic with gold-plated stainless steel spring
  - spring mechanism that holds the clip closed

- Falope ring
  - silastic ring shaped band
  - placed around a loop of the fallopian tube
Hysteroscopic tubal occlusion

Technologies

Commerically available (2)
- Essure®
  - Polyethylene Teraphtelate (PET) fibres, anchored by expanding nickel & stainless steel insert, induce an inflammatory reaction that causes fibrosis
- Ovabloc / Ovalastic®
  - Administration of liquid silicone, mixed with a catalyst forming occlusive rubbery implants

In development
- Altaseal®
  - Immediate mechanical occlusion using a stainless steel implant

Taken off the market
- Adiana
  - Porous, silicone, non-biodegradable implant provokes an occlusive fibrous reaction after initial application of bipolar radiofrequency energy to induce a superficial lesion of the tubal epithelium

Essure® hysteroscopic sterilisation:
Mechanism of action & procedure

The micro-insert consists of a nickel-titanium ('nitinol') outer coil, and a stainless steel inner coil to which PET (Dacron) fibres are attached

The device, with a length of 4 cm, is placed into the fallopian tube using a standard hysteroscope with a 5 French working channel

The dynamically expanding outer coil anchors the insert in the tubo-ovarian junction

The PET fibres induce a benign local tissue response consisting of inflammation and fibrosis, which leads to obliteration and occlusion of the tubal lumen over a 3 month period

Fertility control: laparoscopic versus hysteroscopic tubal obstruction

UNDERSTANDING HOW TO COUNSEL, PERFORM AND FOLLOW UP THE PROCEDURES
Pre-operative counselling and consent

- Information should be given and specific consent sought from each patient regarding:
  - Other long-term reversible methods of contraception
  - Male and female sterilization
  - Method of sterilization (laparoscopic vs. hysteroscopic)
  - Permanent & reversable
  - Failure rate and long-term risk of pregnancy
  - Risk of multiple pregnancy
  - Safety, complications & risks of sterilization
- Avoid pre-existing, unstable or early pregnancy: women should be advised to use effective contraception until the day of the operation (or any pregnancy test) and to continue to avoid if they are menstruating.

Pre-operative counselling and consent:

- Local protocols (Birmingham Women’s Hospital)

Pre-operative counselling and consent:

- Laparoscopic (Filshie Clip)
  
  - Discuss the procedure with your doctor and provide information on the method of sterilization.
  
  - Ask for further advice as needed.
  
  - Ensure you are in a healthy condition.
  
  - If you are pregnant, the procedure may not be performed.
  
  - There is a risk of infection, injury, and complications.

- Hysteroscopic (Essure)

  - Discuss the procedure with your doctor and provide information on the method of sterilization.
  
  - Ask for further advice as needed.
  
  - Ensure you are in a healthy condition.
  
  - If you are pregnant, the procedure may not be performed.
  
  - There is a risk of infection, injury, and complications.
Laparoscopic Filshie clip sterilisation:

Procedure

- Laparoscopy: mechanical occlusion of the tubes by either Filshie clips or rings should be the method of choice
  - Diathermy should not be used as the primary method of tubal occlusion because
    - Failure rate higher, risk of ectopic higher and subsequent successful reversal operation lower
  - Filshie clip may be more effective than the spring Hulka Clip (Dominik R et al; 2000)
- Filshie clip technique (see http://www.coopersurgical.com/Documents/Filshie%20Procedure%20Guide.pdf)
  1. Identify the Fallopian tube
  2. Place clip 1-2 cm from the cornua on the isthmic portion of the tube
  3. The clip should contain the entire circumference of the tube and be perpendicular to the tube
  4. Close the clip with firm pressure; excessive force is not needed.
  5. The upper jaw of the clip should be compressed, flat and securely latched.
  6. Always verify clip placement is on the correct structure and in the correct position
- Repeat process on the opposite side.

Essure® hysteroscopic sterilisation:

Follow up

- Laparoscopy
  - Immediate effect
  - Although advise continuation of contraception until next menstrual period
- Hysteroscopy (Essure)
  - 3 months to occlude tubal lumen
  - Advise continuation of contraception for ≥ 3 months until confirmation testing confirms satisfactory procedure
  - TVU
  - HSG (mandatory in US)
  - Local / national protocols required
Follow up: Confirmation testing (Essure)

- **AXR** (confirmation of satisfactory placement)
  - Skill to interpret
  - Resource to HSG may be required

- **TVU** (confirmation of satisfactory placement)
  - Avoids ionising radiation
  - Provides soft tissue contrast
  - Enhancing ease of interpretation
  - Recourse to HSG may be required in up to 15% of cases (Clark TJ, personal comm 2014)

- **HSG** (confirmation of tubal occlusion)
  - Gold standard
  - Provides evidence of tubal occlusion, not just adequate placement
  - Radiation, invasive and not always feasible or interpretable
  - Higher costs

