

**Recent Advances in Gynaecological Surgery**  
**RCOG**

**Advances in the Medical Management of  
Endometriosis**

Nick Panay

Queen Charlotte's & Chelsea and Westminster Hospitals  
Honorary Senior Lecturer, Imperial College London

# Endometriosis

---

- ◆ Disease characterised by the presence of functional endometrial glands and stroma outside the uterine cavity
- ◆ Endometriosis responds to hormones (oestrogen dependent) and drugs in the same way as eutopic endometrium

# Endometriosis - aetiology

---

Retrograde menstruation (70-80% women)

...other theories:

- Coelomic metaplasia (esp rectovaginal disease)
- Lymphatic / vascular dissemination
- Transplantation at surgery

# Endometriosis – aetiology (Angiogenic Factors)

---

## ◆ VEGF

- Ectopic endometrium must establish blood supply to survive
- Elevated VEGF found in the peritoneal fluid of women with endometriosis
- Esp in red lesions leading to angiogenesis

## ◆ MMPs

- Inappropriately expressed in the endometrium of women with endometriosis
- Reduced sensitivity to progesterone, allowing neovascularisation

# Endometriosis – aetiology (E2/Aromatase/PGE2)

---

## Aromatase / PGE2

- Aromatase p-450 is the key enzyme for estrogen biosynthesis - catalyses conversion of androstenedione and testosterone to estrone and estradiol
- Aromatase activity is not detectable in normal endometrium but is expressed inappropriately in endometriosis and in the eutopic endometrium of endometriosis patients.

# Endometriosis – aetiology (E2/Aromatase/PGE2)

---

## Aromatase / PGE2

- Estrogen up regulates PGE2
- PGE 2 is a potent inducer of aromatase activity in endometriotic cells
- Postive feedback loop is formed leading to repeated proliferation and inflammation within endometriotic deposits
- Thus aberrant expression of aromatase in endometriotic tissue may be involved in disease pathogenesis

# Endometriosis – aetiology (apoptosis /immune system)

## ◆ Apoptosis

- Reduced in endometriosis patients
- Allows survival of endometrial cells from retrograde menses

» Garcia – Velasco & Arici Semin Reprod Med 2004

## ◆ Peritoneal immune system

- Impaired NK cell activity

# Endometriosis: Genetics

---

## International Endogene Study

([www.medicine.ox.ac.uk/ndog/oxegene/oxegene.htm](http://www.medicine.ox.ac.uk/ndog/oxegene/oxegene.htm))

>2500 families with endometriosis for genetic analysis

- Probably polygenic inheritance with complex interaction between susceptibility genes and environmental factors

-Kennedy et al Hum Reprod 2005 ESHRE Guidelines

# Endometriosis: Genetics

---

## Clinical evidence for a genetic basis

- familial clustering
- concordance in mono twins
- similar age of onset in non-twin sisters
- six to nine times increased prevalence amongst first degree relatives of affected women
- 15% of 1st degree relatives have USS/MRI evidence of the disease

# Endometriosis

---

## Treatment Aims

- relieve pain
- promote fertility

## ◆ Options

- » Medical
- » Surgical
- » Combined

# Medical treatment - infertility

---

There is no role for medical therapy with hormonal drugs in the treatment of endometriosis associated infertility (Evidence Level Ia).

# Ovarian suppression -v- placebo (Cochrane Systematic Review)

---

## Conclusions

- Common odds-ratio for pregnancy after ovulation suppression versus placebo or no treatment was 0.83 (95% CI 0.5-1.39)
- Such approaches '*may do more harm than good in women whose major concern is fertility*' because of the lost opportunity to conceive and significant adverse events

Hughes et al (1999)

# Endometriosis - Medical Treatments

---

## ◆ General Principles of Medical therapy

- **Main aim** : relief of endometriosis related pain
- **Chronic disease** : long term/ repeated courses may be required
- **Efficacy** : highest during therapy with significant recurrence rates
- **Benefit** of one medical therapy over another not established

# Endometriosis - Medical Treatments

---

## ◆ General Principles of Medical therapy

- Side effects and cost profile of drugs varies enormously
- Therapy needs to be individualised according to severity of disease and wishes of patient
- Newer therapies aim to target endometriotic deposits more specifically to avoid systemic side effects of cycle suppression

