PRE-CONGRESS COURSE 4

The fallopian tube and reproductive function

Special Interest Group Endometriosis / Endometrium
Munich - Germany, 29 June 2014

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The fallopian tube and reproductive function

Munich, Germany
29 June 2014

Organised by
The ESHRE Special Interest Group Endometriosis/Endometrium

Contents

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

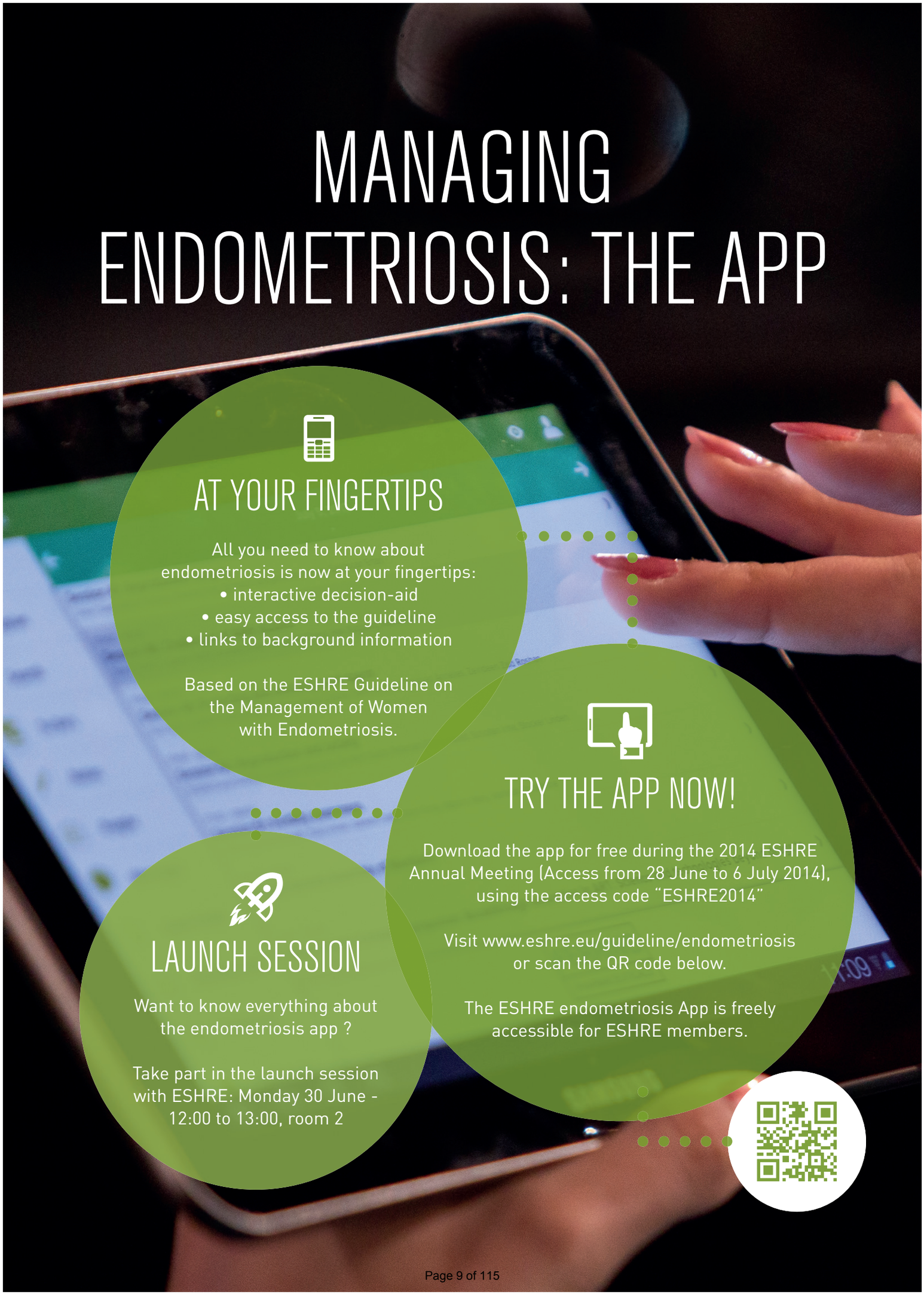
Scientific programme

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



Normal Fallopian tube function

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Department of Women's and Children's Health
Uppsala University
anneli.stavreus-evers@kbh.uu.se

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

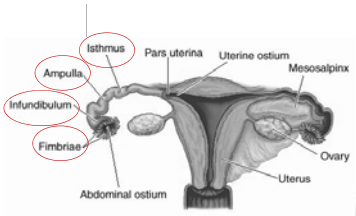
- Fallopian tube, oviduct, uterine tubes, salpinx (salpinges, greek for trumpet)

Oviduct -- the non-mammlian eqivalent

The Fallopian tube

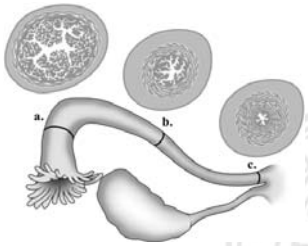
- Gabrielle Fallopio
- 1561, Italy
- Believed function: Simple connection between the uterus and the ovary

The Fallopian tube



- Isthmus
- Ampulla
- Infundibulum
- Fimbriae

Cross section of the Fallopian tube



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

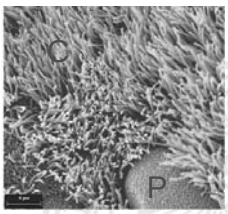
RA Lyons et .al. The reproductive significance of human Fallopian tube cilia *Hum. Reprod. Update (July/August 2006) 12 (4): 363-372.*

Tubal transport

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

Ciliated cells

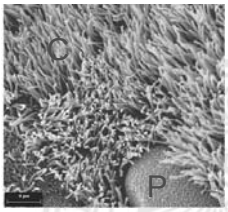
- Cilia reach peak activity at the time of ovulation
- Estrogen increases cilia formation
- Cilia disrupt and remove cumulus mass
- Prostaglandins stimulat cilia beat frequency



Baczynska A et al. Hum. Reprod. 2007;22:968-979

Peg cells

- Peg cells produce follicular fluid
- Progesterone increases the number of peg cells

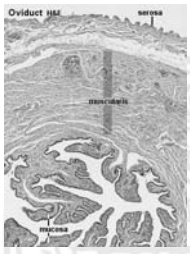


Tubal fluid

- 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

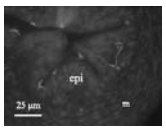
Muscular layers (Subserosa)

- The outermost sheath has longitudinal muscular fibers
- The middle layer has circular muscular fibers
- The innermost layer has spirally arranged muscular fibers,

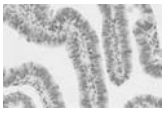


http://legacy.owensboro.kctcs.edu/gcaplan/anat2/histology/histo%20c%20female%20reproductive.htm

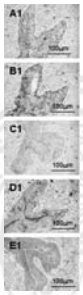
Estrogen receptors, progesterone receptors and prostaglandin receptors



ERα (red) and ERβ(green)



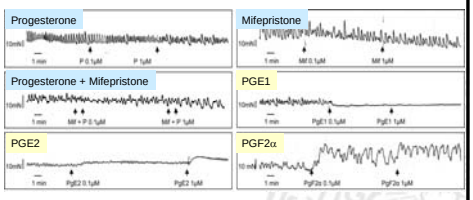
PR



EP1
EP2
EP3
EP4
FP

Shao et al. American Journal of Physiology - Endocrinology and Metabolism, 2006
Shao R et al , American Journal of Physiology - Endocrinology and Metabolism, 2007
Wånggren K et al. Mol. Hum. Reprod. 2006;12:577-585

Tubal contractility after treatment



Wånggren K et al. Hum. Reprod. 2008;23:2359-2368

Functions of the Fallopian tube

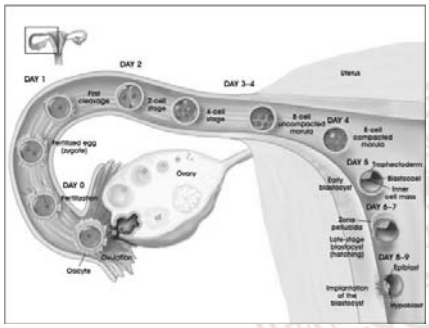
- Transport the sperm from the uterus to the site of fertilization
- Facilitate optimal milieu for the sperm and aid in capacitation
- Moving the embryo using muscular contractions and movement of the cilia
- A period of residence in the tube seem to be a requisite for full development of the embryo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

Sperm binding to the Fallopian tube

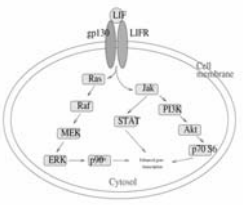
- Sperm reach the Fallopian tube in on hour
- The reservoir in the isthmus is receptor mediated
- The binding make the sperm viable for longer time
- The binding might delay sperm transport
- Capacitation is promoted

Suarez and Pacey, hum Rep Update, 2006 12, 23-37
Holt and Fazeli Molecular Reproduction and Development 2010, 77. 934-943

Fertilisation and transport of the embryo to the uterine cavity



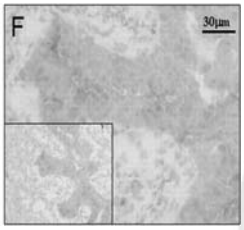
Leukaemia inhibitory factor (LIF)



•Maternal LIF is essential for implantation in mice

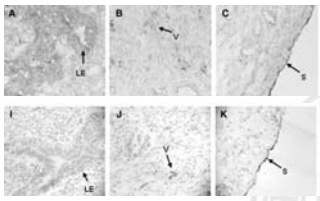
•LIF and its receptors are expressed in the human embryo, endometrium and Fallopian tube

Expression of LIF in the human Fallopian tube



Li H et al. Mol. Hum. Reprod. 2004;10:489-493

Expression of LIFR and gp130 in human Fallopian tube



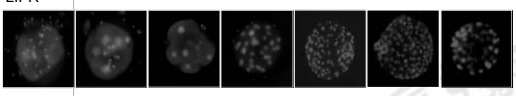
LIFR

gp130

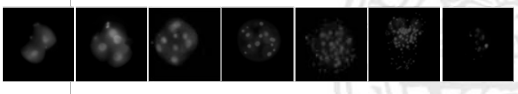
Wånggren K et al. Mol. Hum. Reprod. 2007;13:391-397

LIF receptors in Human embryo

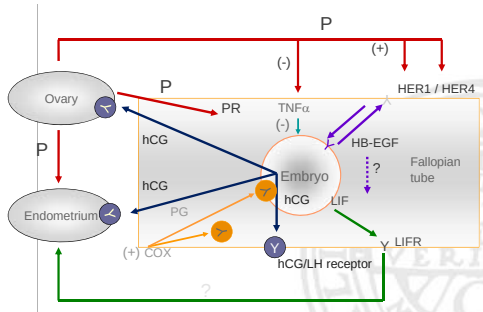
LIFR



Gp130



Signaling in the Fallopian tube



Thank you

References

- RA Lyons et .al. *Hum. Reprod. Update (July/August 2006) 12 (4): 363-372.*
- Baczynska A et al. Hum. Reprod. 2007;22:968-979
- Wånggren K et al. Mol. Hum. Reprod. 2006;12:577-585
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- **Wånggren K et al. Hum. Reprod. 2008;23:2359-2368**
- 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
- **Li H et al. Mol. Hum. Reprod. 2004;10:489-493**

Modelling the fallopian tube: lessons from animal models – Håkan Billig (Sweden)

Contribution not submitted by the speaker

Fallopian Tube as the Origin of Ovarian Cancer

Prof Stephen G. Hillier PhD DSc FRCPath FRCOG

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Fallopian Tube as the Origin of Ovarian Cancer

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:

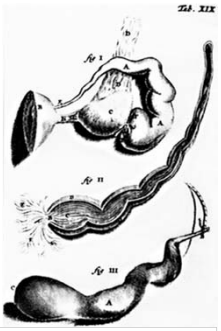
- Discuss theories of ovarian cancer pathogenesis.
- Summarize evidence for fallopian tube as a source of serous ovarian and peritoneal cancers.
- Appraise controversies linking reproductive factors and ovarian cancer.