Follow up: Confirmation testing (Essure): Protocols

- **Birmingham Women’s Hospital, UK**
- **Netherlands**

---

Fertility control: laparoscopic versus hysteroscopic tubal occlusion

APPRECIATE THE RELATIVE ADVANTAGES AND DISADVANTAGES
Laparoscopic versus hysteroscopic tubal obstruction: Preferences

- **Outpatient hysteroscopic occlusion preferred:**
  - Of 100 consecutive women attending a nurse-led clinic seeking sterilisation 67% preferred the outpatient hysteroscopic method (Clark TJ, Personnel Comm 2014 – data presented as a poster at 19th ESGE conference in Barcelona 2010)
  - Women preferring outpatient HTO:
    - Very short hospital stay, absence of scars (59%), perceived safety, avoidance of general anaesthesia (50%), and absence of surgical incisions (35%)
    - Preference for short hospitalization of postoperative pain
  - Similar study of 100 women (Chapa et al; 2012) found that 93% preferred hysteroscopic over laparoscopic tubal occlusion
    - Of the 93 women preferring outpatient HTO – their prime reason was:
      - 24 feared general anaesthesia; 25/93 feared surgical incisions; 32/93 ‘cost’; 12/93 return to routine activity

Laparoscopic versus hysteroscopic tubal obstruction: Feasibility

- **Laparoscopic tubal occlusion is more successful**
  - Laparoscopic sterilisation is estimated to be successfully completed in 99% of cases (Gariepy AM et al; 2011)
  - Successful bilateral placement of Essure microinserts ranges from 80%-97%, with most series reporting rates >90% (Clark TJ; 2012)
  - One uncontrolled comparative series of laparoscopic sterilisation (Filshie clip) vs. hysteroscopic sterilisation (Essure) (Duffy S et al; 2005)
    - 24/24 (100%) LS vs. 48/59 (81%) HS successful

- **Feasibility of hysteroscopic procedures optimised by avoidance of secretory phase of the menstrual cycle and larger uteri (Sinha et al; 2007)**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Success Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic sterilisation</td>
<td>100</td>
</tr>
<tr>
<td>Hysteroscopic sterilisation</td>
<td>81</td>
</tr>
</tbody>
</table>

* P < 0.05, statistically significant.
Laparoscopic versus hysteroscopic tubal obstruction: Feasibility

- Reasons for failure using hysteroscopy (Sinha et al; 2007)

<table>
<thead>
<tr>
<th>Reason for failure (Sinha)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroflexion of the uterine (2)</td>
<td>Usually needed for insertion of catheter, but can be managed with slight patient rotation or slight rotation of the catheter.</td>
</tr>
<tr>
<td>Uterine fibroids (4)</td>
<td>May require hysteroscopic resection to achieve adequate uterine visualization.</td>
</tr>
<tr>
<td>Uterine polyps (2)</td>
<td>May require hysteroscopic resection to achieve adequate uterine visualization.</td>
</tr>
<tr>
<td>Uterine cornual distortion (2)</td>
<td>May require hysteroscopic resection to achieve adequate uterine visualization.</td>
</tr>
<tr>
<td>Uterine septum (1)</td>
<td>May require hysteroscopic resection to achieve adequate uterine visualization.</td>
</tr>
<tr>
<td>Uterine diverticulum (2)</td>
<td>May require hysteroscopic resection to achieve adequate uterine visualization.</td>
</tr>
<tr>
<td>Uterine atrophy (6)</td>
<td>May require hysteroscopic resection to achieve adequate uterine visualization.</td>
</tr>
<tr>
<td>Uterine adhesions (10)</td>
<td>May require hysteroscopic resection to achieve adequate uterine visualization.</td>
</tr>
<tr>
<td>Uterine anomalies (1)</td>
<td>May require hysteroscopic resection to achieve adequate uterine visualization.</td>
</tr>
<tr>
<td>Uterine atrophy (6)</td>
<td>May require hysteroscopic resection to achieve adequate uterine visualization.</td>
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<td>May require hysteroscopic resection to achieve adequate uterine visualization.</td>
</tr>
<tr>
<td>Uterine anomalies (1)</td>
<td>May require hysteroscopic resection to achieve adequate uterine visualization.</td>
</tr>
</tbody>
</table>

Laparoscopic versus hysteroscopic tubal obstruction: Setting

- Hysteroscopic tubal occlusion routinely feasible in a convenient outpatient setting
  - Laparoscopic sterilisation can be safely performed in a conscious outpatient (MacKenzie IZ; 1987) but is rarely performed
  - Hysteroscopic sterilisation is routinely performed as an outpatient with or without conscious sedation / local anaesthesia
    - No differences in success between outpatient 'office' and day case theatre under general anaesthesia / sedation (Anderson TL et al; 2013)

Laparoscopic versus hysteroscopic tubal obstruction: Setting

- Hysteroscopic tubal occlusion routinely feasible in a convenient outpatient setting
  - Quick
Laparoscopic versus hysteroscopic tubal obstruction: Effectiveness