# Endometriosis - Medical Treatments

---

## ◆ 4 chief medical approaches

- Analgesics / anti inflammatories
- Suppression of ovulation / oestrogen production
- Direct action on endometrial deposits
- Modulation of the Immune response

# Endometriosis - Medical Treatments

---

- Analgesia

- NSAIDS

- Ovulation / Oestrogen suppression

- Contraceptive pill / high dose progestogens
- Danazol
- Gestrinone
- GnRH agonists +/- add back therapy

- Direct action on deposits

- Mirena (levonorgestrel intrauterine system)
- Progesterone antagonists
- Selective Progesterone Receptor Modulators
- Selective Estrogen Receptor Modulators
- Aromatase Inhibitors
- Estrogen Receptor Ligands
- Angiogenesis Inhibitors
- Statins

- Immunomodulation

# Analgesia

---

# Endometriosis

---

## Medical Treatment

- Analgesia:
- NSAIDS
  - » There is inconclusive evidence to show whether NSAIDs treat endometriosis associated pain
  
- One RCT from recent Meta analysis
- Naproxen v placebo
- OR 3.27 (0.61-17.69)
  - Allen C et al Cochrane Database Syst Rev 2000

# Ovarian suppression

---

# Endometriosis

---

## Medical Treatment

- Oral contraceptive pill
  - » used for 6-9 months tricycling / continuously
    - ◆ Side effects: weight gain, headaches, breast tenderness, nausea thromboembolism
    - ◆ New long cycle pills (Yaz) and continuous pills (Mylybrel) on the way

– Moore J Kennedy SH Prentice Cochrane Database 2000; (2): CD000346

# Endometriosis

---

## Medical Treatment

### – Progestogens

- » orally or depot

- » e.g. MPA 10mg tds

- » used for 3-6 months

- ♦ side effects: weight gain, bloating, mood changes

# Endometriosis

---

## Medical Treatment

### – Danazol

- » 17 $\alpha$  ethinyl testosterone
- » Androgenic : anabolic
- » 400 - 800mg daily for 6-9 months
- » Relief 85%
  
- » Recurrence in 40% in 36 months
  - ◆ Side effects: weight gain, acne, fluid retention, masculinisation

– Selak V et al Cochrane Database 2001; (4): CD000068

# Endometriosis

---

## Medical Treatment

### – **Gestrinone**

- » Synthetic trienic 19 norsteroid
- » Mildly androgenic
- » Antigonadotrophic
- » 2.5 - 5mg twice weekly for 6-9 months
- » Relief 85%
- ◆ Side effects: weight gain, break through bleeding, reduced breast size, cramps, uncommonly masculinisation



Zoladex

depot 3.6 mg

Contains one depot  
in a prefilled  
injection applicator.  
For subcutaneous  
injection.

Goserelin 3.6 mg

Contains one depot  
in a prefilled  
injection applicator.  
For subcutaneous  
injection.

ZENECA

Zoladex

depot 3.6 mg

ZENECA

ZENECA

Store below 25°C.

Zoladex  
depot 3.6 mg

# Endometriosis

---

## Medical Treatment

- **GnRH agonists**

- » Reversible medical menopause

- » Intranasal or subcutaneously daily, depot for 6-9 months

- » Recurrence rates as for danazol & gestrinone

- Prentice et al Cochrane database 2000; (2): CD000346

# Endometriosis

---

## Medical Treatment

- **GnRH agonists**

- » Side effects: hypo-oestrogenisation, hot flushes, vaginal dryness, headaches, reduced libido.