Fallopian Tube as the Origin of Ovarian Cancer

Conflict of Interest Statement

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

Gabrielis Fallopius(1523–62)



"…Fallopian tubes in women and every kind of female animal are the real delivering vessels, or, if you prefer, the oviducts. It is through them that the eggs of the 'testicles are transferred to the uterus" Regnier De Graaf (1668) *Tractatus De Virorum Organis Generationi Inservientibus* [Jocelyn HD and Setchell BP (1972) J Reprod Fertil Suppl. 17]

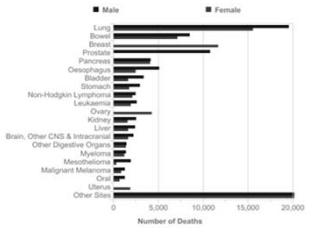
Ovarian Cancer

- Metrics
- Mechanisms
- Mysteries

Ovarian Cancer

- **Metrics**
- Mechanisms
- Mysteries

The 20 Most Common Causes of Cancer Death in 2011
Number of Deaths, UK



Malignant brain, other central nervous system and intracranial tumours only and bowel excludes anus
Cancer of other digestive organs (ICD-10 C26) includes the spleen, unspecified parts of the intestinal tract, and overlapping and ill-defined sites within the digestive system.

Please include the citation provided in our Frequently Asked Questions when reproducing this chart: http://info.cancerresearchuk.org/cancerstats/faqs/#How
Prepared by Cancer Research UK

CANCER RESEARCH UK

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

www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/uk-ovarian-cancer-statistics#riskfactors

EOC Risk Factors

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

www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/uk-ovarian-cancer-statistics#riskfactors

EOC Risk Factors

- Reproductive factors
- Medical conditions

Factor/Condition	Effect on EOC risk
Pregnancy	reduced
Breastfeeding	conflicting
Infertility	increased
Breast density	increased
Oral Contraceptive	reduced
HRT	increased
Endometriosis	increased
Ovarian cysts	increased
Hysterectomy	reduced
Tubal sterilisation	reduced
IUD	increased
NSAIDs	conflicting
Paracetamol	confliction
Diabetes	increased

www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/uk-ovarian-cancer-statistics#riskfactors

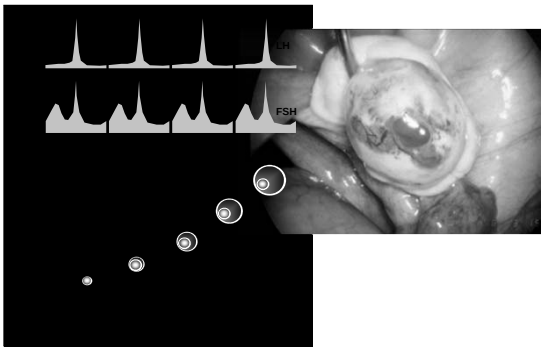
Ovarian Cancer

- Metrics
- **Mechanisms**
- Mysteries

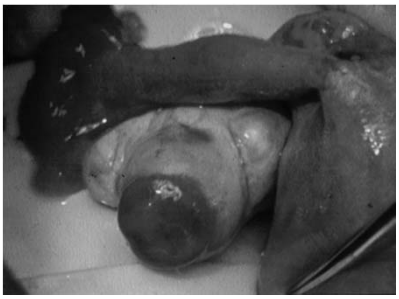
Ovarian cancer pathogenesis

- 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

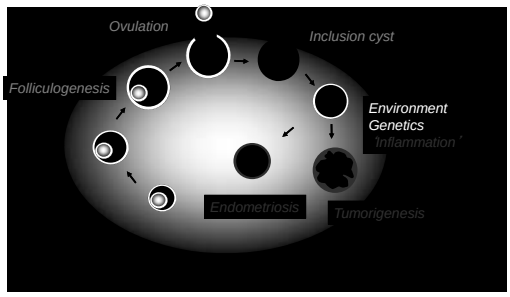
Ovulation as Injury



Ovulation as Inflammation

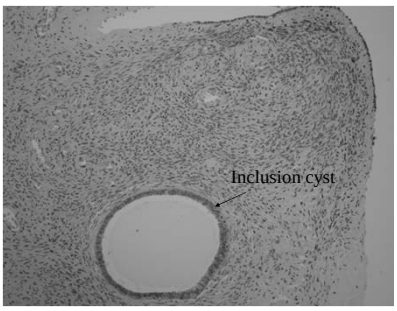


From ovulation to cancer:

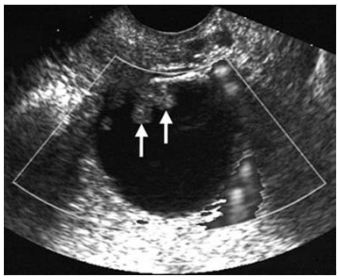


Okamura et al 2003

Familial ovarian cancer history



Ovarian cancer characterised by ultrasound

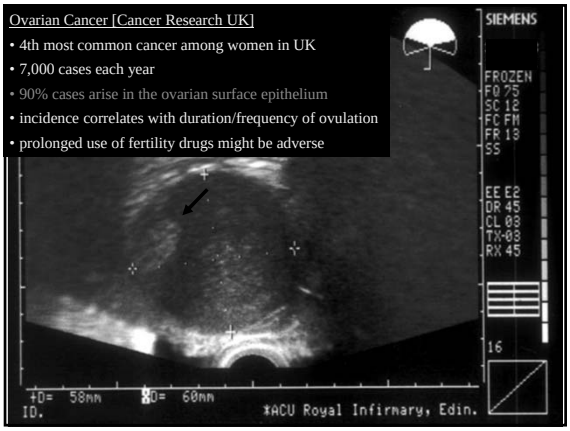


Papillary projections (arrows) within adnexal mass. Doppler study shows flow within papillary projections, confirming that they represent solid, neoplastic elements

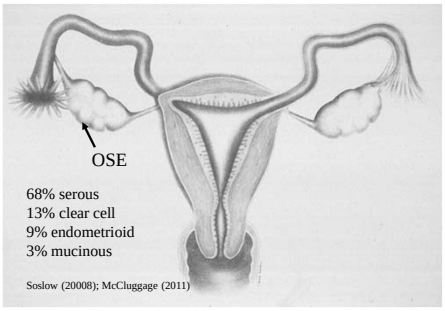
Taken from: Hricak H, Oakley F, Bergman A. Atlas of Cancer. Edited by Maurie Markman, Richard R. Barakat, William J. Hoskins. ©2002 Current Medicine LLC

Ovarian Cancer [Cancer Research UK]

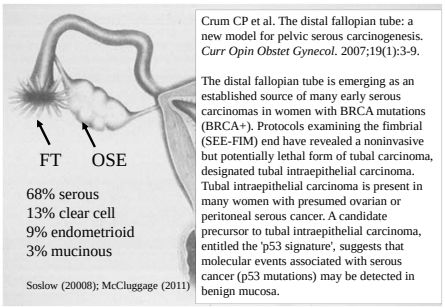
- 4th most common cancer among women in UK
- 7,000 cases each year
- 90% cases arise in the ovarian surface epithelium
- incidence correlates with duration/frequency of ovulation
- prolonged use of fertility drugs might be adverse



Origins of epithelial ovarian cancer



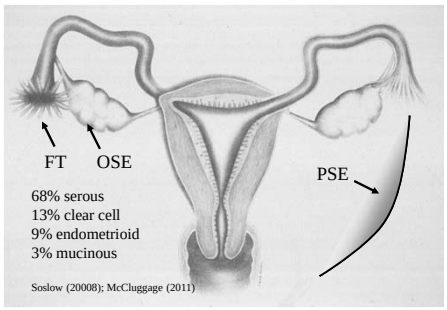
Origins of ovarian cancer



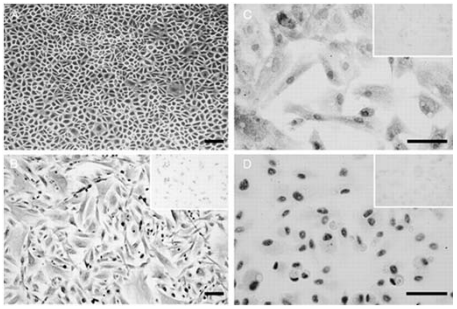
Crum CP et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. *Curr Opin Obstet Gynecol*. 2007;19(1):3-9.

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



Inflammation-associated gene expression in human peritoneal cells



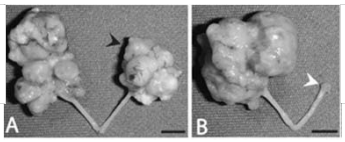
Fegan KS, Rae MT, Critchley HO, Hillier SG. Fegan K S Anti-inflammatory steroid signalling in the human peritoneum. *J Endocrinol* 2008;196:369-376

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
  - Paik et al 2012

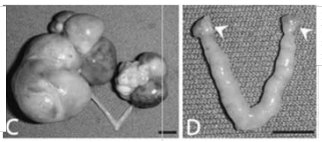
Fallopian tube is the origin of high-grade serous carcinomas in *Dicer-Pten DKO mice*

A. Tumor (black arrowhead) in an 8-mo-old DKO mouse after unilateral removal of the ovary.



B. No tumors in the ovary (white arrowhead) in an 8-mo-old DKO mouse with the fallopian tube removed unilaterally.

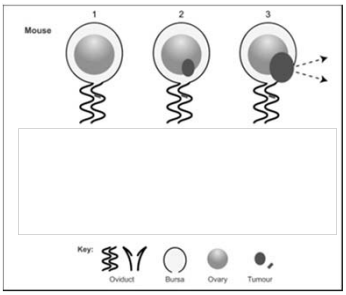
C. After removal of both ovaries, massive tumors still form from the fallopian tubes in a 10.5-mo-old DKO mouse.



D. No tumors with both fallopian tubes removed in an 11.5-mo DKO mouse

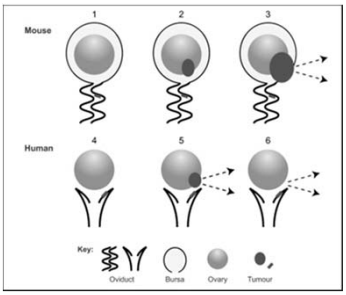
Kim J, Coffey DM, Creighton CJ, Yu Z, Hawkins SM, Matzuk MM. Proc Natl Acad Sci *USA.* 2012 Mar 6;109(10):3921-6.

Nonovarian origins of ovarian cancer



Hillier SG. *Proc Natl Acad Sci USA.* 2012 Mar 6;109(10):3608-9.

Nonovarian origins of ovarian cancer



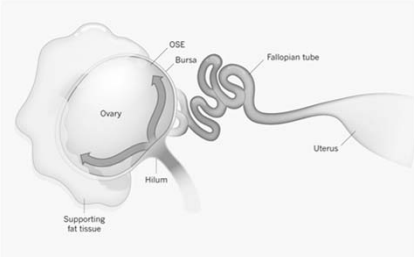
Hillier SG. *Proc Natl Acad Sci USA.* 2012 Mar 6;109(10):3608-9.

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.

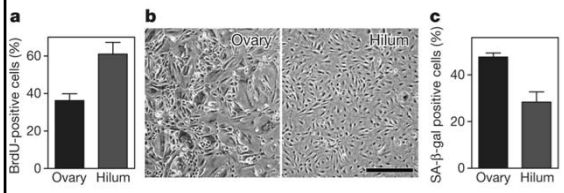
Dubeau L. The cell of origin of ovarian epithelial tumours. *Lancet Oncol.* 2008 Dec;9(12):1191-7
Ernst Lengyel E. Ovarian Cancer Development and Metastasis. *Am J Pathol.* Sep 2010; 177(3): 1053–1064.