- Both methods of sterilisation have comparably high rates of effectiveness
  - 5 year effectiveness for the best laparoscopic occlusive method (Filshie clip) and the best hysteroscopic occlusive method are 2-3 /1000 procedures (Kovacs et al, 2002 & Bradley L, 2008)
  - More data are available for laparoscopic occlusion
  - Immediate effect (laparoscopic) vs. delayed effect ≥ 3 months (hysteroscopy)

Laparoscopic versus hysteroscopic tubal obstruction: Effectiveness - Laparoscopy

- The US Collaborative Review of sterilisation (CREST) study (Chen et al, 1996) followed 12,484 sterilised women for up to 24 years following sterilisation. The study found that:
  - Tubal ligation is highly effective
  - Effectiveness varies by method evaluated and by patient age, race and parity
  - The cumulative 5 year probability of pregnancy following tubal ligation was 12% / 1000 procedures (95% CI 7.3 – 16.5)
  - The cumulative 5 year probability of pregnancy following tubal occlusion was 36% / 1000 procedures (95% CI 15.6 – 21.8)
  - Tubal occlusion is highly effective
  - Effectiveness varies by method evaluated and by patient age, race and parity
  - The cumulative 5 year probability of pregnancy following tubal occlusion was 12% / 1000 procedures (95% CI 7.3 – 16.5)

Laparoscopic versus hysteroscopic tubal obstruction: Effectiveness - Hysteroscopy

- Hysteroscopic sterilisation using the Essure method is highly effective
  - The pivotal trial data has recorded no pregnancies to date (Cooper JM et al, 2010) and the estimated cumulative 5-year effectiveness rate is 99.7% (Bradley L, 2006)
  - Based upon the largest published series to date from a single centre (follow-up ≥ 3 months - 7 years), the effectiveness rate was 7/4108 (99.8%) (Povedano et al, 2012)
  - Based upon the number of reported cases of unintended pregnancy worldwide 2000-2010 divided by the number of Essure kits sold worldwide, corresponds to a success rate of 99.7% (794/804/805) (Mavros MS et al, 2014)
  - Although the figure is likely to be an underestimate, the efficacy rate is generally consistent with similar sterilisation devices. At least, the short and medium term, is consistent with the published series
Laparoscopic versus hysteroscopic tubal obstruction: Effectiveness – reasons for failure

**Laparoscopic**
- Operator dependant
  - Clip / ring applied to non-tubal structure (most common)
  - Incomplete tubal occlusion and/or patent lumen
- Non-operator dependant
  - Tubo-peritoneal fistula formation
  - Spontaneous recanalisation

**Hysteroscopic**
(Purema MI et al, 2014)

Laparoscopic versus hysteroscopic tubal obstruction: Cost-effectiveness

- **Hysteroscopic tubal occlusion appears to be more cost-effective than conventional laparoscopic approaches**
  - Several economic papers assessing hysteroscopic sterilisation. A systematic search identified 33 such papers but could only include 3 cost-analyses in the review on which to base its findings (McMartin K, 2013)
  - Equipment costs greater for hysteroscopic sterilisation BUT cost-effectiveness of hysteroscopy driven by avoidance of inpatient admission; use of expensive operating theatre resources and quicker recovery time

Laparoscopic versus hysteroscopic tubal obstruction: Cost-effectiveness

- **There are caveats however:**
  - No robust cost-effective or cost-utility analyses published of laparoscopic occlusion vs. hysteroscopic tubal occlusion taking into account
    - Comparative effectiveness
    - Side-effects
    - Full failure rate data and additional costs associated with hysteroscopic methods
    - Societal perspectives
    - Quality of life, satisfaction
  - Transferability across health regions and internationally is limited due to the peculiarities of health care systems, including associated costs and funding
Laparoscopic versus hysteroscopic tubal obstruction:

Satisfaction

- Both laparoscopic and hysteroscopic tubal occlusion methods are associated with high levels of patient satisfaction
  - Patient satisfaction at day 30 post-procedure (% "very satisfied" or "somewhat satisfied":)
    - 82% (673/819) vs. 93% (57/60) (P=0.008)
  - Post-operative pain and recovery:
    - In 2007 (Duffy et al., 2002)
    - Postoperative pain was experienced by 60/76 (79%), 95% (68–88%) women, with 87% (6) describing this pain as severe.
    - In the majority of women, the duration of this postoperative pain was less than 24 hours. Only 8/60 (13%) describing such pain as lasting greater than 6 hours.
  - Hysteroscopic tubal obstruction vs. hysteroscopic sterilization (Duffy et al., 2002)
    - Tolerance of procedure (% "good" or "excellent"): 41% vs. 82% (P=0.0002)
    - Post-procedure pain in recovery room (% "moderate" or "severe"): 63% vs. 31% (P=0.0002)

Laparoscopic versus hysteroscopic tubal obstruction:

Satisfaction & patient experience

- Patient experience of hysteroscopic sterilisation (Essure) (Sinha et al.; 2007)
  - Pain or discomfort was experienced during the procedure by 57/76 (75%), 95% (68–85%) women, with 82/76 (11%) describing the pain as severe.
  - A minority of women (5/76, 12%, 95% CI 6–21%) when asked whether they would have preferred a general anaesthetic with hindsight answered yes.
  - Postoperative pain was experienced by 60/76 (79%), 95% (68–88%) women, with 87% (6) describing this pain as severe.
  - In the majority of women, the duration of this postoperative pain was less than 24 hours. Only 8/60 (13%) describing such pain as lasting greater than 6 hours.
  - Hysteroscopic sterilisation vs. hysteroscopic sterilisation (Duffy et al., 2002)
    - Tolerance of procedure (% "good" or "excellent"): 41% vs. 82% (P=0.0002)
    - Post-procedure pain in recovery room (% "moderate" or "severe"): 63% vs. 31% (P=0.0002)

Laparoscopic versus hysteroscopic tubal obstruction:

Adverse effects

- Both procedures are safe and associated with a low incidence of adverse events
  - Hysteroscopic methods are associated with severe pain and vaso-vagal reactions in up to 20% of cases (Veale et al., 2003), although a larger series from Spain reported lower rates of severe pain (4%) and vaso-vagal reactions (5%) (Romero et al., 2012)
  - The authors of this centre reported side effects in 12/30 (40%) of hysteroscopic procedures which included 2 severe reactions, 2 skin reactions, in 2 patients, 1 case of pelvic inflammatory disease, 1 case of uterine perforation, 1 case of pelvic pain and 2 cases of pressure ulceration.
  - No deaths were reported.
  - Laparoscope under general anaesthesia has the potential for rare but serious adverse events including visceral injury and death (McNally et al., 1977-1988). There were 29 deaths reported to the Centers for Disease Control and Prevention after tubal sterilisation, of which 5 were major vessel injuries.
  - In a study sponsored by the World Health Organization, 85% women undergoing IUC with hysterectomy or tubal loop sterilization experienced nausea or vomiting in 40% of the women and 6% of the women reported to have a complication requiring re-admission. The majority of complications were related to nausea or vomiting (40% of the women and 6% of the women reported to have a complication requiring re-admission. The majority of complications were related to nausea or vomiting).
Laparoscopic versus hysteroscopic tubal obstruction: Adverse effects

• Comparison between approaches (from Duffy et al, 2002)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Laparoscopic Tubal Occlusion</th>
<th>Hysteroscopic Tubal Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure time</td>
<td>30 min</td>
<td>15 min</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Minimal</td>
<td>Mild</td>
</tr>
<tr>
<td>Adhesions</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

Fertility control: laparoscopic versus hysteroscopic tubal obstruction

GAIN INSIGHT INTO THE CURRENT EVIDENCE BASE, RECENT DEVELOPMENTS AND FUTURE RESEARCH

Laparoscopic versus hysteroscopic tubal obstruction: Future research - contraception

• Laparoscopic vs hysteroscopic tubal occlusion
  - Patient selection
  - Large scale national data to identify predictors factors for success, optimal experiences.
  - RCT with parallel cost-effectiveness / cost utility analysis
  - Outcomes?
    - Pregnancy rates not feasible (large sample size & event rate low & long term FU needed)
    - Surrogates e.g. Quality of life; patient satisfaction; successful procedure completion

• Hysteroscopic sterilisation:
  - Optimising patient experience & feasibility
    - Patient selection
    - Technical aspects e.g. anaesthesia; cameraless; saline inflow; video; magnification
  - Confirmatory testing
    - WHO or confirmatory testing required patient selection
    - Optical confirmatory tests - evaluate new technologies e.g. 3D USS
  - Use outside of developed countries
  - Feasibility of mass production & indications
  - Evaluation of new technology (e.g. hand sewn) or adaptations of existing technology (e.g. removal embolisation agent via gold standard HSG and follicular aspiration)

• Laparoscopic sterilisation:
  - Feasibility of outpatient mini-laparoscopy
  - Single port surgery
What should be the research priorities?

Opinions of BSGE members – OUTPATIENT HYSTEROSCOPY

- Touch (vaginoscopy) vs. no-touch (speculum) vs. No-touch + local anaesthesia outpatient hysteroscopy
  - Outcomes to include pain, patient satisfaction, feasibility and infection
  - 46/80 (58%)

- Laparoscopic sterilisation vs. hysteroscopic sterilisation
  - Outcomes to include patient satisfaction, pregnancy rates, morbidity, costs
  - 62/80 (78%)

- Uterine polypectomy vs. non-polypectomy (i.e. conservative management) in women with abnormal uterine bleeding and/or sub fertility
  - Outcomes to include resolution of abnormal bleeding, patient satisfaction, HRQL, further surgery, costs
  - 55/80 (69%)

Laparoscopic versus hysteroscopic tubal obstruction:

Future research – contraception

- Laparoscopic vs hysteroscopic tubal occlusion
  - Patient selection
  - Large observational data sets to identify predictors for success, optimal experiences
  - RCT with parallel cost-effectiveness / cost utility analysis
  - Surrogates: e.g. Quality of life, patient satisfaction, successful procedure completion

- Hysteroscopic sterilisation:
  - Optimising patient experience & feasibility
  - Technical aspects e.g. analgesia, anaesthesia, conscious sedation, warming, saline, vaginoscopy
  - Confirmatory testing
  - Effectiveness: one-shot testing required, patient selection
  - Optimised confirmatory tests: evaluate new technologies e.g. 3D USS
  - Use outside of developed countries
  - Feasibility of mass production & indemnity costs
  - Evaluation of new technologies e.g. intentional evaluation in adaptations of existing hysteroscopy technology (e.g. hysteroscopic embolisation, guided sutures, staplers, etc.)