- » Bone loss and symptoms may be balanced by “add-back” tibolone / low dose cc HRT

- » Data for up to 2 years add back effective at preventing loss of bone mineral density

- Sagsveen et al Cochrane Database 2003; (4): CD0011297

# Endometriosis

---

## Medical Treatment

- **GnRH / LH antagonists**

- » ?Role in avoiding initial up regulation with agonists in women with severe endometriosis / symptoms

- » Data needed

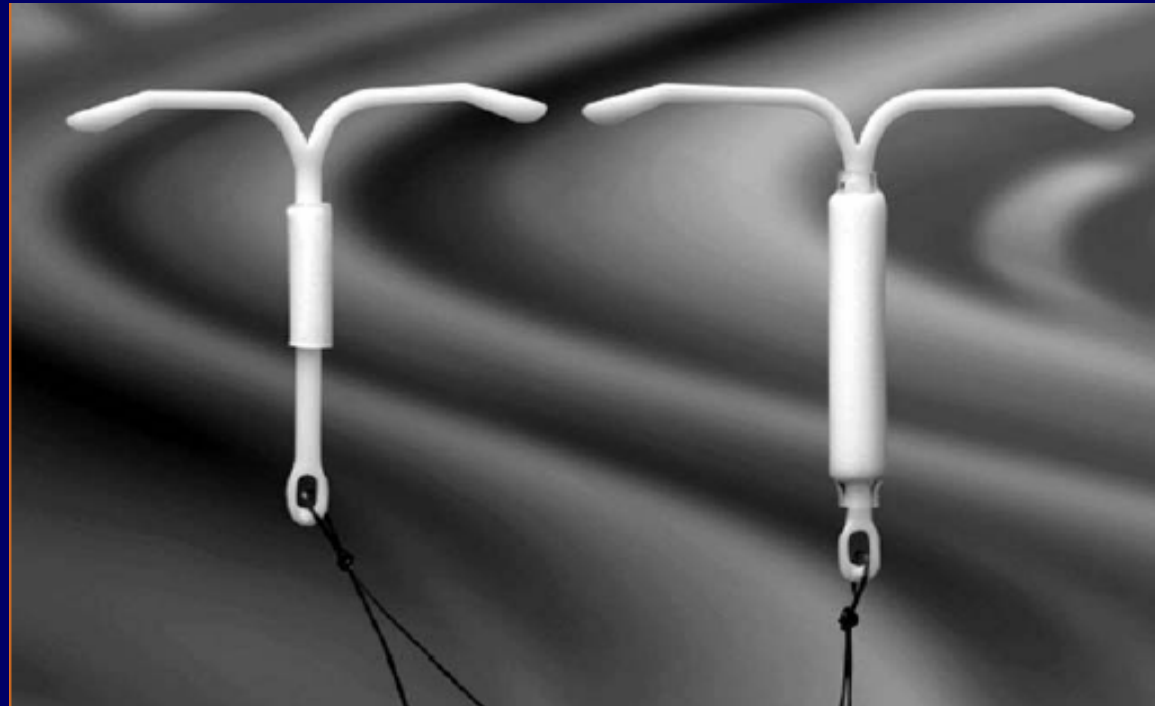
# Direct action

---

# MLS\* & Mirena

\*Schering decision not to launch in 2006

---



# Endometriosis

---

Medical Treatment : LNG IUS (Mirena)

Direct effect of levonorgestrel on endometriotic deposits through peritoneal fluid (?via haematogenous spread)

Lockhat, et al Fertility & Sterility, 2005

Pilot studies showed great improvement in pain control

Reduction in ultrasonographic size of rectovaginal nodules

Improvement in AFS staging of disease

Vercellini et al Fertil Steril 1999; Fedele et al Fertil Steril 2001; Lockhat et al Hum Reprod 2004

# Endometriosis

---

Medical Treatment : LNG IUS (Mirena) 2 RCTs

- 40 women Open Label trial
- Expectant Mx v Immediate Rx with LNG IUS after laparoscopic surgery
  - » 12 month review – sig lower pain scores in LNG IUS arm
    - Vercellini et al Fertil Steril 1999
- 83 women with Stage I to IV endometriosis
- GnRHa v LNG IUS – 6 month review
  - » Sig pain relief in both groups – no statistically sig difference
    - Petta et al Hum Reprod 2005

# Endometriosis

---

## Medical Treatment : LNG IUS (Mirena) 3 year trial

34 women with laparoscopically confirmed minimal to moderate symptomatic endometriosis offered insertion of an IUS at diagnostic laparoscopy followed up at 1, 3 and 6 months, and every 6 months for 3 years.