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



Brenton JD, Stingl J. Anaromy of an ovarian cancer. Nature. 2013 Mar 14;495(7440):183-4

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



Flesken-Nikitin A, Hwang CI, Cheng CY, Michurina TV, Enikolopov G, Nikitin AY. Nature. 2013 Mar 14;495(7440):241-5

Ovarian Cancer

- Metrics
- Mechanisms
- **Mysteries**

EOC Risk Factors

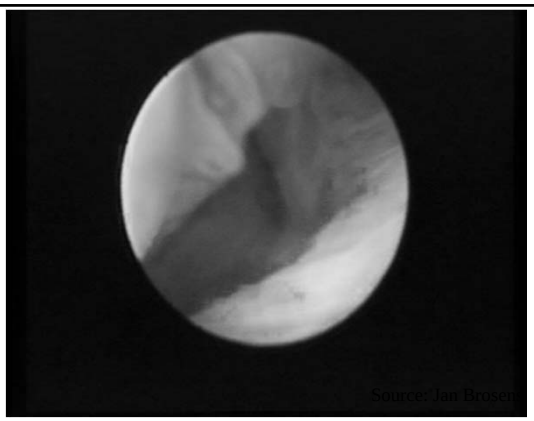
- Reproductive factors
- Medical conditions

Factor/Condition	Effect on EOC risk
Pregnancy	reduced
Breastfeeding	conflicting
Infertility	increased
Breast density	increased
Oral Contraceptive	reduced
HRT	increased
Endometriosis	increased
Ovarian cysts	increased
Hysterectomy	reduced
Tubal sterilisation	reduced
IUD	increased
NSAIDs	conflicting
Paracetamol	confliction
Diabetes	increased

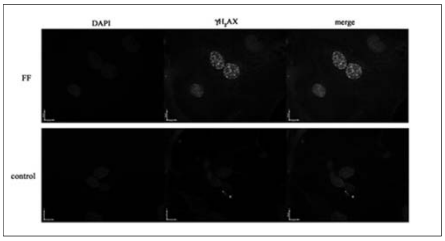
www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/uk-ovarian-cancer-statistics#riskfactors

Fallopian tube as the origin of ovarian cancer

- Tubal ligation reduces ovarian cancer risk
  Rice MS et al. Tubal ligation, hysterectomy and epithelial ovarian cancer in the New England Case-Control Study. *Int J Cancer.* 2013 Nov 15;133(10):2415-21
- How?
  Cibula D et al. Underlying mechanisms of ovarian cancer risk reduction after tubal ligation. Acta Obstet Gynecol Scand. 2011 Jun;90(6):559-63

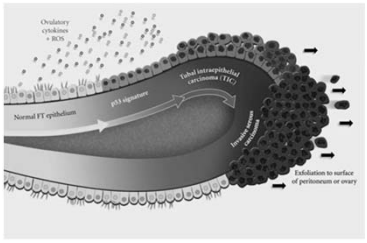


DNA damage is enhanced in FT epithelium exposed to follicular fluid (FF)



Bahar-Shany, Brand H, Sapoznik S, Jacob-Hirsch J, Yung Y, Korach J, Perri T, Cohen Y, Hourvitz A, Levanon K. Exposure of fallopian tube epithelium to follicular fluid mimics carcinogenic changes in precursor lesions of serous papillary carcinoma *Gynecologic Oncology* 2014,132;322-7

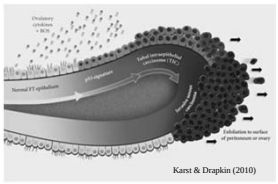
Model for ovarian cancer origination in distal fallopian tube



Karst AM, Drapkin R. Ovarian cancer pathogenesis: a model in evolution. J Oncol. 2010;2010:932371

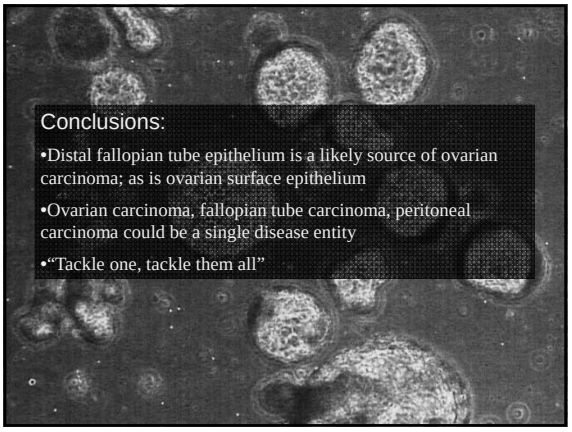
How could tubal ligation reduce ovarian cancer risk?

Cibula D et al. *Acta Obstet Gynecol Scand.* 2011 Jun;90(6):559-63



Karst & Drapkin (2010)

(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



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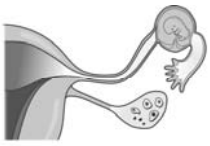
European Commission FPV

The effect of the environment on Fallopian tube function



Andrew Horne

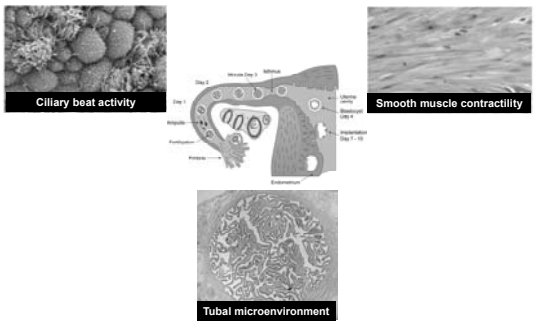
THE UNIVERSITY of EDINBURGH

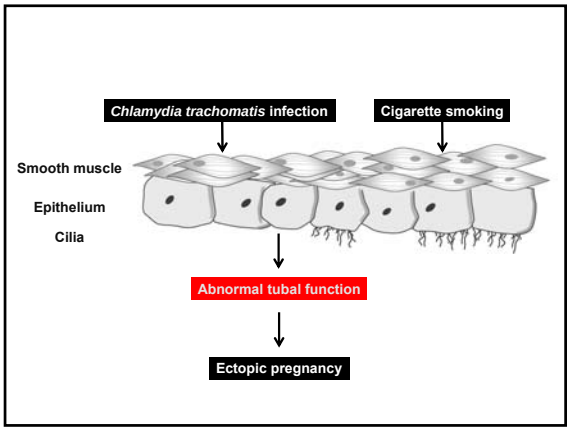
MRC Centre for Reproductive Health

Learning objectives

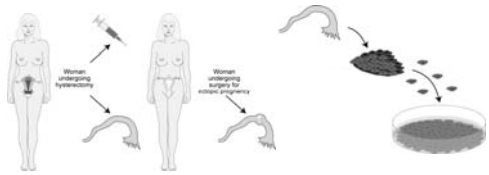
- Understand what biological factors are important for normal tubal function
- Understand the potential mechanisms explaining how environmental factors interfere with normal tubal function

Fallopian tube function





Tissue resources



- Serum and Fallopian tube biopsies
- Immortalised oviductal epithelial cell line (OE-E6/7)

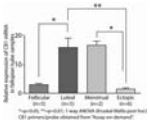
Cigarette smoking

- 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

Jurkovic and Wilkinson 2011; Shao et al. 2012; ASH-UK Smoking Statistics 2014

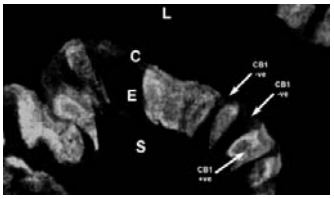
Endocannabinoid system (ECS)

- 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 expressed in human Fallopian tube smooth muscle and epithelium
- Ectopic pregnancy is associated with reduced expression of CB1 in human Fallopian tube



Wang et al. *Nat Med 2004; Horne* et al. *PLoS One 2008*

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

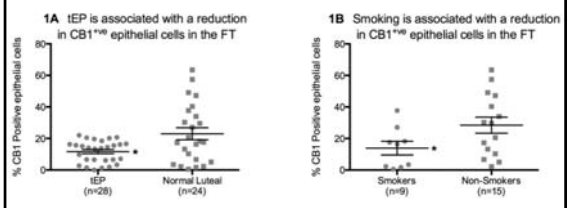
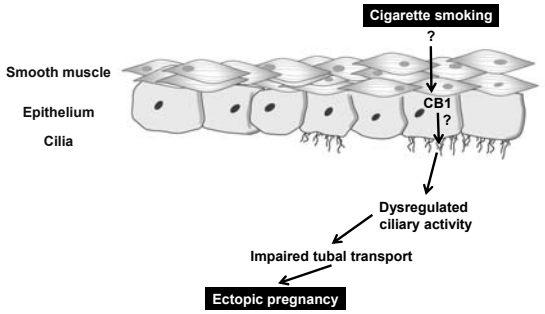
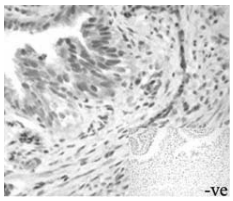


Fig 1: Stereological quantification of the proportion of human FT epithelial cells expressing CB1.



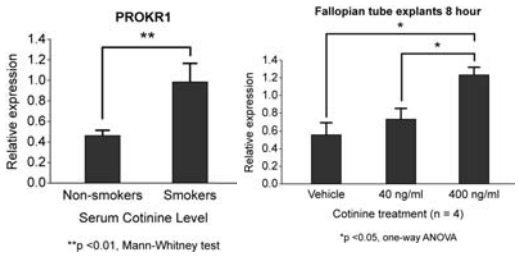
Prokineticins



- 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

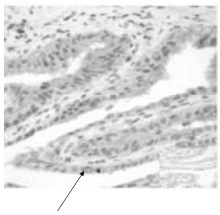
Shaw et al. *Fertil Steril 2010*

Tubal PROKR1 expression and smoking

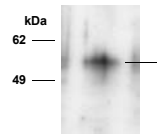


Shaw et al. *Am J Path 2010*

Nicotinic acetylcholine receptor ⟨ -7 expression in human Fallopian tube



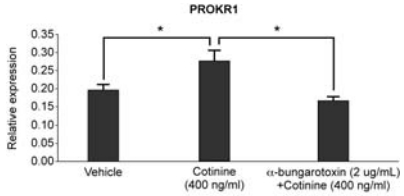
OE-E6/E7 cell lysates



nAChR⟨ -7 expression in the Fallopian tube epithelium

Shaw et al. *Am J Path 2010*

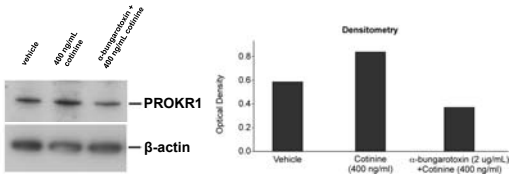
Cotinine increases tubal PROKR1 via nAChR⟨ -7