- Laparoscopic sterilisation:
  - Feasibility of outpatient mini laparoscopy
  - Single port surgery

Hysteroscopic tubal obstruction:
Optimising pain relief and patient experience

Hysteroscopic sterilisation
Optimising performance and patient experience:
Local anaesthesia

- Outpatient = improving patient experience
Laparoscopic versus hysteroscopic tubal obstruction:
Future research – contraception

- Laparoscopic vs hysteroscopic tubal occlusion
  - Patient selection
    - Laparoscopic data are one to identify pre-existing factors for success, minimal experience.
  - RCT vs parallel cost-effectiveness / cost utility analysis
    - Pregnancy rates not feasible (large sample size and randomised case & long-term follow-up)
    - Surrogates: e.g. Quality of the patient satisfaction, success / procedure completion
- Hysteroscopic sterilisation:
  - Optimising patient experience & feasibility
    - Postoperative: e.g. anaesthesia, antibiotic, concurrent evaluation, nursing, saline irrigation
  - Confirmatory testing
    - Initial: in pilot study: needed; patient selection
    - Optimal confirmatory tests: future for lower technologies (e.g. US, USS)
  - Use outside of developed countries
    - Possibility of mass production & reimbursement
    - Evaluation of new technologies (e.g. physical, radiological) vs addictions of existing (e.g. metal and folic acid)
- Laparoscopic sterilisation:
  - Feasibility / minimally invasive sterilisation
  - Single port surgery

Laparoscopic versus hysteroscopic tubal obstruction:
Future developments – training

- A multi-centre prospective study of 578 hysteroscopic sterilisations from 76 operators in the US (Lejeu et al. 2011) to assess experienced practitioners (n=39) with newly trained physicians (n=37)
  - Longer treatment time in revision on average by 3.7 minutes (95% CI 3.7 minutes)
  - No significant difference in successful placement rates
- Use of simulators / training packages
  - Simulation laboratory teaching significantly improved resident knowledge, comfort level, and technical skill performance of hysteroscopic sterilisation (Chaudhry S et al. 2009)
  - Feasible and construct validity (Penev P et al. 2012)
  - Time to proficiency

Laparoscopic versus hysteroscopic tubal obstruction:
Future research – assisted conception

- Treatment of hydrosalpinges
  - Proven observational data (Lejeu et al. 2011 and several other case series) from failed hysteroscopic sterilisations and from treatment on hydrosalpinges prior to IVF suggest:
  - Feasible
  - Where hysteroscopic approaches have failed or on consideration complex
    - RCT of laparoscopic vs hysteroscopic tubal occlusion +/- parallel cost-effectiveness / cost utility analysis
    - Outcomes: safety, feasibility, pregnancy rate, hormonal.
CONCLUSIONS

Laparoscopic versus hysteroscopic tubal obstruction: Conclusions

- Both approaches to tubal occlusion are safe, acceptable, feasible and effective
  - Laparoscopic occlusion has the advantage of greater feasibility
  - Hysteroscopic occlusion has the advantage of a convenient, outpatient ‘office’ treatment setting and reduced costs
  - Longer term follow up data are required to more precisely ascertain the cumulative failure rate of hysteroscopic sterilisation to allow comparison against more established laparoscopic sterilisation
  - An RCT is needed to evaluate the relative effectiveness and cost-effectiveness of both techniques

Laparoscopic versus hysteroscopic tubal obstruction: References

1. Cooper CL, Veersema S, Munro MG. Hysteroscopic sterilisation using the Essure device: a prospective analysis comparing 3 months with 1 year follow up. BJOG 2013;120:145–149
3. Turner JK, Cooper CL, Munro MG. Hysteroscopic sterilisation using the Essure device: a prospective analysis comparing 3 months with 1 year follow up. BJOG 2013;120:145–149
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Thank you for your attention

Any Questions?
Management of tubal pregnancy: salpingectomy vs. salpingostomy

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on behalf of the ESEP study group
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Disclosure

• This study was supported by grants from the Netherlands Organisation for Health Research and Development (ZonMw grants 92003328 and 90700154)

Learning objectives

• To be able to summarize the evidence to apply salpingotomy or salpingectomy in terms of primary treatment success, future fertility, costs and patients perspective.