- Continuation rates were 85%, 68%, 62% and 56% at, 6, 12, 24 and 36 months.
- Discontinuation rates were highest at <12 months, and most of these were for irregular bleeding and persistent pain.
- An improvement in symptoms was observed through the 36 months.
- Greatest changes in pain assessed by VAS between the pretreatment scores and those at 12 months (7.7 v 3.5 VAS,  $P < 0.001$ )
  - Lockhat et al Hum Reprod 2005

# Endometriosis

---

## Progesterone antagonists (Mifepristone RU486)

- Anti progesterone effect
- Blocks progesterone receptors in endometrium
- Loss of functional integrity / shedding
- Early work showed improvement in pain

Prentice Cochrane database 2000; (2): CD002122; Chabbert –  
Buffet et al HR Upd 2005

# Endometriosis

---

## Progesterone antagonists (Mifepristone RU486)

- 100mg daily for three months in women with laparoscopically diagnosed pelvic endometriosis,
- Mifepristone induced amenorrhoea and reduced pelvic pain.
- Problem with erratic bleeding
- Results have to be confirmed by larger studies.

◆ Kettel LM et al Preliminary report on the treatment of endometriosis with low-dose mifepristone;AM Obstet Gynecol;1998;178;1151-1156.

# Endometriosis

---

- ◆ Selective progesterone receptor modulators
  - New class of progesterone receptor ligands
  - Progesterone receptor agonist/antagonist of mixed effects on various progesterone receptor target tissues in vivo
  - Asoprisnil is first SPRM to reached advanced stages of clinical development for Rx of Endometriosis and Fibroids
  - Anti-proliferative effect in endometrium

# Endometriosis

---

- ◆ Selective progesterone receptor modulators : asoprisnil
  - Dose dependent suppression of menstruation in phase I and phase II trials
  - Effective in reducing non menstrual pain and dysmenorrhoea in phase I trials of subjects with endometriosis

# Endometriosis

---

- ◆ Selective progesterone receptor modulators : asoprisnil
  - One RCT in 130 women with lap diagnosis of endometriosis and mod to severe pelvic pain (dose finding)
  - Significant reduction in pelvic pain and dysmenorrhoea
  - Bleeding pattern: 83% amenorrhoea @ 12 weeks (25mg dosage)

# Asoprisnil

Advantages over preexisting Rxs e.g. GnRHa

---

## Normal oestrogen levels

- No menopausal symptoms
- No concerns re osteoporosis / CV disease

## ◆ Other

- No PMS side effects!
- ?Minimal Effect on Breast

# Endometriosis

---

- ◆ Selective estrogen receptor modulators (SERMs) e.g. raloxifene
  - Anti proliferative effect on endometriotic tissue
  - No human studies as yet
  - Two animal studies
  - Significant regression of implants at 10mg/kg dosage

# Endometriosis

---

## Aromatase Inhibitors – Clinical Studies

- ◆ Limited published studies thus far: 7 case reports/series (40 patients) only 1 RCT
- ◆ Treatment with an AI has been described in combination with a progestogen and a COCP
  - Ailawadi et al Fertil Steril 2004 (Letrozole/NETA) - Chicago
  - Amsterdam et al Fertil Steril 2005 (Anastrozole/20mcgEE+LNG) - Minneapolis
- ◆ Reduction in Laparoscopic AFS scores and 90-93% pelvic pain relief in both studies

# Endometriosis

---

## Aromatase Inhibitors – Clinical Studies

### ◆ One RCT (Turkey)

- 80 patients with treatment resistant severe endometriosis
- Goserelin GnRH + Anastrozole v GnRH alone for 6 months
- Sig > improvement in pain scores in combined arm ( $p < 0.0001$ )
- Minimal side effects and no sig bone loss
  - » The effects of post-surgical administration of goserelin plus anastrozole compared to goserelin alone in patients with severe endometriosis: a prospective randomised trial Soysal et al Human Reproduction 2004

# Endometriosis

---

## Estrogen Receptor Ligand – Mechanism of Action

- First in class compound
- Highly selective binding to ER beta (200 times greater than alpha)
- Estrogen receptor beta (ER $\beta$ ) ligand showed anti-inflammatory activity in preclinical models.
- Mechanism otherwise not fully understood

# Endometriosis

---

## Estrogen Receptor Ligand – Pre Clinical Data

- ERBL was associated with a 40 – 75% lesion regression in an experimentally induced model of endometriosis.
- ERBL did not prevent ovulation in the rat.