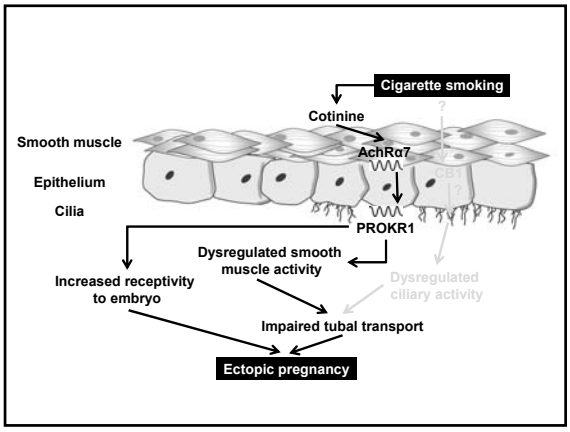
*p <0.05, one-way ANOVA

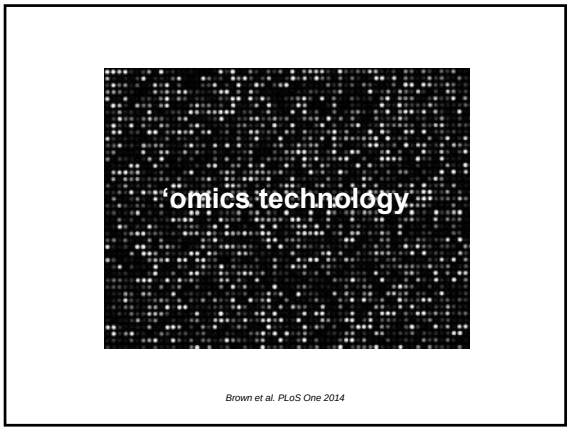
Shaw et al. *Am J Path 2010*

Cotinine increases tubal PROKR1 via nAChR⟨ -7

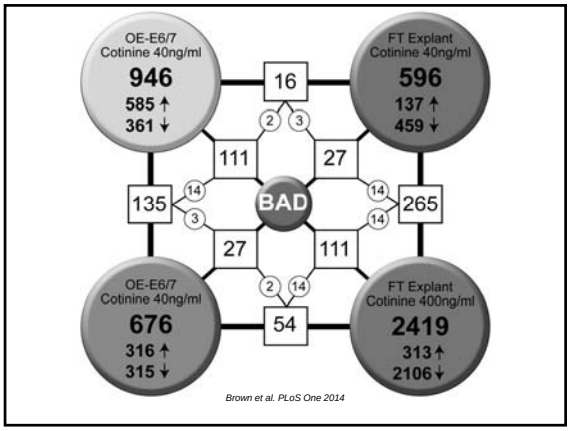


Shaw et al. *Am J Path 2010*



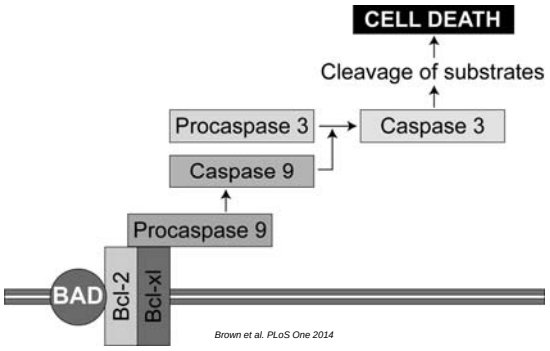


Brown et al. PLoS One 2014



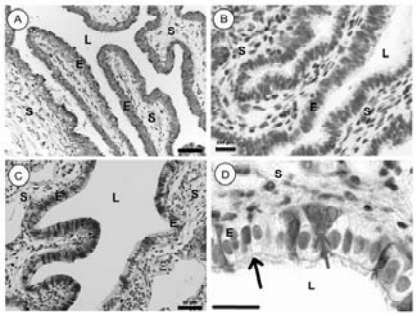
Brown et al. PLoS One 2014

The role of BAD



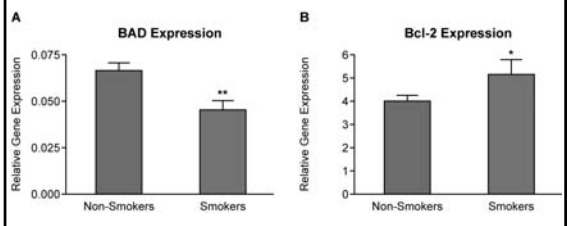
Brown et al. PLoS One 2014

BAD and Bcl-2 expression in Fallopian tube



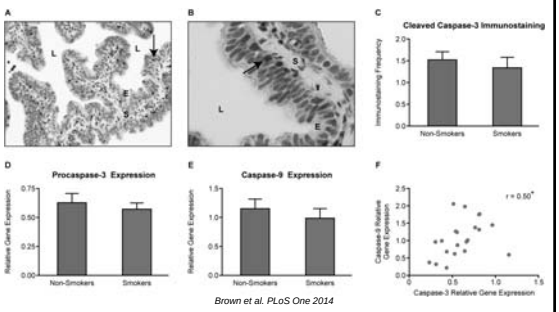
Brown et al. PLoS One 2014

BAD and Bcl-2 expression in Fallopian tube of smokers



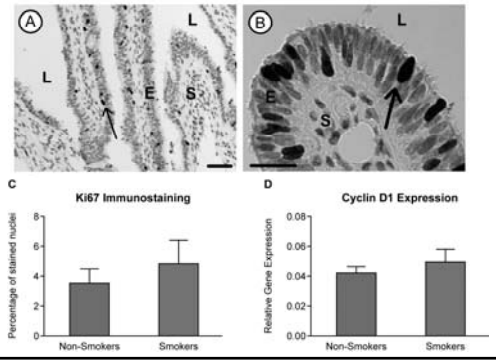
Brown et al. PLoS One 2014

Caspase expression in Fallopian tube of smokers

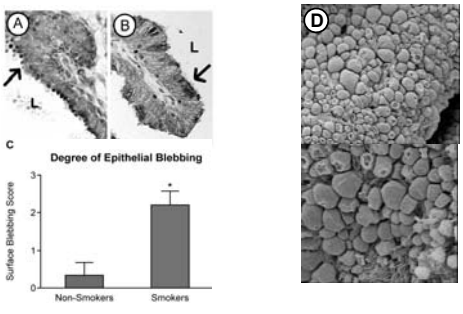


Brown et al. PLoS One 2014

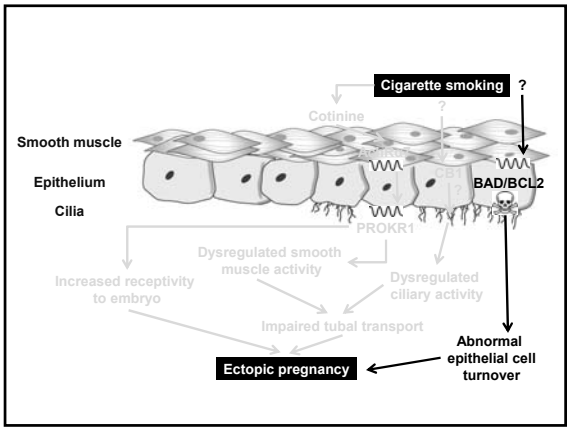
Expression of proliferation markers in Fallopian tube of smokers



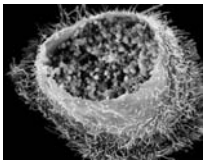
Structural changes in the Fallopian tube of smokers



Brown et al. PLoS One 2014



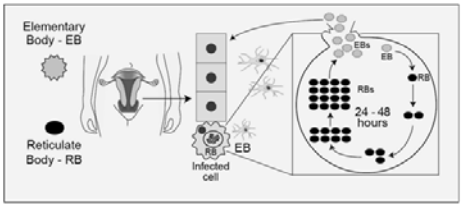
Chlamydia trachomatis infection



- 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

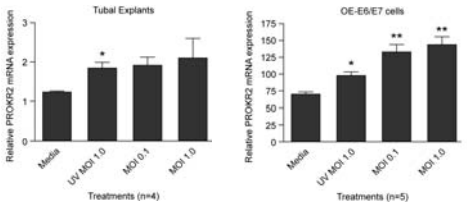
Howie et al. Discov Med 2011; Shaw & Horne Mol Cell Endocrinol 2012

Life cycle of *Chlamydia trachomatis*



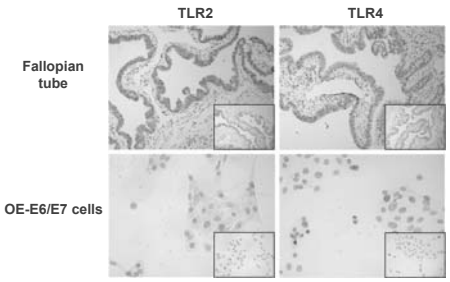
http://bitesized.immunology.org/pathogens-disease/chlamydia-trachomatis

Prokineticins and *Chlamydia*



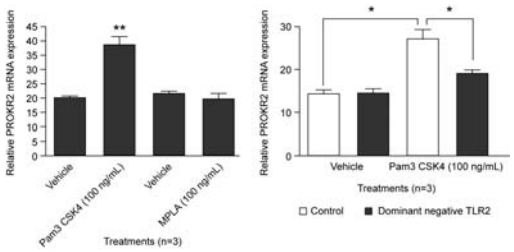
- PROKR2 mRNA expression levels were significantly increased in OE-E6/E7 cells treated with live *C. trachomatis* and UV-killed *C. trachomatis* after 8 hours of treatment

Shaw et al. *Am J Path 2011*



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

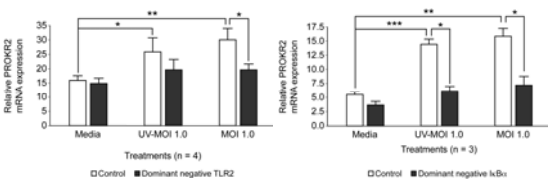
Shaw et al. *Am J Path 2011*



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

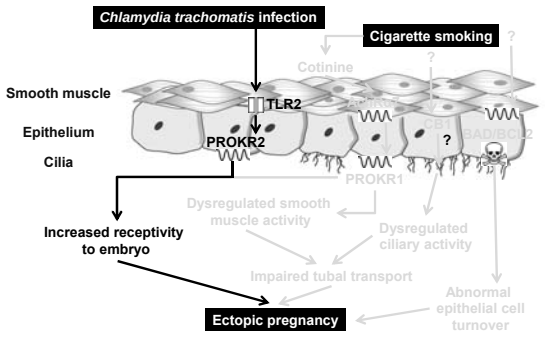
Shaw et al. *Am J Path 2011*

Prokineticins and *Chlamydia*



- *C. trachomatis* infection increases Fallopian tube PROKR2 via TLR2 and NFκB activation resulting in a microenvironment predisposed to ectopic pregnancy

Shaw et al. *Am J Path 2011*

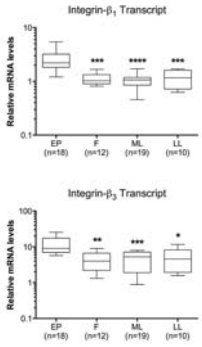


Integrins

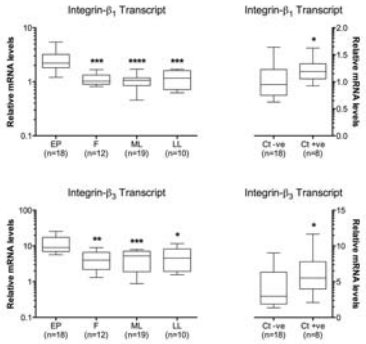
- Family of widely-expressed heterodimeric cell surface receptors that mediate cell – cell and cell – extracellular matrix adhesion
- Integrins (α1β1, α4β1, αvβ3) are markers of receptivity to the presenting embryo in the uterus
- Functional data limited as homozygous β1 and α4 mutations are embryonic 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

Lessey. Hum Rep 1998; Brown et al. Mol Hum Rep 2012

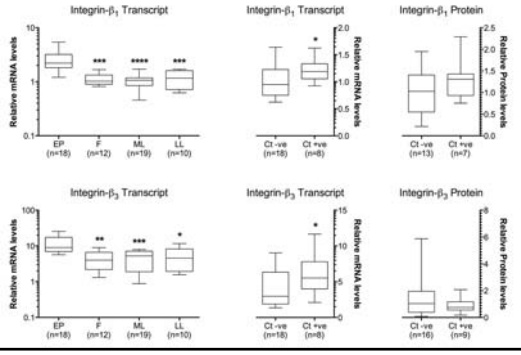
Integrin expression in human Fallopian tube



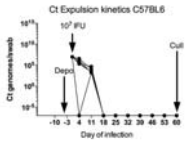
Integrin expression in human Fallopian tube



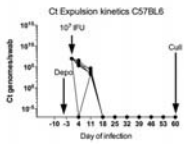
Integrin expression in human Fallopian tube

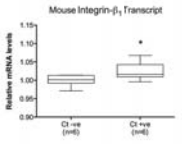


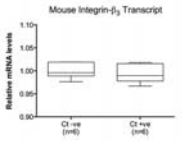
Mouse model mimicking past exposure to *Chlamydia trachomatis* infection



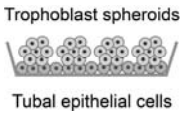
Mouse model mimicking past exposure to *Chlamydia trachomatis* infection