• To select the surgical treatment for women with tubal pregnancy
Concept of the 'stucked embryo'

1669 Benoit Vassal, Paris, France
1641-1673 Reinier de Graaf, Delft, the Netherlands


Pioneer salpingectomy - 1883

- Robert Lawson Tait
  "Inevitably doomed to die, unless some active measure wrest her from the grave"

- Asepsis vs. antisepsis

- 1883 first successful salpingectomy
  - synonyms: salpingectomy or tubectomy

Pioneer salpingotomy - 1922

- Beckwith Whitehouse
  "Is it justified to sacrifice the tube in all occasions?"

- 1920 first successful salpingotomies
  - synonyms: salpingotomy or tubotomy
Salpingotomy ↔ salpingectomy

Salpingotomy was introduced without any evidence that this intervention had better outcomes for future fertility

Despite observed disadvantages:
1. Persistent trophoblast (PT)
2. Repeat ectopic pregnancy

Pioneer in laparoscopy

Laparoscopy 2014
Pioneers in laparoscopic surgery for EP

- 1973 Salpingectomy (Shapiro, USA)
- 1980 Salpingotomy (Bruhat, Fr)

What is known?

- Laparoscopy is cost-effective compared to open surgery.

- MTX is cost-effective compared to laparoscopic salpingotomy in asymptomatic women with hCG < 3,000 IU/L.

- 1 week expectant as effective as single dose MTX in women with persisting PUL or EP.

Future fertility
Objective

• To assess the fertility prognosis after salpingotomy versus salpingectomy in women with tubal ectopic pregnancy and a normal contra lateral tube

Methods - population

• Women ≥ 18 years of age
• Suspected ectopic pregnancy, scheduled for surgery
• Confirmed ectopic pregnancy and normal contra lateral tube at surgery
• Exclusion criteria:
  – shock
  – no wish to conceive
  – pregnancy after IVF
  – known bilateral tubal pathology (HSG or laparoscopy) or solitary tube

Methods - intervention

• Salpingotomy or salpingectomy according to local standards

• Per-operative online randomisation
  – stratification per centre, age, history of tubal pathology
Methods - follow-up

Short term
• Persistent trophoblast - weekly serum hCG monitoring*

Long term
• Fertility follow up - every six months

* Hajenius PJ, 1995

Methods - outcome measures

Primary outcome
• Time to ongoing pregnancy in months from surgery to LMP
  – ongoing pregnancy: viable pregnancy at 12 weeks or life birth

Secondary outcome
• Persistent trophoblast
• Repeat ectopic pregnancy

Methods - subgroups

Prespecified subgroups
• Maternal age
  – < 30 or ≥ 30 years
• History of a previous ectopic pregnancy
• Pre-operative serum hCG-level
  – < 3,000 IU/l, 3,000 - 6,000 IU/l, > 6,000 IU/l
• Size of the ectopic mass on ultrasound
  – < 4 cm or ≥ 4 cm
Methods - statistics

Sample size*
• 450 women (alpha error 5%, beta error 20%, LFU 10%)
• Clinical significance: improvement in ongoing pregnancy rate at 2 years from 40% to 55%

Statistical analysis
• Primary outcome: ITT, KM curves, Log rank test, Fecundity Rate Ratio (FRR, 95% CI)
• Secondary outcomes: ITT, RR (95% CI)
• Per protocol analysis
• Subgroup analysis: Cox proportional hazard analysis

* Schoenfeld, 1983

Enrollment  September 2004 - November 2011

Results - baseline characteristics
(Serious) adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Salpingectomy (n=222)</th>
<th>Salpingectomy (n=222)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortion</td>
<td>2 (1%)</td>
<td>2 (1%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Complications</td>
<td>10 (5%)</td>
<td>8 (4%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Other complications</td>
<td>7 (3%)</td>
<td>7 (3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Therapeutic procedure</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Initial bleeding</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>Initial bleeding</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>0.50</td>
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<td>0</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Table 3: Adverse events*

Primary outcome

![Graph showing primary outcome comparison between Salpingectomy and Salpingectomy (n=222)]

Secondary outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Salpingectomy (n=222)</th>
<th>Salpingectomy (n=222)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent trophoblast</td>
<td>14 (6%)</td>
<td>5 (2%)</td>
<td>0.3 (0.1-0.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Repeated ectopic pregnancy</td>
<td>18 (8%)</td>
<td>12 (5%)</td>
<td>1.6 (0.8-3.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Reproductive failure</td>
<td>2 (1%)</td>
<td>2 (1%)</td>
<td>1.0 (0.1-10.0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Complications</td>
<td>10 (5%)</td>
<td>8 (4%)</td>
<td>0.5 (0.2-1.2)</td>
<td>0.39</td>
</tr>
<tr>
<td>Other complications</td>
<td>7 (3%)</td>
<td>7 (3%)</td>
<td>1.0 (0.4-2.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Therapeutic procedure</td>
<td>0</td>
<td>0</td>
<td>1.0 (0.1-10.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Initial bleeding</td>
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<td>0</td>
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<td>1.0 (0.1-10.0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Table 3: Secondary outcomes*
Per protocol analysis

- 164 completed salpingotomy
  - 87 ongoing pregnancy by natural conception (cumulative 62.3%)