# Endometriosis

---

## Estrogen Receptor Ligand – Clinical studies (Phase II)

- Healthy cycling women received up to 150 mg daily doses of ERBL for 28 days.
- TVUSS to detect follicular development and ovulation, hormonal measurements (LH, FSH, estradiol, progesterone), and records of menses for 3 cycles

# Endometriosis

---

## Estrogen Receptor Ligand – Clinical studies

- All subjects had normal ovulatory reproductive hormone profiles and ovulation during the 3 cycles, and normal menses occurred at the end of each cycle.
- Preliminary phase 2 data indicate that ERB-L reduces symptoms of endometriosis, supporting further investigation in phase 3.
- The preclinical and human data generated to date suggest that ERB-L will be well tolerated and may have efficacy in the treatment of endometriosis.

# Endometriosis

---

## Angiogenesis Inhibitors – Clinical studies

- Inhibition of proangiogenic factors VEGF/MMPs
- Efficacy of angiostatic compounds has been demonstrated in mouse model
- Only one Human Study using Thalidomide

# Endometriosis

---

## Angiogenesis Inhibitors – Clinical studies

- Inhibition of proangiogenic factors VEGF/MMPs
- Efficacy of angiostatic compounds has been demonstrated in mouse model
- Only one Human Study using Thalidomide

# Endometriosis

---

## Statins – In vitro

- Statins lower blood cholesterol by inhibition of HMG – CoA reductase
- In vitro data suggest that statins can inhibit the growth of human endometrial cells
- Requires confirmation in clinical studies

# Immunomodulation

---

# Endometriosis

---

## Immuno-modulators / Inflammatory modulators

- Certain similarities between endometriosis and autoimmune disease
- Elevated levels of cytokines & Decreased cell apoptosis
- TNF alpha binding protein inhibits development of endometriosis in rodent & baboon model – no human studies

◆ D'Antonio et al J Reprod Immunol 2000; D'Hooge Fertil Steril 2001

# Endometriosis

---

## Combined Treatment

### ◆ Empirical Rx or after “first look” procedure

- Medical treatment may reduce the vascularity of lesions, but excision may be more difficult

### ◆ Post surgical Rx

- Benefit demonstrated for GnRHa / Mirena Rx after surgery to reduce risk of recurrence

### ◆ RCT's required!

# Clinical case senarios

---

# Endometriosis

---

## Medical Treatment Post TAH BSO

- Progestogenic opposition desirable e.g. ccHRT / tibolone
- Case reports of re-activation of endometriosis / endometrial carcinoma in unopposed E2 users

# Endometriosis – Conclusions

---

## ◆ General / Medical

1. Advances in understanding of mode of polygenic inheritance will improve diagnosis and management of disease
2. Specific targeting of ectopic endometrium will maximise the benefits of therapy whilst minimising the side effects and risks.

# Endometriosis - Conclusions

---

## ◆ Suggested Rx algorithm with available therapies

- 1<sup>st</sup> Line: NSAIDS / COCP / Oral progestogens
- 2<sup>nd</sup> Line: Mirena (if acceptable to patient)
- 3<sup>rd</sup> Line: GnRH analogues +/- add back / Danazol?
- 4<sup>th</sup> Line: Aromatase inhibitors +/- COCP/GnRH $\alpha$ /Progestogen
- 5<sup>th</sup> Line: ?Mifepristone / Raloxifene / Statins

# Endometriosis – Advances

---

THANK YOU FOR LISTENING!

- ◆ Further Info:
- ◆ ESHRE guideline for the diagnosis and treatment of endometriosis  
<http://guidelines.endometriosis.org/>
- ◆ RCOG green top guidelines  
<http://www.rcog.org.uk/index.asp?PageID=517>
- ◆ nickpanay@msn.com