In-vitro model of embryo attachment



Kodithuwakku et al Lab Invest 2012

In-vitro model of embryo attachment

+/- neutralising antibody to β1

Trophoblast spheroids

Tubal epithelial cells

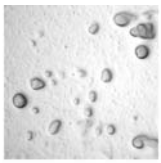
Kodithuwakku et al Lab Invest 2012

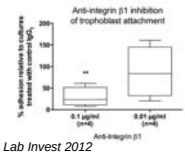
In-vitro model of embryo attachment

+/- neutralising antibody to β1

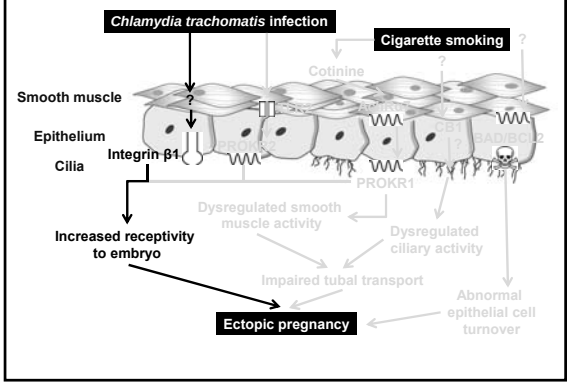
Trophoblast spheroids

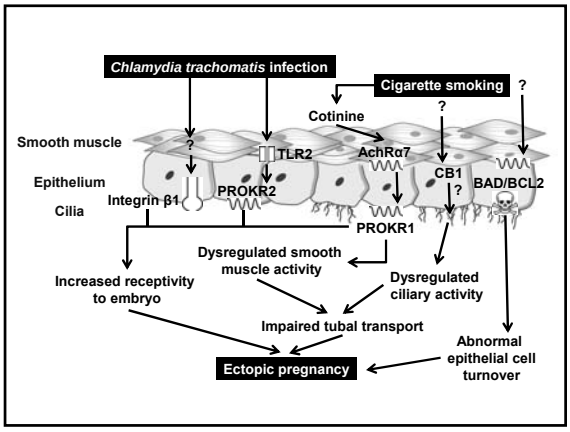
Tubal epithelial cells





Kodithuwakku et al Lab Invest 2012





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Medical management of tubal ectopic pregnancy

Professor Stephen Tong, MBBS, PhD

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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 take methotrexate

Ectopic Pregnancy

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

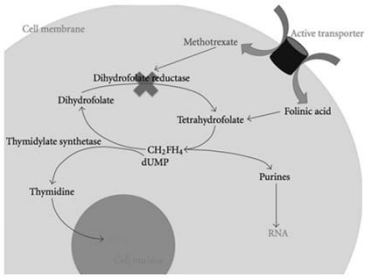
1956: Methotrexate used to cure choriocarcinoma
- **First cure of a solid tumour**

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
- **Tanaka et al (1982)**

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:

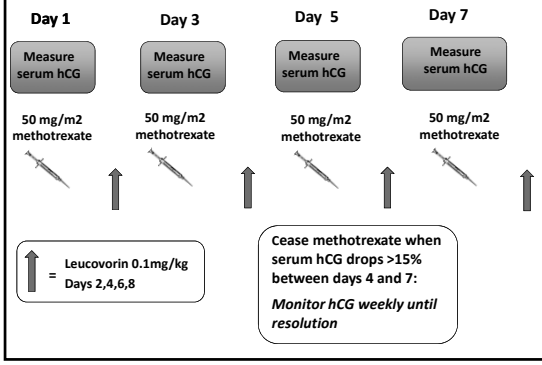
- monitor hCG weekly until resolution

Serum hCG has NOT dropped >15% between days 4 and 7:

- Give second dose of methotrexate, redo this protocol ('new' day 4 and 7)

ACOG Bulletin no 94. (2008)
Barnhart et al (2007)

Methotrexate protocol – multi dose regimen



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

Pretreatment serum hCG of <5000 IU/L:

Supported by:

ACOG Guidelines (2008)

NICE Guidelines (pdated 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)

Pretreatment serum hCG of <3000 IU/L:

Supported by

RCOG (Green Top) Guidelines

Reasons to justify this lower cut-off are from cost-economic analyses', not success rates!

Mol et al (1999)

- Cost analysis on trial data (n=100)
- Medical treatment cost = surgical if pretreatment hCG <1500 IU/L
- Medical treatment costs more than surgical if hCG >1500 IU/L

Sowter et al (2001)

- Economic cost analysis on trial data (n=62)
- Same conclusion: methotrexate cost effective if pretreatment hCG <1500 IU/L

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 betweens 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)

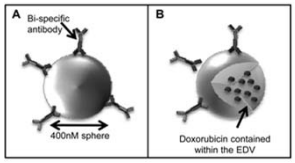
Larger RCT evidence required

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)

Summary

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

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Tubal hydrosalpinx and embryo implantation

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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

Human Reproduction vol.9 no.5 pp.861–863, 1994

Hydrosalpinx reduces in-vitro fertilization/embryo transfer pregnancy rates

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[1]To whom correspondence should be addressed

A retrospective study was designed to examine whether the presence of a hydrosalpinx influenced pregnancy outcome following in-vitro fertilization (IVF) treatment in stimulated

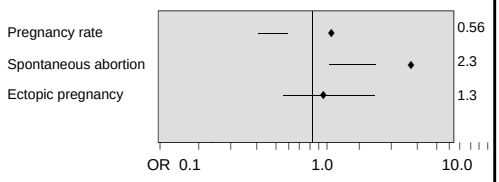
to find out if there w
pregnancy rate and

Materials and meth

The records of all
treatment at the Sahlg
1990 and June 199
exclusion of severe

Meta-analysis of retrospective studies

12 studies, including 6 713 cycles

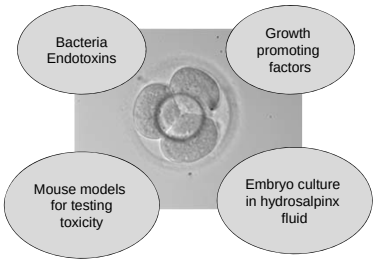


Zeyneloglu et al. 1998

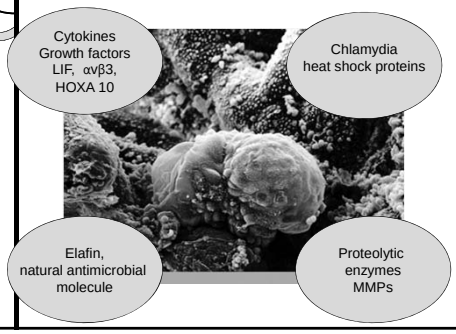
Theories of mechanism

- Embryo toxic properties of the fluid
- Altered endometrial receptivity
- Mechanical hindrance

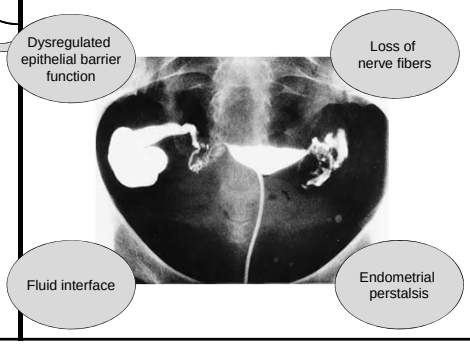
Embryo toxic properties of the fluid



Altered endometrial receptivity



Mechanical hindrance



Main treatment options prior to IVF

- Salpingectomy
- Tubal occlusion
- Transvaginal aspiration

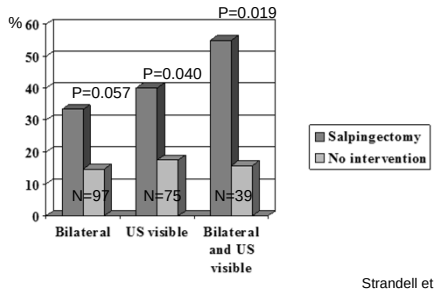
Additional suggested treatments

- Salpingostomy
- Tubal embolization
- Sclerotherapy
- Antibiotic treatment

Salpingectomy

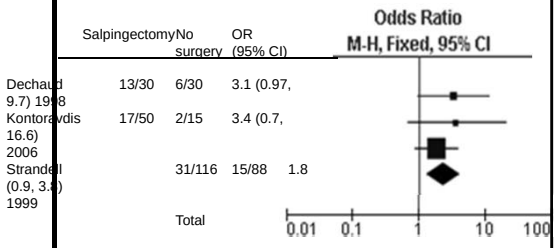
- Scandinavian multicenter RCT
- Salpingectomy vs no surgery prior to IVF
- The importance of fluid
  Ultrasound visible
  Bilateral hydrosalpinges

Effect of salpingectomy on birth rates in patients with hydrosalpinx



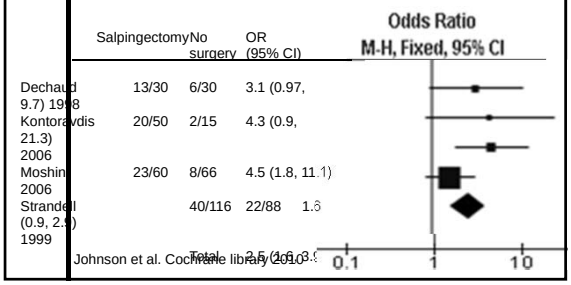
Strandell et al. 1999

Meta-analysis of randomized studies of salpingectomy prior to IVF
Outcome: Ongoing pregnancy



Johnson et al. Cochrane library 2010

Meta-analysis of randomized studies of salpingectomy prior to IVF
Outcome: Pregnancy

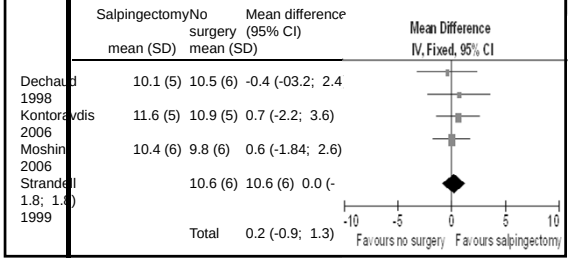


Johnson et al. Cochrane library 2010

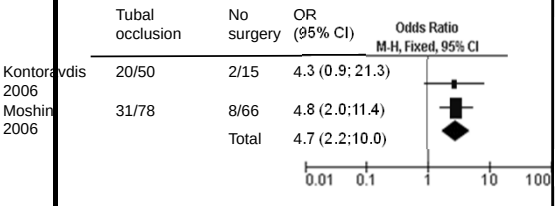
Ovarian function?

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

Meta-analysis of randomized studies of salpingectomy vs. no surgery
Outcome: Number of oocytes

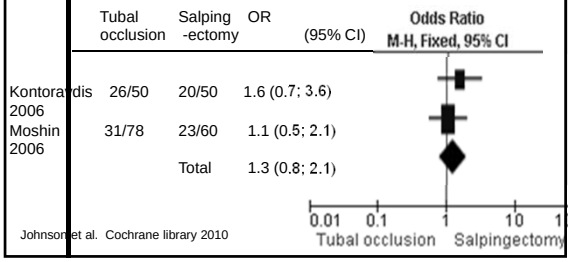


Tubal occlusion vs. no surgery
Outcome: Clinical pregnancy



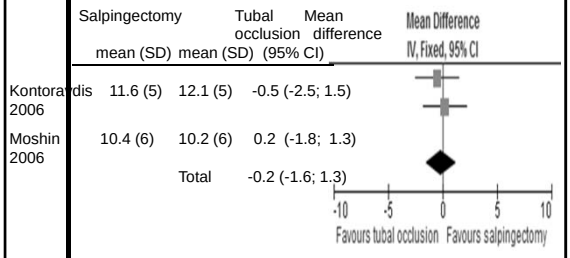
Johnson et al. Cochrane library 20

Tubal occlusion vs. Salpingectomy Outcome: Clinical pregnancy



Johnson et al. Cochrane library 2010

Salpingectomy vs. Tubal occlusion Outcome: Retrieved oocytes



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

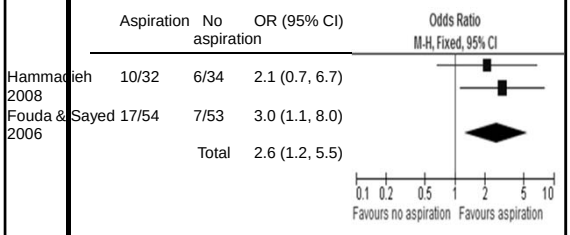
- 115 patients in 11 studies reported
- No controlled studies
- Successful placement in 96% of women
- Tubal occlusion in 98%
- Complications reported
- Pregnancy rate per transfer 38%
- Live birth rate per transfer 28%
- Spontaneous pregnancy after unilateral placement.