- 231 women who were assigned to and received salpingectomy
  - 114 ongoing pregnancy by natural conception (cumulative 56.2%)

- Fecundity Rate Ratio 1.10, 95% CI 0.83–1.46; log-rank p=0.492

Prespecified subgroups (pre planned post hoc analysis)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Salpingotomy</th>
<th>Salpingectomy</th>
<th>Fecundity rate ratio (95% CI)</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 years</td>
<td>77 (54%)</td>
<td>55 (38%)</td>
<td>1.46 (1.04–2.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>≥30 years</td>
<td>55 (10%)</td>
<td>90 (16%)</td>
<td>0.95 (0.66–1.39)</td>
<td></td>
</tr>
<tr>
<td>History of previous ectopic pregnancy</td>
<td>Yes</td>
<td>0/9</td>
<td>1/15 (0.04)</td>
<td>0.05</td>
</tr>
<tr>
<td>No</td>
<td>100/100 (100%)</td>
<td>113/100 (100%)</td>
<td>1.00 (0.84–1.18)</td>
<td>-</td>
</tr>
<tr>
<td>Pregnancy on scan ≤10G7</td>
<td>≤2 ≤5 cm</td>
<td>64/50 (31%)</td>
<td>31/100 (31%)</td>
<td>1.94 (1.28–3.25)</td>
</tr>
<tr>
<td>≥2 ≤5 cm</td>
<td>42/100 (42%)</td>
<td>89/100 (45%)</td>
<td>0.90 (0.60–1.35)</td>
<td>-</td>
</tr>
<tr>
<td>Size of ectopic mass on ultrasound</td>
<td>≤2 cm</td>
<td>20/64 (48%)</td>
<td>30/60 (50%)</td>
<td>0.99 (0.59–1.65)</td>
</tr>
<tr>
<td>≥2 cm</td>
<td>34/64 (53%)</td>
<td>22/60 (37%)</td>
<td>1.36 (0.83–2.22)</td>
<td>-</td>
</tr>
</tbody>
</table>

Conclusion

- In women with a tubal pregnancy and a normal contra lateral tube, salpingotomy does not improve 3-year pregnancy rates or time to pregnancy as compared to salpingectomy

- Salpingotomy does more often lead to persistent trophoblast
Conclusion

- In women with a tubal pregnancy and a normal contra lateral tube, salpingotomy does not improve 3-year pregnancy rates or time to pregnancy as compared to salpingectomy.
- Salpingotomy does more often lead to persistent trophoblast.
- Salpingectomy should be the procedure of choice in women with a tubal pregnancy and a normal contra lateral tube.

DEMETER study

- Women were divided into two arms according to the activity of the EP (defined by Fernandez’s score).
- Sample size n=230, randomised n=190.
- Similar result with respect to cumulative ongoing pregnancy rates (HR 1.13, 95% CI 0.73–1.74).
- Persistent trophoblast not reported.

Meta-analysis n=649

- No statistical heterogeneity observed.

Mol F, 2014

DEMETER study

Fernandez H, 2013
Clinical heterogeneity

<table>
<thead>
<tr>
<th>DEMETER</th>
<th>ESEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>contralateral tubal disease included</td>
</tr>
<tr>
<td>Intervention</td>
<td>Salpingotomy with prophylactic dose MTX</td>
</tr>
<tr>
<td>Outcome</td>
<td>Composite outcome including miscarriages and pregnancy terminations</td>
</tr>
<tr>
<td></td>
<td>Time to pregnancy calculated from desire for pregnancy</td>
</tr>
<tr>
<td>Sample size</td>
<td>20% difference</td>
</tr>
</tbody>
</table>

Summary future fertility

- Cannot exclude the possibility of a very small benefit from salpingotomy.
- Women with a strong preference for maximising their future pregnancy prospects might still opt for salpingotomy.
- We believe that salpingectomy should be the preferred surgical treatment in women with a tubal pregnancy and a healthy contralateral tube.

Costs
Objective

To evaluate the cost-effectiveness of salpingotomy compared to salpingectomy

Costs

Direct medical costs from randomisation:

1. Initial treatment
   surgery material, duration, conversions

2. Re-admittance

3. Treatment for persistent trophoblast

4. Treatment for repeat ectopic pregnancy

Methods

• Cost-effectiveness study alongside RCT

• Unit costs
  – Unit prices of 1 academic hospital (Dutch)

• Volumes of resource use
  – Initial treatment
  – Re-admissions
  – Persistent trophoblast
  – Repeat ectopic pregnancy
Analysis

- Time horizon
  - until ongoing pregnancy by natural conception, or 36 months

- 3 outcomes: ongoing pregnancy, PT, repeat EP

- Incremental cost-effectiveness ratio
  - salpingotomy vs. salpingectomy (=reference)

- Cost-effectiveness planes (1000 random samples)