Arora et al. 2014

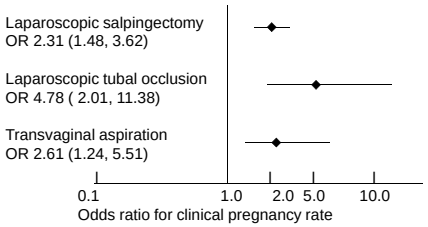
Transvaginal aspiration

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

Transvaginal aspiration vs. no aspiration
Outcome: Clinical pregnancy rate



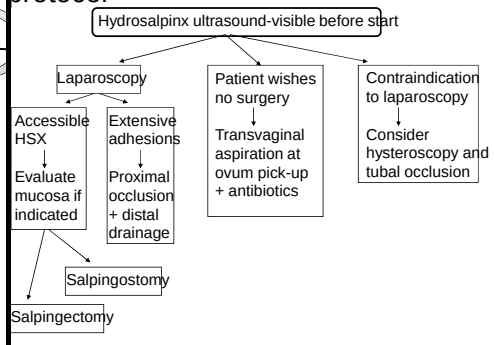
Summary estimates for interventions for hydrosalpinx prior to IVF



Quality of evidence for effect

	Salpingectomy	Tubal occlusion	Transvaginal aspiration
Effective?	Yes	Yes	Yes
Quality of Evidence	High	Low?	Moderate
GRADE	⊕⊕⊕⊕	⊕⊕◯◯	⊕⊕⊕◯
Reason for downgrading		High risk of bias	Precision

Hydrosalpinx and IVF:A treatment protocol



Hydrosalpinx and IVF:A treatment protocol

Hydrosalpinx NOT ultrasound-visible before start

↓

Visible during stimulation

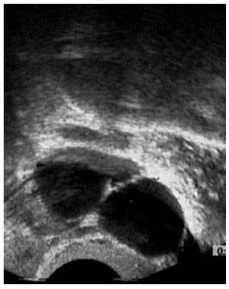
↓

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

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Fertility control: laparoscopic versus hysteroscopic tubal obstruction

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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, 2005)
- 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 (2005) 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
  - Setting
  - Effectiveness
  - Cost-effectiveness
  - Adverse effects
- Gain an insight into the current evidence base, recent developments and the direction of future research

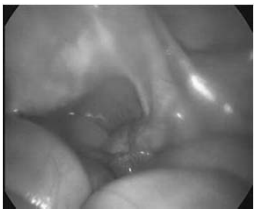
Fertility control: laparoscopic versus hysteroscopic tubal obstruction

UNDERSTANDING THEIR MECHANISMS OF ACTION

Laparoscopic tubal occlusion:

Mechanisms of action

- Mechanical occlusion
  - Later fibrosis
  - Clips may migrate



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Laparoscopic tubal occlusion:

Mechanisms of action cont.

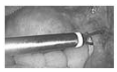
Filshie Clip

- 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

Commercially available (2)

- Essure®
  - Polyethylene Teraphtelate (PET) fibres, anchored by expanding nickel-titanium & 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

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Essure® hysteroscopic sterilisation :

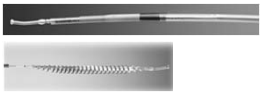
Mechanism of action & procedure

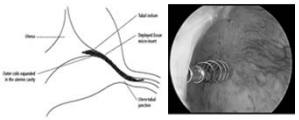
The micro-insert consists of a nickel titanium ('nitinol') outer coil and a stainless steel inner coil to which PET (Dacron) fibres are attached

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-cornual 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





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Fertility control: laparoscopic versus hysteroscopic tubal obstruction

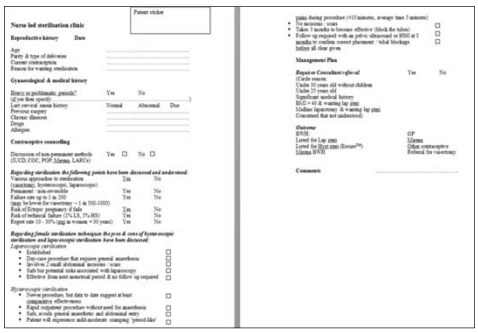
UNDERSTANDING HOW TO COUNSEL, PERFORM AND FOLLOW UP THE PROCEDURES

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 sterilisation
  - Method and route (laparoscopic vs. hysteroscopic)
  - Permanency & reversal
  - Failure rates and long term risk of pregnancy
  - Risk of ectopic pregnancy
  - Safety, complications & risks of laparoscopy
  - Avoid pre-existing, undetectable early pregnancy - women should be advised to use effective contraception until the day of the operation (urinary pregnancy test) and to continue to use it until their next menstrual period

Pre-operative counselling and consent:

Local proforma (Birmingham Women's Hospital)


Patient sticker

Nurse led sterilisation clinic

Reproductive history **Date**

Age
Parity & type of deliveries
Current contraception
Reason for wanting sterilisation

Gynaecological & medical history

History on problematic periods?: Yes / No
(if yes then specify: ...)
Last cervical smear history: Normal / Abnormal / Date
Previous surgery
Chronic illnesses
Drugs
Allergies

Contraceptive counselling

Discussion of non-permanent methods: Yes ☐ No ☐
(IUCD, COC, POP, Mirena, LARCs)

Regarding sterilisation the following points have been discussed and understood:

	Yes	No
Various approaches to sterilisation (vasectomy, hysteroscopic, laparoscopic)		
Failure rate up to 1 in 200	Yes	No
may be lower for vasectomy – 1 in 500-1000)	Yes	No
Risk of Ectopic pregnancy if fails	Yes	No
Risk of technical failure (3%LS, 5%HS)	Yes	No
Regret rate (1 - 10% (age in women <30 years))	Yes	No

Regarding female sterilisation techniques the pros & cons of hysteroscopic sterilisation and laparoscopic sterilisation have been discussed:

Laparoscopic sterilisation
- Established ☐
- Day-case procedure that requires general anaesthesia ☐
- Involves 2 small abdominal incisions / scars ☐
- Safe but potential risks associated with laparoscopy ☐
- Effective from next menstrual period & no follow up required ☐

Hysteroscopic sterilisation
- Newer procedure, but data to date suggest at least comparative effectiveness ☐
- Rapid outpatient procedure without need for anaesthesia ☐
- Safe, avoids general anaesthetic and abdominal entry ☐
- Patient will experience mild-moderate cramping 'period-like' ☐

[pain during procedure (<20 minutes, average time 5 minutes)] ☐
- Not 100% effective ☐
- Takes 3 months to become effective (block the tubes) ☐
- Follow up required with an pelvic ultrasound or HSG at 3 months to confirm correct placement / tubal blockage ☐
- before all clear given

Management Plan

Regain or Consultant referral Yes / No
Under 16 years old
Under 35 years old without children
Under 25 years old
Significant medical history
BMI > 40 & waiting lap. clinic
Midline laparotomy & waiting lap clinic
Concerned that not understood

Outcome

BWH	GP
Listed for Lap clinic	Mirena
Listed for Hyst clinic (Essure™)	Other contraceptive
Mirena BWH	Referral for vasectomy

Comments

Pre-operative counselling and consent:

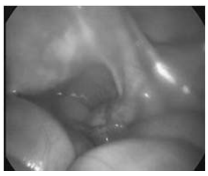
Specific risks of sterilisation

- Laparoscopic (Filshie Clip)
  - Common risks
    - Bruising and discomfort around the scars on your abdomen.
    - Shoulder-tip pain which should be short-lived and not require more than simple painkilling tablets to relieve.
  - Rare but more serious risks
    - Failure, resulting in unplanned pregnancy: the lifetime failure rate is 1 in 200. Pregnancy can occur several years after the procedure.
    - The possibility of a future pregnancy occurring in the fallopian tube (called an ectopic pregnancy) if failure occurs.
    - Pregnancy following a failed sterilisation is more likely to be an ectopic pregnancy than under normal circumstances.
    - Uterine perforation (i.e. accidentally making a small hole in the womb).
    - Damage to internal structures including bowel, bladder or internal blood vessels are serious but infrequent risks
    - (3 in every 1000 procedures).
    - Approximately 5 women in every 100,000 undergoing laparoscopy die as a result of complications.
  - It is possible that the doctor may be unable to gain entry to the abdomen.
    - If the above complications do occur, the doctor may decide to perform open surgery - a laparotomy. This involves having a larger cut to your tummy (abdomen). If necessary, repair of any damage to bowel, bladder or blood vessels would then be carried out. Please be reassured that every effort is made to reduce the chances of this happening.
- Hysteroscopic (Essure)
  - Serious or Frequently Occurring Risk:
    - Pain and or bleeding,
    - Infection requiring antibiotics
    - Fainting episode
    - Injury or perforation of womb or tube
    - Injury to adjacent organ requiring further surgery
    - This procedure is irreversible and must be considered to be a permanent form of contraception
    - Failure to complete procedure in up to 10% of cases
    - Further surgery may be required if the sterilisation devices are found to be in the incorrect position after the procedure
    - Need to use additional contraception for at least 3 months after the procedure until you are informed by the hospital that the confirmation test is satisfactory
    - Failure rate/pregnancy rate after procedure is 1:200
    - If sterilisation should fail and you become pregnant, there may be an increased risk of an ectopic pregnancy

Laparoscopic Filshie clip sterilisation :

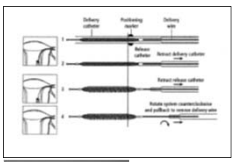
Procedure

- 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 :

Procedure



Insert Video

T Justin Clark MD (Hons) MRCOG, Birmingham Women's Hospital

Follow up

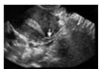
- Laparoscopy
  - Immediate effect
    - Although advise continuation of contraception until next menstrual period
- Hysteroscopy (Essure)
  - 3 months to occlude tubal lumen
  - Advise continuation of contraception for ≥ 3 months until confirmation testing confirms satisfactory procedure
    - AXR
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

Follow up

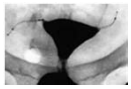
Confirmation testing (Essure)

- **AXR** **(confirmation of satisfactory placement)**
  - Skill to interpret
    - Poor inter-rater reliability (*Veersema S et al; 2010*)
  - Recourse 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*)

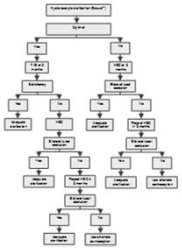
- **HSG** **(confirmation of tubal occlusion)**
  - Gold standard – provides evidence of tubal occlusion, not just adequate placement
  - Radiation, invasive and not always feasible or interpretable
  - Higher costs



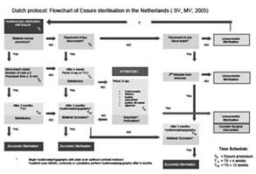
Follow up

Confirmation testing (Essure): Protocols

- **Birmingham Women's Hospital, UK**



- **Netherlands**



Fertility control: laparoscopic versus hysteroscopic tubal obstruction

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 'office'
      - valued perceived safety, absence of scars (59%), convenience (33%) and avoidance of general anaesthesia (72%) and hospital stay (50%) *(Sinha et al; 2007)*
    - Women preferring day-case
      - Valued avoidance of peri-operative 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 'office' – their prime reasons were
      - 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

Laparoscopic versus hysteroscopic tubal obstruction:
Feasibility

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

Table 2. Relation of potential prognostic clinical factors to successful completion of outpatient hysteroscopic sterilisation (Essure™) procedure: results of univariable and multivariable analyses (see Methods for details)

Prognostic factor	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
BMI (increasing)	1.04	0.94–1.14	0.45			
Phase of menstrual cycle (nonsecretory versus secretory)	11.2	1.35–92.6	0.03*	10.2	1.13–91.0	0.04*
Need for cervical dilatation (no versus yes)	1.3	0.15–11.7	0.81			
Uterine axis (anteflexed versus nonanteflexed)	0.61	0.12–3.1	0.55			
Uterine size (≤8 weeks versus >8 weeks)	15.7	3.19–77.1	0.001*	14.0	2.5–79.5	0.003*
Operator (T.J.C. versus J.K.G.)	1.95	0.45–8.5	0.37			

*$P < 0.05$, statistically significant.

Laparoscopic versus hysteroscopic tubal obstruction:
Feasibility

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

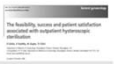


Table 1. Reasons for failure to bilaterally place Essure™ devices

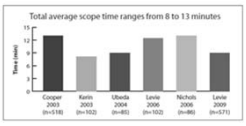
Reason for failed placement (n)	Details
Anatomic factors (5)	
Inability to access the uterine cavity (1)	Severe cervical stenosis (two previous caesarean sections) and procedure abandoned after cervical perforation with Hegar dilators
Nonidentification of one tubal ostia (2)	In one woman, the ostia was obscured by a submucous fibroid; in the other woman, one ostia was apparently absent
Stenosis of tubal ostia (2)	Failure to cannulate tubal ostia despite optimal tubal access
Patient factors (2)	
Obesity + large uterus (1)	Working length of hysteroscope using vaginoscopic approach insufficient to reach tubal ostia
Anxiety (1)	Failure to tolerate hysteroscopic procedure due to high levels of anxiety
Operative factors (2)	
Poor visualisation of tubal ostia (1)	Congested and ragged secretory endometrium obscuring adequate visualisation
Inability to optimally site hysteroscope (1)	'Lateralised' tubal ostia precluding approximation of hysteroscope to enable Essure™ device deployment

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




One-stop health care for women... and it can all be done in your lunch hour!

The sterilisation took about ten minutes

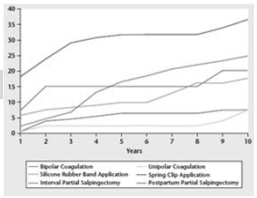
I did not want any more kids

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 occluive 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 Sterilization (CREST) study (*Peterson HB et al; 1996*) followed 10,685 sterilised women for up to 14 years following their tubal occlusion. The study found that:
  - Tubal ligation is highly effective
  - Effectiveness varies by method employed and by patient age, race and ethnicity
  - The cumulative 5-year probability of pregnancy following tubal ligation was 13 / 1000 procedures (95% CI 7.5-36)
  - The cumulative 10-year probability of pregnancy following tubal ligation was 18.5 / 1000 procedures (95% CI 15.1-21.8)
    - Pregnancy rates were highest following laparoscopic Hulka- Clemens clip sterilization (36.5 /1000 procedures) and lowest following unipolar coagulation (7.5 / 1000 procedures)
  - Filshie clips were not included in this study as they were not available in the USA but a study by *Kovacs GT et al; 2002* reported a pregnancy rate of 2-3 / 1000 procedures at up to 5 years follow up



Laparoscopic versus hysteroscopic tubal obstruction:
Effectiveness - Hysteroscopy

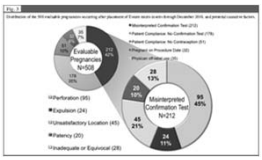
- Hysteroscopic sterilisation using the Essure method is highly effective
  - The pivotal trial data has recorded no pregnancies to date (*Cooper JM et al; 2003*) and the estimated cumulative 5-year effectiveness rate is 99.7% (*Bradley L; 2008*)
  - Based upon the largest published series to date from 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 2001-2010 divided by the number of Essure kits sold worldwide, corresponds to a success rate of 99.74% (748/497 305) (*Munro MG et al; 2014*).
    - Although this figure is likely to be an underestimate, the efficacy rate in general gynaecological practice, at least in 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

(from Munro MG 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 90 post-procedure (% "very satisfied" or "somewhat satisfied") - *(from Duffy et al; 2002)*
    - 81% (LS) vs. 94% (HS) at 3 months (P>0.05)

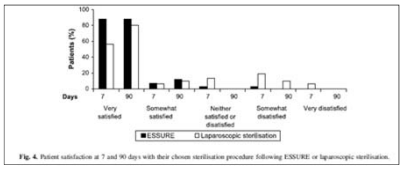


Fig. 4. Patient satisfaction at 7 and 90 days with their chosen sterilisation procedure following ESSURE or laparoscopic sterilisation.

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% CI 64–84%) women, with 10/57 (17%) describing the pain as severe.
  - A minority of women (9/76, 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% CI 68–88%) women, with 6/76 (8%) describing this pain as severe.
  - In the majority of women, the duration of this postoperative pain was less than 4 hours (37/60, 62%), with only 8/60 (13%) describing such pain as lasting greater than 8 hours.
- Laparoscopic 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=0.008)

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 *(Sinha et al; 2007)* although a larger series from Spain reported lower rates of severe pain (4%) and vaso-vagal reactions (2%) *(Povedano et al' 2012)*
    - The authors of this series reported side effects in 115/4306 (3%) of Essure procedures which included 21 device expulsions, two device migrations, one tubal perforation, one case of pelvic inflammatory disease, one case of persistent pelvic pain and two presumed nickel allergies.
  - Laparoscopy under general anaesthesia has the potential for rare but serious adverse events including visceral injury and death *(Greenberg JA; 2008)*
    - Between 1977 and 1981, there were 29 deaths reported to the Centers for Disease Control and Prevention after tubal sterilization, of which 3 were major vessel injuries
    - In a trial sponsored by the World Health Organization, 819 women undergoing LTL with electrocautery in 8 centres around the world major surgical complications occurred in 0.9% of the women and another 0.9% experienced significant anaesthetic-related complications

Laparoscopic versus hysteroscopic tubal obstruction:
Adverse effects

- Comparison between approaches *(from Duffy et al; 2002)*

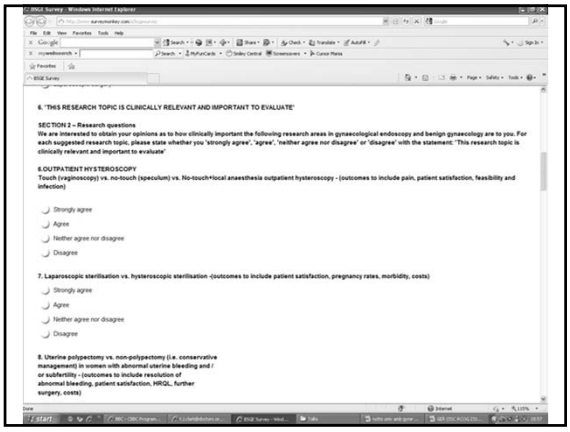
End point	Hysteroscopic Sterilization (n = 59)	Laparoscopic Sterilization (n = 24)	*P* Value
Adverse events in recovery room (number of patients)	2 vasovagal reaction 2 postoperative pain 1 cervical bleeding 1 suspected tubal perforation	3 cervical tear 1 nausea and vomiting 1 postoperative pain 1 uterine fundal perforation	NS (*P* value not reported)
Adverse events reported 1 week postprocedure (number of patients)	1 pain/infection in perineum/bleeding/thrush/mood swings 1 headache 1 vaginal spotting	1 inflammation of umbilicus/retention of urine 1 backache and cramp 1 constipation/hemorrhoids/wound infection 1 headache/dizziness/abdominal pain	NS (*P* value not reported)
Adverse events reported 3 months postprocedure (number of patients)	2 right-sided abdominal pain 1 mild pain on left side of abdomen 1 bilateral pelvic pain 1 musculoskeletal pain in right lower quadrant 1 possible salpingitis	2 wound infections 1 lower abdominal pain 1 inflammation of umbilicus 1 weeping wound 1 headaches and reflux esophagitis	NS (*P* value not reported)

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 observational data sets to identify predictive factors for success, optimal experience etc.**
  - **RCT with parallel cost-effectiveness / cost utility analysis**
    - **Outcomes?**
    - **Pregnancy rates not feasible (large sample size as 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. analgesia; anaesthesia; conscious sedation; warming saline; vaginoscopy**
  - **Confirmatory testing**
    - **Who? – is universal testing required; patient selection**
    - **Optimal confirmatory tests – evaluate new technologies e.g. 3D USS**
  - **Use outside of developed countries**
    - **Feasibility of mass production & reduced costs**
    - **Evaluation of new technologies (e.g. altaseal; ovalastic) or adaptions of existing Essure technology (e.g. immediate occlusion) against current gold standards (Essure and Filshie clip)**
- **Laparoscopic sterilisation:**
    - **Feasibility of outpatient mini-laparoscopy**
    - **Single port surgery**



Hysteroscopic sterilisation

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 satisfactio

  55/80 (69%)

Laparoscopic versus hysteroscopic tubal obstruction:

Future research - contraception

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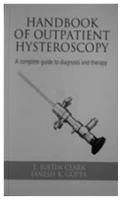
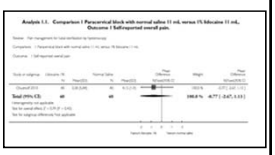
Hysteroscopic tubal obstruction:

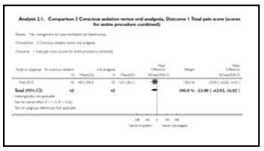
Optimising pain relief and patient experience

Hysteroscopic tubal obstruction:

Optimising pain relief and patient experience

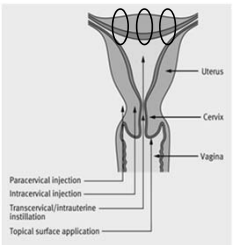






Optimising performance and patient experience: Local anaesthesia

- Outpatient = improving patient experience



Laparoscopic versus hysteroscopic tubal obstruction:

Future research - contraception

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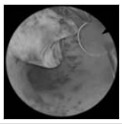
Laparoscopic versus hysteroscopic tubal obstruction:

Future developments- training

- A multi-centre prospective study of 578 hysteroscopic sterilisations from 76 operators in the US (*Levie et al; 2011*) to assess experienced practitioners (n=39) with newly trained physicians (n=37)
  - Longer treatment time in novices on average by 1.7 minutes (9 vs. 10.7 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 *(Chudnoff S et al; 2009)*
  - Face and construct validity *(Panel P et al; 2012)*
  - Time to proficiency



Laparoscopic versus hysteroscopic tubal obstruction:

Future research – assisted conception

- **Treatment of hydrosalpinges**
  - Provisional observational data (*Galen D et al; 2011 and several other case series*) from failed hysteroscopic sterilisations and from treatment of hydrosalpinges prior to IVF suggest:
    - Feasible
      - also where laparoscopic approaches have failed or considered too complex
    - (Effective)
    - No increase in adverse pregnancy outcomes
  - RCT of laparoscopic vs hysteroscopic tubal occlusion +/- parallel cost-effectiveness / cost utility analysis
    - Outcomes:
      - Safety
      - Feasibility
      - Pregnancy rate
      - Neonatal?
      - Economic

Fertility control: laparoscopic versus hysteroscopic tubal obstruction

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

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Thank you for your attention

Any Questions?

Management of tubal pregnancy: salpingectomy vs. salpingostomy

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The Health & Medical Care Committee of the Region Västra Götaland, Sweden.

Disclosure

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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

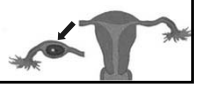
1641-1673 Reinier de Graaf, Delft, the Netherlands

De Graaf B, 1963. Ankum WM, 1996

Pioneer salpingectomy - 1883

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

- Asepsis vs. antisepsis
- 1883 first successful salpingectomy
  - synonyms: salping**ec**tomy or tub**ec**tomy -

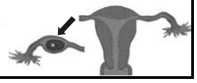


Tait RL. 1882, 1884, 1888

Pioneer salpingotomy - 1922

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

- 1920 first successful salpingotomies
  - synonyms: salping**o**tomy or tub**o**tomy -



Whitehouse B. 1922

Salpingotomy ↔ salpingectomy

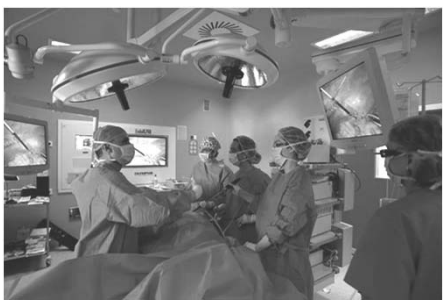
Salpingotomy was introduced without any evidence that this intervention had better outcomes for future fertility

Despite observed disadvantages:

1. Persistent trophoblast (PT) Richards BC. 1984
2. Repeat ectopic pregnancy Rosenblum JM. 1960

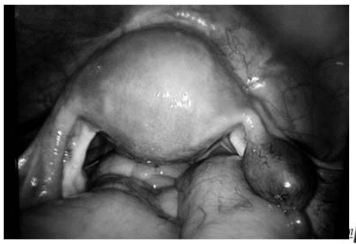
Pioneer in laparoscopy

Laparoscopy 2014



Pioneers in laparoscopic surgery for EP

- 1973 Salpingectomie (Shapiro, USA)
- 1980 Salpingotomie (Bruhat, Fr)



Professor Maurice - Antoine Bruhat (1934 - 2014) Founder of ESGE

What is known?