Results – resource use and unit prices

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Salpingotomy (n= 215)</th>
<th>Salpingectomy (n= 231)</th>
<th>Unit price (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopy start-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopy (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conversion open surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conversion salpingectomty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management with salpingectomy for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>suspected bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloodtransfusion (unit)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial admission day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsequent days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloodtransfusion (unit)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consultation out patient clinic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hCG serum including consultation by telephone</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results – resource use and unit prices

<table>
<thead>
<tr>
<th>Re-admission</th>
<th>Salpingotomy (n= 215)</th>
<th>Salpingectomy (n= 231)</th>
<th>Unit price (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-admission only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-admission with surgical or elec.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>taneous laparotomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendectomy salpingectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Removal of fallopian tube</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-admission day – no.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Results – resource use and unit prices

<table>
<thead>
<tr>
<th>Persistent trophoblast</th>
<th>Salpingotomy (n=215)</th>
<th>Salpingectomy (n=231)</th>
<th>Unit price (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of injections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX single dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX multiple dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment (METEX)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Results – resource use and unit prices

<table>
<thead>
<tr>
<th>Repeat ectopic pregnancy</th>
<th>Salpingotomy (n=215)</th>
<th>Salpingectomy (n=231)</th>
<th>Unit price (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX single dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX multiple dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment (METEX)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Results – mean costs per woman

...
Cost-effectiveness plane

\[ \text{ICER} = \frac{\Delta \text{costs}}{\Delta \text{effects}} \]

Reference strategy is at origin.

CEA plane  ongoing pregnancy by natural conception

CEA plane  persistent trophoblast
CEA plane: repeat ectopic pregnancy

Summary CEA

- Costs of salpingotomy are higher than for salpingectomy, for no additional medical benefit (ongoing pregnancy) with health loss due to treatment failure (persistent trophoblast)

Patient’s perspective
What do women prefer?

Patients' preferences for salpingotomy relative to salpingectomy in tubal ectopic pregnancy

What is the decision making factor?

Discrete choice experiment

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Yellow Red Green</td>
</tr>
<tr>
<td>Upholstery</td>
<td>Leather Textile Leather</td>
</tr>
<tr>
<td>Price</td>
<td>$16,000 $12,000 $4,000</td>
</tr>
</tbody>
</table>

Salping

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUP</td>
<td>40% 30% 20%</td>
</tr>
<tr>
<td>MTX</td>
<td>5% 1% 0%</td>
</tr>
<tr>
<td>Repeat EP</td>
<td>10% 5% 0%</td>
</tr>
</tbody>
</table>
Example choice set

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Relative Importance ($)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous IUP rate within one year</td>
<td>+0.11</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Treatment with MTX for persistent trophoblast</td>
<td>-0.03</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Risk of repeat EP in the same tube</td>
<td>-0.18</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Relative importance of the attributes

All attributes significantly contribute to preference. The negative effect of repeat EP was 1.6 times (0.18/0.11) stronger compared to the positive effect of the spontaneous IUP rate.

Summary patient preference

- Avoiding a repeat EP is the decision making factor.
- The risk of repeat EP is only accepted if compensated by a much better spontaneous IUP outcome after salpingotomy.
Take home

• Always be prepared for salpingotomy in women with wish to conceive again.

• If you are not trained for salpingotomy: make arrangements with your local team when you get home.

ESEP study group

The Netherlands

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- Penn Fertility Care, University of Pennsylvania, Philadelphia, Pennsylvania, K. Barnhart, MD PhD

Surgical management of tubal pregnancy

Ferdi Mol

f.mol@amc.nl
References


### UPCOMING ESHRE EVENTS

#### ESHRE CAMPUS EVENTS

<table>
<thead>
<tr>
<th>Event</th>
<th>Location</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESHRE's 30th Annual Meeting</td>
<td>Munich, Germany</td>
<td>29 June - 2 July 2014</td>
</tr>
<tr>
<td>Epigenetics in reproduction</td>
<td>Lisbon, Portugal</td>
<td>26-27 September 2014</td>
</tr>
<tr>
<td>Endoscopy in reproductive medicine</td>
<td>Leuven, Belgium</td>
<td>15-17 October 2014</td>
</tr>
<tr>
<td>Making OHSS a complication of the past: State-of-the-art use of GnRH agonist triggering</td>
<td>Thessaloniki, Greece</td>
<td>31 October-1 November 2014</td>
</tr>
<tr>
<td>From gametes to blastocysts – a continuous dialogue</td>
<td>Dundee, United Kingdom</td>
<td>7-8 November 2014</td>
</tr>
<tr>
<td>Controversies in endometriosis and adenomyosis</td>
<td>Liège, Belgium</td>
<td>4-6 December 2014</td>
</tr>
<tr>
<td>Bringing evidence based early pregnancy care to your clinic</td>
<td>Copenhagen, Denmark</td>
<td>11-12 December 2014</td>
</tr>
<tr>
<td>An update on preimplantation genetic screening (PGS)</td>
<td>Rome, Italy</td>
<td>12-13 March 2014</td>
</tr>
</tbody>
</table>

For information and registration: [www.eshre.eu/calendar](http://www.eshre.eu/calendar) or contact us at info@eshre.eu