Surgery 	Laparoscopy is cost-efffective compared to open surgery.	Hajenius PJ, 2007
Methotrexate 	MTX is cost-effective compared to laparoscopic salpingotomy in asymptomatic women with hCG < 3.000 IU/L	Hajenius PJ, 2007
Expectant management 	1 week expectant as effective as single dose MTX in women with persisting PUL or EP	Van Mello NM, 2013

Future fertility

Objective

- To asses 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

Published protocol Mol.F, 2008

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*

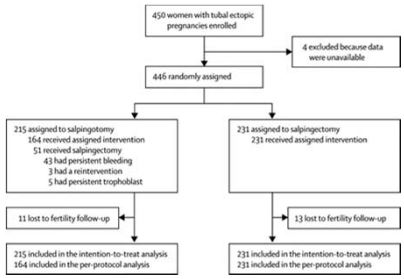
- 450 women (alpha error 5%, beta error 20%, LFU 10%)
- Clinical significance: improvement in ongoing pregnancy rate at 2 years from 40% to 55%

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

	Salpingotomy (n=215)	Salpingectomy (n=231)
Mean age (years)	30·9 (5·5)	30·9 (5·5)
Age ≥ 35 years	110 (51%)	118 (51%)
Risk factors for tubal disease		
Known tubal disease*	6 (3%)	4 (2%)
History of chlamydia	26 (12%)	22 (10%)
History of pelvic inflammatory disease	5 (2%)	9 (4%)
History of ectopic pregnancy	9 (4%)	5 (2%)
History of termination of pregnancy	41 (19%)	54 (23%)
Intrauterine device in situ	3 (1%)	2 (1%)
Symptoms		
None	13 (6%)	10 (4%)
Pelvic pain only	38 (18%)	34 (15%)
Vaginal bleeding only	24 (11%)	25 (11%)
Pelvic pain and vaginal bleeding	138 (64%)	155 (67%)
Ultrasound findings		
Ectopic mass	139 (65%)	154 (67%)
Mean size of ectopic mass (cm)†	2·6 (1·3)	2·4 (1·4)
Fetal heart beat present	18 (8%)	26 (11%)
Median preoperative serum hCG (IU/L)‡	2181 (860–4298)	2409 (920–6036)
Location of tubal pregnancy at surgery		
Ampulla	163 (76%)	177 (77%)
Fimbriae	14 (7%)	26 (11%)
Isthmus	31 (14%)	22 (10%)
Tubal rupture present during surgery	0	1 (<1%)§

(Serious) adverse events

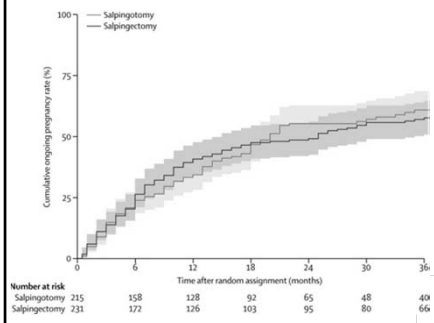
	Salpingotomy (n=215)	Salpingectomy (n=231)
Conversion to open surgery	3 (1%)	3 (1%)
Conversion to salpingectomy	43 (20%)	NA
Blood transfusion	14 (7%)	7 (3%)
Initial admission		
Repeat laparoscopy with salpingectomy for suspected bleeding*	2 (1%)	0
Readmission*		
Repeat laparoscopy with salpingectomy for suspected bleeding	1 (<1%)	0
Repeat laparoscopy with salpingectomy for persistent trophoblast	5 (2%)	0
Other surgical reintervention	4 (2%)	2 (1%)
Readmission only	10 (5%)	3 (1%)

Data are n (%). *Repeat laparoscopy and readmissions were regarded as serious adverse events.

Table 2: **Adverse events**

am center for reproductive medicine

Primary outcome



Secondary outcomes

	Salpingotomy (n=215)	Salpingectomy (n=231)	Relative risk (95% CI)	p value
Persistent trophoblast	14 (7%)	1 (<1%)	15·0 (2·0–113·4)	0·01
Repeat ectopic pregnancy	18 (8%)	12 (5%)	1·6 (0·8–3·3)	0·19
Ipsilateral tube	7 (3%)	3 (1%)	2·5 (0·7–9·6)	0·18
Contralateral tube	8 (4%)	7 (3%)	1·2 (0·5–3·4)	0·69
Persisting pregnancy of unknown location	3 (1%)	2 (1%)	1·6 (0·3–9·5)	0·60
Ongoing pregnancy by:				
Ovulation induction	0	3 (1%)	..	..
Intrauterine insemination	0	1 (<1%)	..	..
In-vitro fertilisation	7 (3%)	2 (1%)	3·8 (0·8–17·9)	0·10

Data are n (%), unless otherwise indicated.

Table 3: **Secondary outcomes**

am center for reproductive medicine

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)

	Salpingotomy	Salpingectomy	Fecundity rate ratio (95% CI)	Interaction p value
Age group				
<31 years	57/105 (54%)	55/113 (49%)	1·16 (0·80–1·68)	0·56
≥31 years	51/110 (46%)	59/118 (50%)	0·95 (0·65–1·39)	..
History of previous ectopic pregnancy				
Yes*	0/9	1/5 (20%)	..	0·95
No	108/206 (52%)	113/226 (50%)	1·10 (0·84–1·43)	..
Preoperative serum hCG†				
<2335 IU/L	64/109 (59%)	63/110 (57%)	1·14 (0·80–1·61)	0·57
≥2335 IU/L	43/103 (42%)	48/116 (41%)	0·98 (0·65–1·48)	..
Size of ectopic mass on ultrasound‡				
<2·1 cm	29/61 (48%)	30/62 (48%)	0·99 (0·59–1·65)	0·42
≥2·1 cm	34/64 (53%)	27/67 (40%)	1·36 (0·82–2·27)	..

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

Mol F, 2014

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

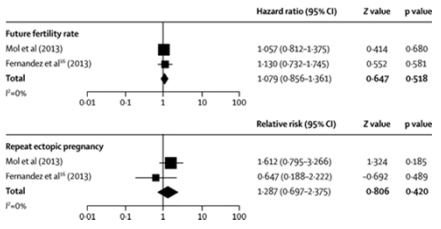
Mol F, 2014

DEMETER study

- Inclusion 2005-2009, 17 centres France
- 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

Fernandez H, 2013

Meta-analysis n=649



No statistical heterogeneity observed

Mol F, 2014

Clinical heterogeneitiy

	DEMETER	ESEP
Population	contralateral tubal disease included	contralateral tubal disease excluded
Intervention	Salpingotomy with profylactic dose MTX	Salpingotomy without MTX
Outcome	Composite outcome including miscarriages and pregnancy terminations	Ongoing pregnancy by natural conception
	Time to pregnancy calculated from desire for pregnancy	Time to pregnancy from random assignent
Sample size	20% difference	15% difference

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.

Mol F, 2013

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)

ICER=
Δ costs/Δ effects

- Cost-effectiveness planes (1000 random samples)

Results – resource use and unit prices

Initial treatment	Salpingotomy (n= 215)	Salpingectomy (n= 231)	Unit price (€)
Laparoscopy-start up			
Laparoscopy (min)			
Conversion open surgery			
Conversion salpingectomy			
Re-laparoscopy with salpingectomy for suspected bleeding			
Bloodtransfusion (unit)			
Initial admittance day			
Subsequent days			
Bloodtransfusion (unit)			
Consultation out patient clinic			
hCG serum including consultation by telephone			

Results – resource use and unit prices

Re-admission	Salpingotomy (n= 215)	Salpingectomy (n= 231)	Unit price (€)
Re-admission only			
Re-admission with surgical re-intervention			
◦ diagnostic laparoscopy			
◦ laparoscopic salpingectomy			
◦ surgical exploration at trocar site			
Re-admission day – no.			

Results – resource use and unit prices

Persistent trophoblast	Salpingotomy (n= 215)	Salpingectomy (n= 231)	Unit price (€)
Kidney liver serum check			
Number of injections			
MTX total mg			
Daycare per injection			
Laparoscopic salpingectomy			

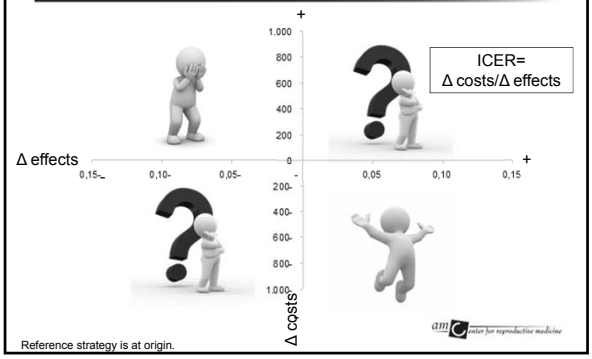
Results – resource use and unit prices

Repeat ectopic pregnancy	Salpingotomy (n= 215)	Salpingectomy (n= 231)	Unit price (€)
Laparoscopic salpingotomy			
Laparoscopic salpingectomy			
MTX single dose			
MTX multiple dose			
No treatment (METEX)			

Results – mean costs per woman

* 95% CI calculated by 1,000 non parametric bootstrap replications

Cost-effectiveness plane



ICER=
Δ costs/Δ 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)

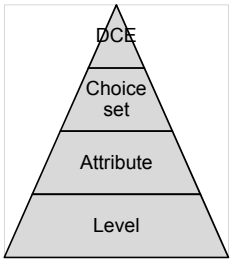
Patient's perspective

What do women prefer?

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

What is the decision making factor?

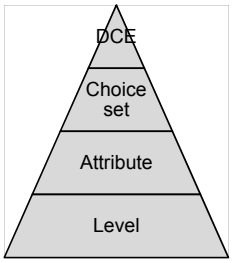
Discrete choice experiment



	 Car A	 Car B	 Car C
Color	Yellow	Red	Green
Upholstery	Leather	Textile	Leather
Price	$ 16.000	$ 12.000	$ 4.000

Ref Ryan. Discrete choice experiments in health care; BMJ 2004

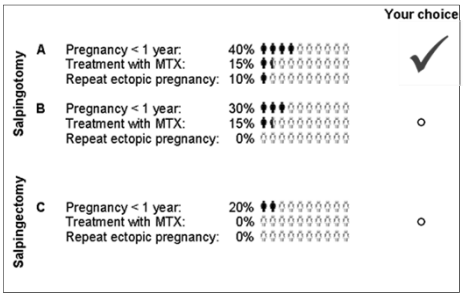
Discrete choice experiment



			
IUP	40%	30%	20%
MTX	5%	1%	0%
Repeat EP	10%	5%	0%

Ref Ryan. Discrete choice experiments in health care; BMJ 2004

Example choice set



Relative importance of the attributes

Attributes	Relative importance (ß)	*P* value
$ß_1$ Spontaneous IUP rate within one year	+0.11	<0.001*
$ß_2$ Treatment with MTX for persistent trophoblast	-0.03	<0.001*
$ß_3$ Risk of repeat EP in the same tube	-0.18	<0.001*

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

van Mello NM, 2010

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.

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Surgical management of tubal pregnancy

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UPCOMING ESHRE EVENTS

// ESHRE CAMPUS EVENTS

ESHRE's 30th Annual Meeting

www.eshre2014.eu

Munich, Germany
29 June - 2 July 2014

Epigenetics in reproduction

www.eshre.eu/lisbon

Lisbon, Portugal
26-27 September 2014

Endoscopy in reproductive medicine

www.eshre.eu/endoscopyoct

Leuven, Belgium
15-17 October 2014

Making OHSS a complication of the past: State-of-the-art use of GnRH agonist triggering

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Thessaloniki, Greece
31 October-1 November 2014

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www.eshre.eu/liege

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Rome, Italy
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